Colorectal Liver Metastases

Ahmed Abdelrafee, MD, PhD

Lecturer of General Surgery

Gastro-intestinal Surgery Center

Mansoura University

* Colorectal cancer (CRC) is the third most commonly diagnosed cancer with significant morbidity and mortality (more 600000 deaths each year), 2/3 from liver metastases.

* The liver is the most common metastatic site.

* Half of patients will eventually develop colorectal liver metastasis (CRLM) during the course of the disease.

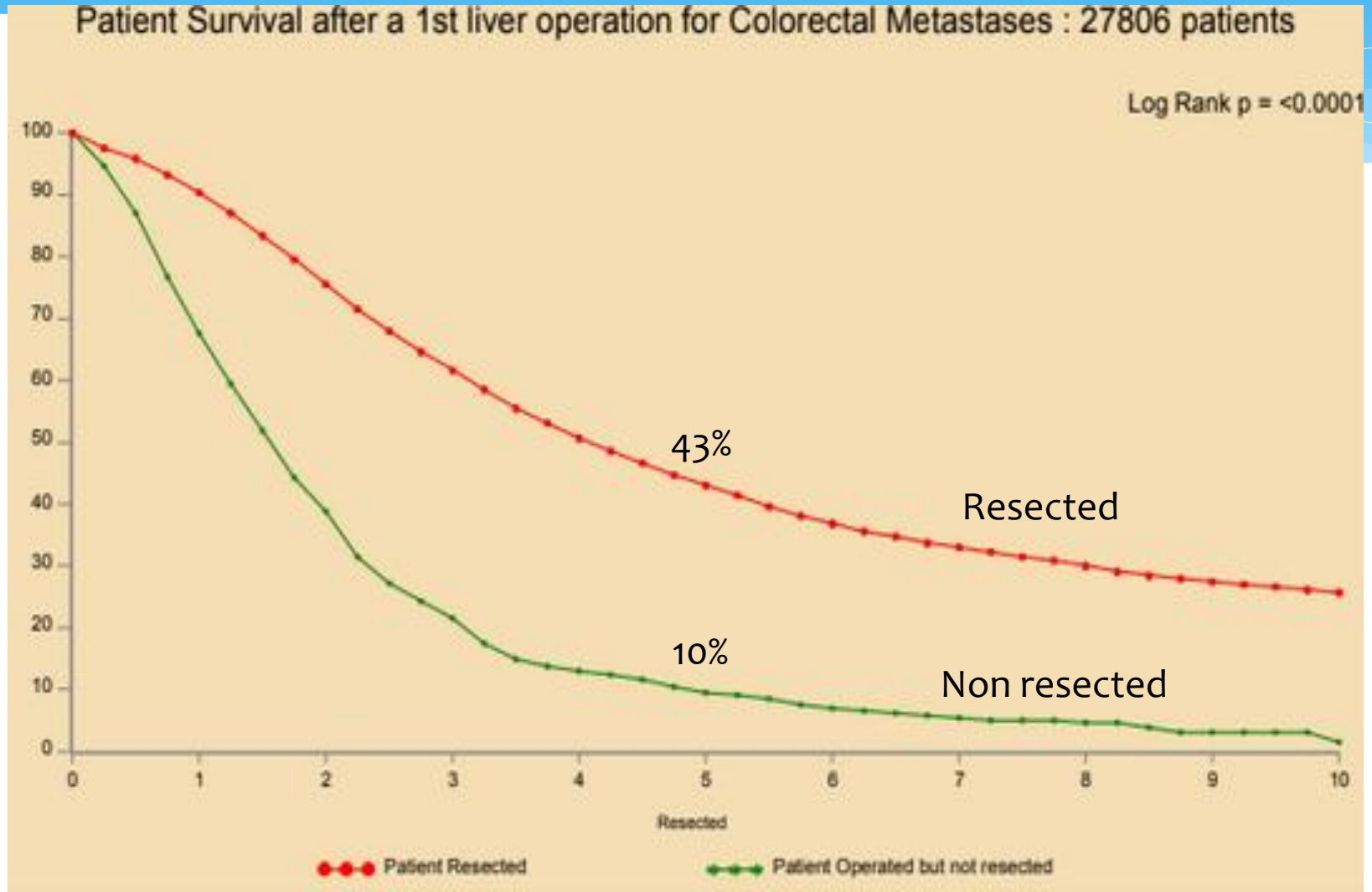
Siegel et al. CA cancer J Clin. 2016
Brenner et al. Lancet. 2014
Adam et al. Gastrointest Cancer Res. 2009

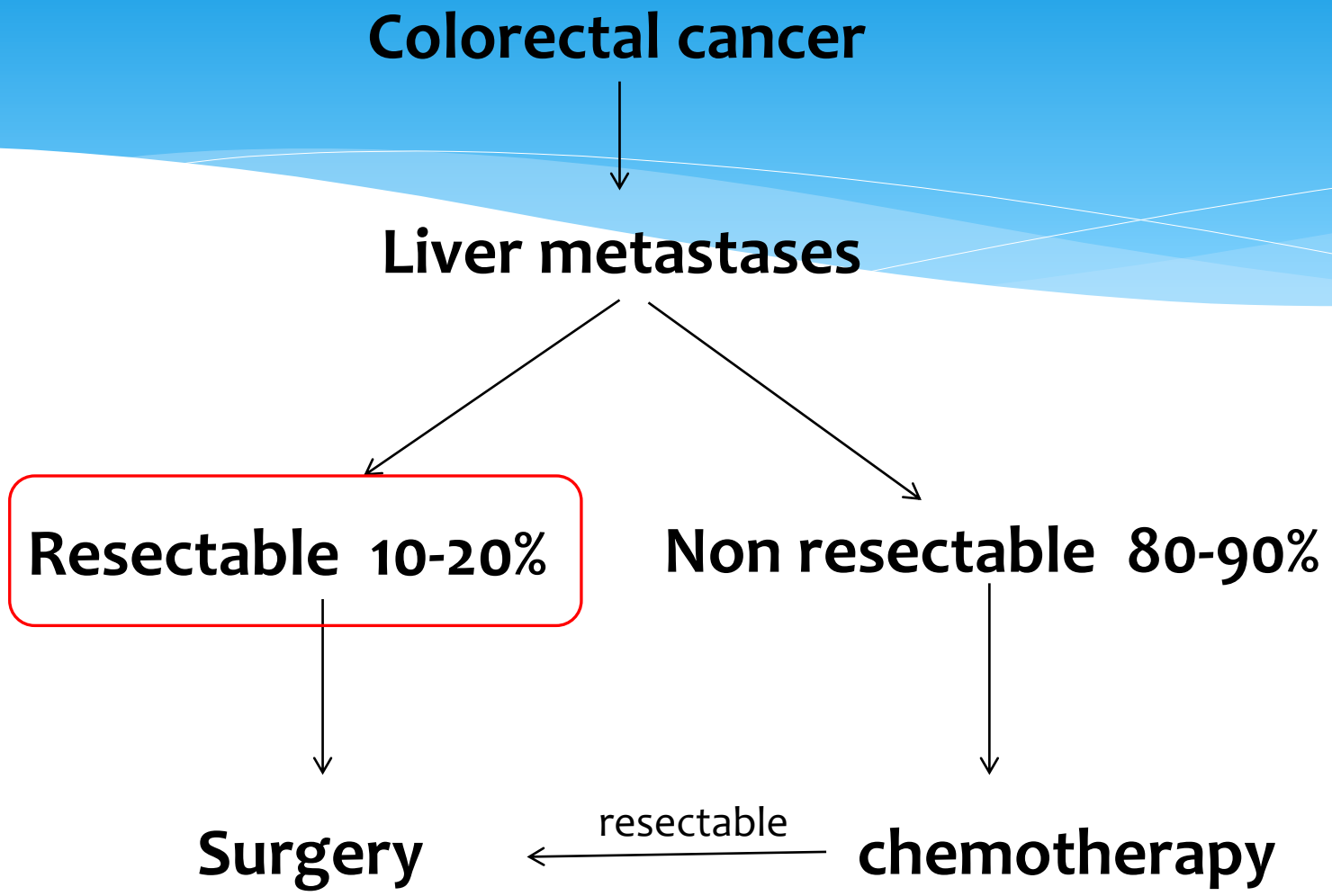
* Hepatic resection remains the cornerstone in the treatment of CRLM providing the possibility of prolonged survival or even cure. The 5-year OS after resection reaching 45-60% in selected patients.
* Unfortunately, minority of patients (15-20%) with CRLM are eligible for resection at the time of presentation.
* Consequently, the treatment strategy for CRLM should be directed toward their potential resectability.

Adam et al. The Oncologist. 2012
Chow et al. World J Hepatol.2019
Adam et al. Ann Gastroenterol Surg. 2019

International liver met survey registry

OS




Colorectal cancer
Liver metastases
Resectable 10-20%
Non resectable 80-90%
Surgery
resectable
chemotherapy

- Recent innovations in the treatment of CRLM have been introduced leading to increased resectability of this group of patients.

1. First, advancement in systemic chemotherapy with or without targeted therapy and HAI resulted in downsizing of the tumour and converting the initially unresectable CRLM to be resectable (response rate 50-80%), what is called OncoSurg approach.

Poston et al, J Clin Oncol. 2005

Adam R et al, Cancer Treat Rev. 2015

2. Immunotherapy (immune check point blockade such as anti-PD1 for MMR deficient gene)

3. Pushing the limits regarding the criteria of resectability of CRLM.

4. Innovations in surgical techniques such as TSH, ALPPS, liver venous deprivation, PVE, liver tunneling, etc.

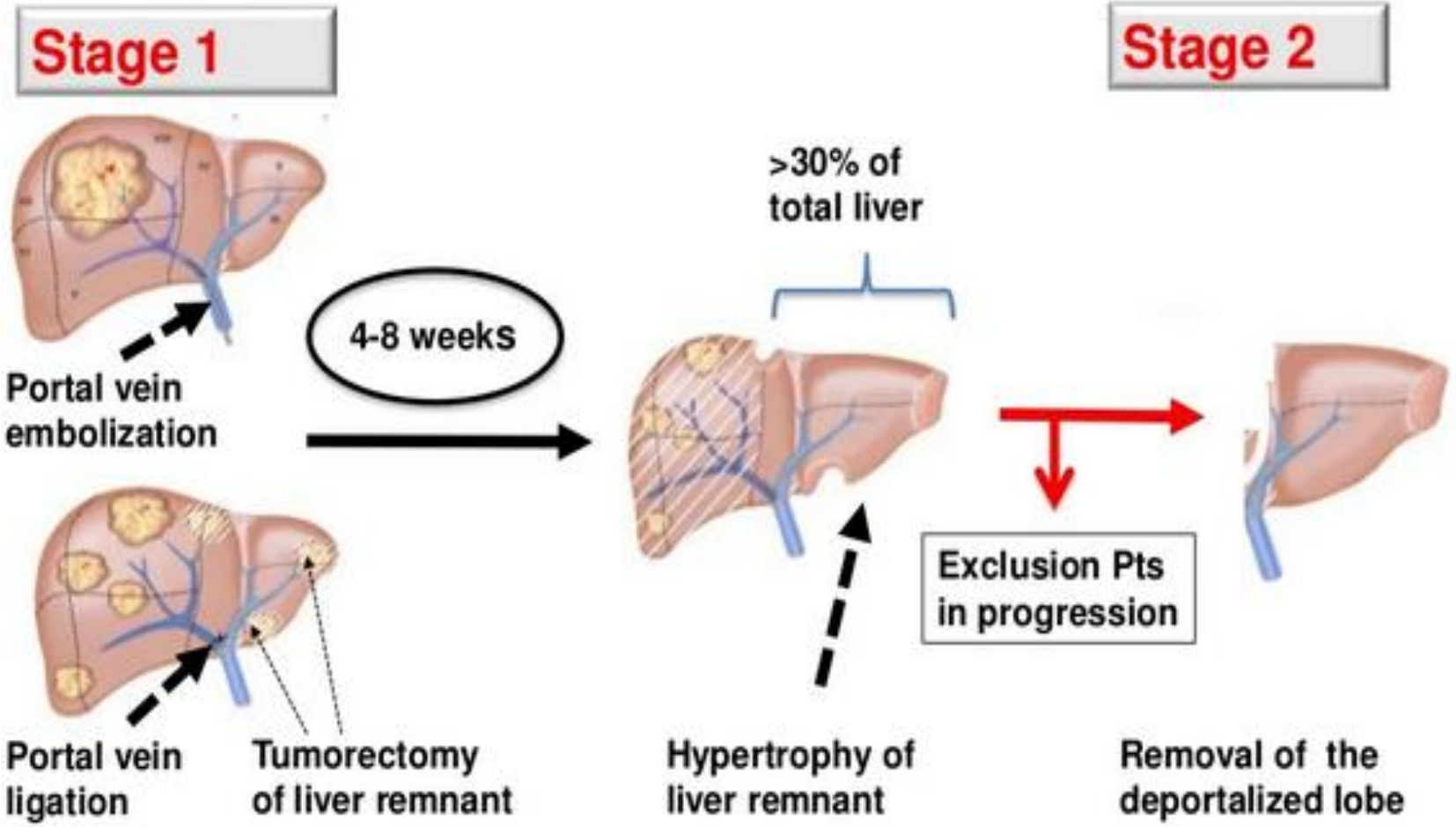
5. Use of associated local ablative therapy like RFA

Margonis et al. Ann Surg. 2018

Imai K et al. Ann Surg. 2015

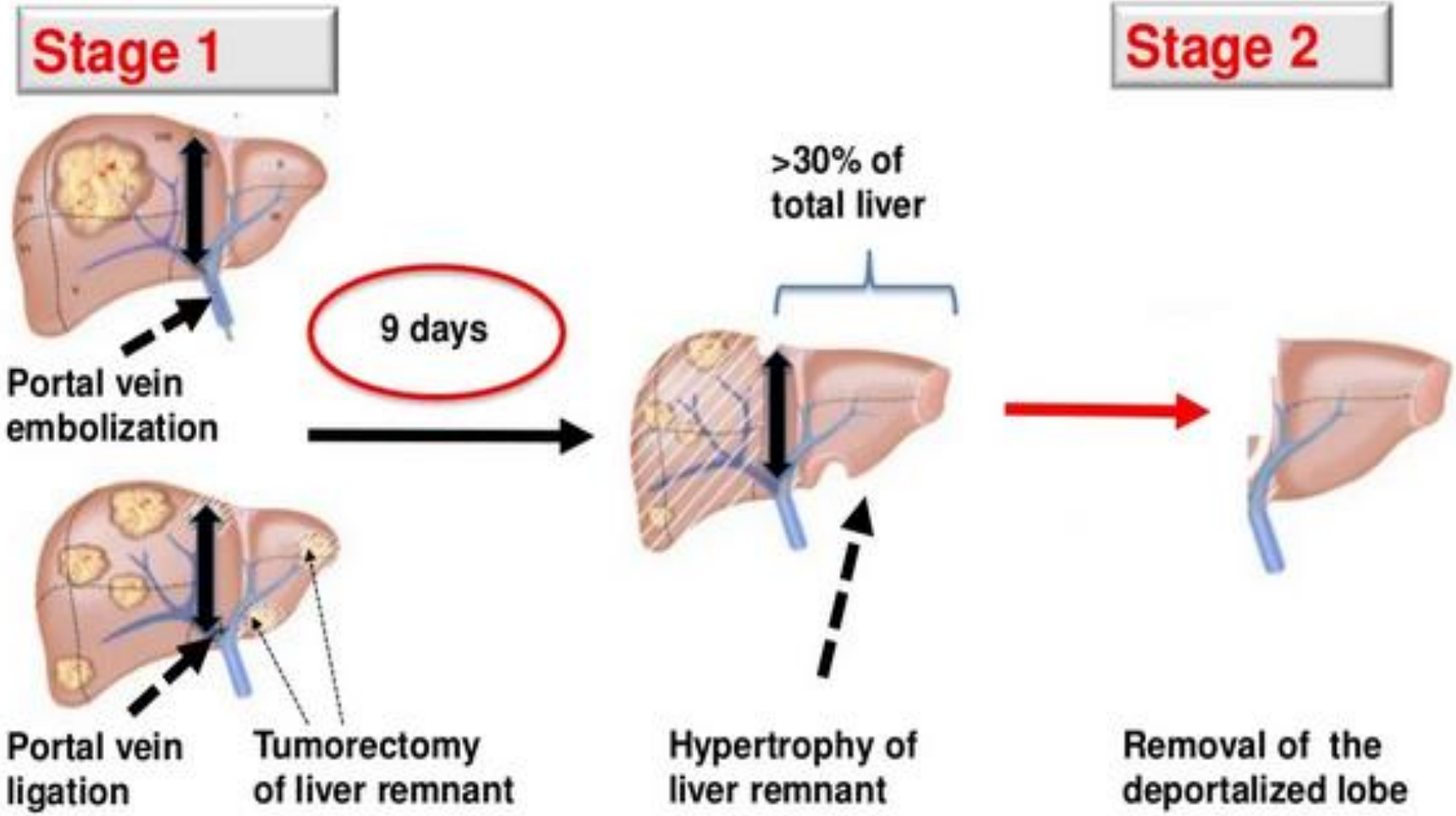
De Santibanes et al. Ann Surg. 2012

The Selective Staged method…
Two-stage Hepatectomy



Clavien et al. Strategies for safer liver surgery. NEJM, 2017

The fast-surgery method…: ALPPS



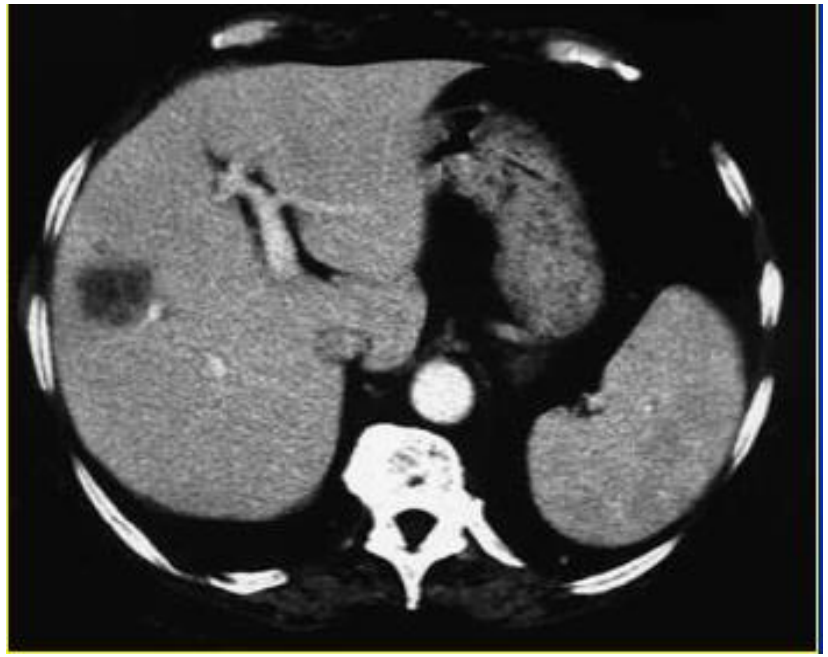
Clavien et al. Strategies for safer liver surgery. NEJM, 2017

* Many factors influence the treatment strategy such as: initial resectability, synchronicity of CRLM, timing of surgery in relation to primary CRC, role of laparoscopy, type of chemotherapy regimen and perioperative use, tumour biology like mutant KRAS).
* Consequently, the plan of treatment should be personalized for each patient.
* To achieve this goal, multidisciplinary team (MDT) approach must be implemented.

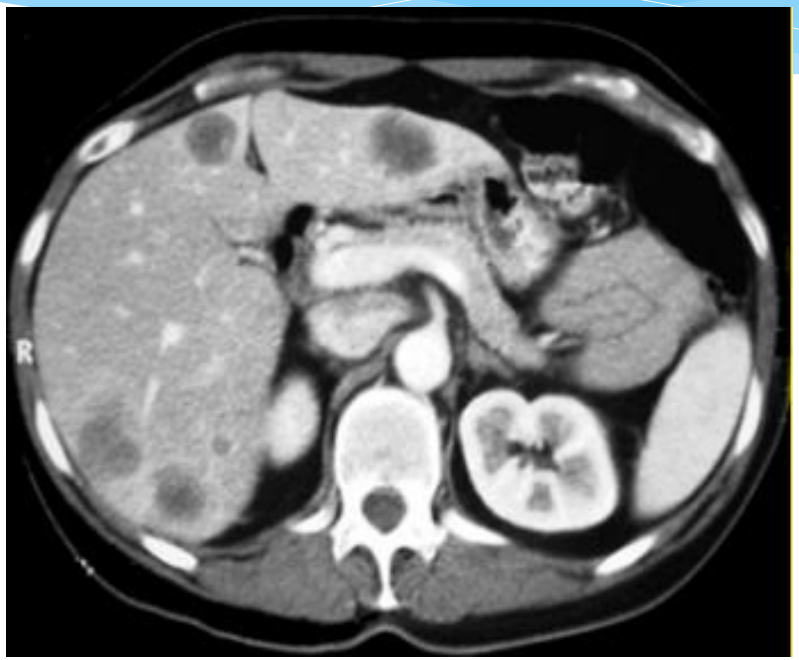
Adam R et al, Cancer Treat Rev. 2015

Torzilli et al. Liver Cancer. 2016

Definition of resectability



Ekberg et al. BJS. 1986 (<4LM)



Van dam et al. HPB 2014 (≥4 LM)
Vigano et al. BJS 2015 (≥8 LM)
Allard et al. BJC 2017 (≥10 LM)

Recent resectability criteria adopted in expert center and detected by multidisciplinary team (MDT)

Item	Traditional criteria	Current criteria
EHMD	No EHMD	Stable or resectable EHMD (excluding portal lymphadenopathy)
LM number	Fewer than 4 lesions	No limit
LM distribution	Unilateral	No limit
Vascular invasion	No involvement	Amenable to venous resection or reconstruction
Resection margin width	More than 1 cm	Beyond 1 mm with a tumor-free margin
% of FLR of total liver volume	> 20%	> 20% for normal liver and slight chemotherapy-associated liver dysfunction;
		> 30%–40% for severe chemotherapy-associated liver disease

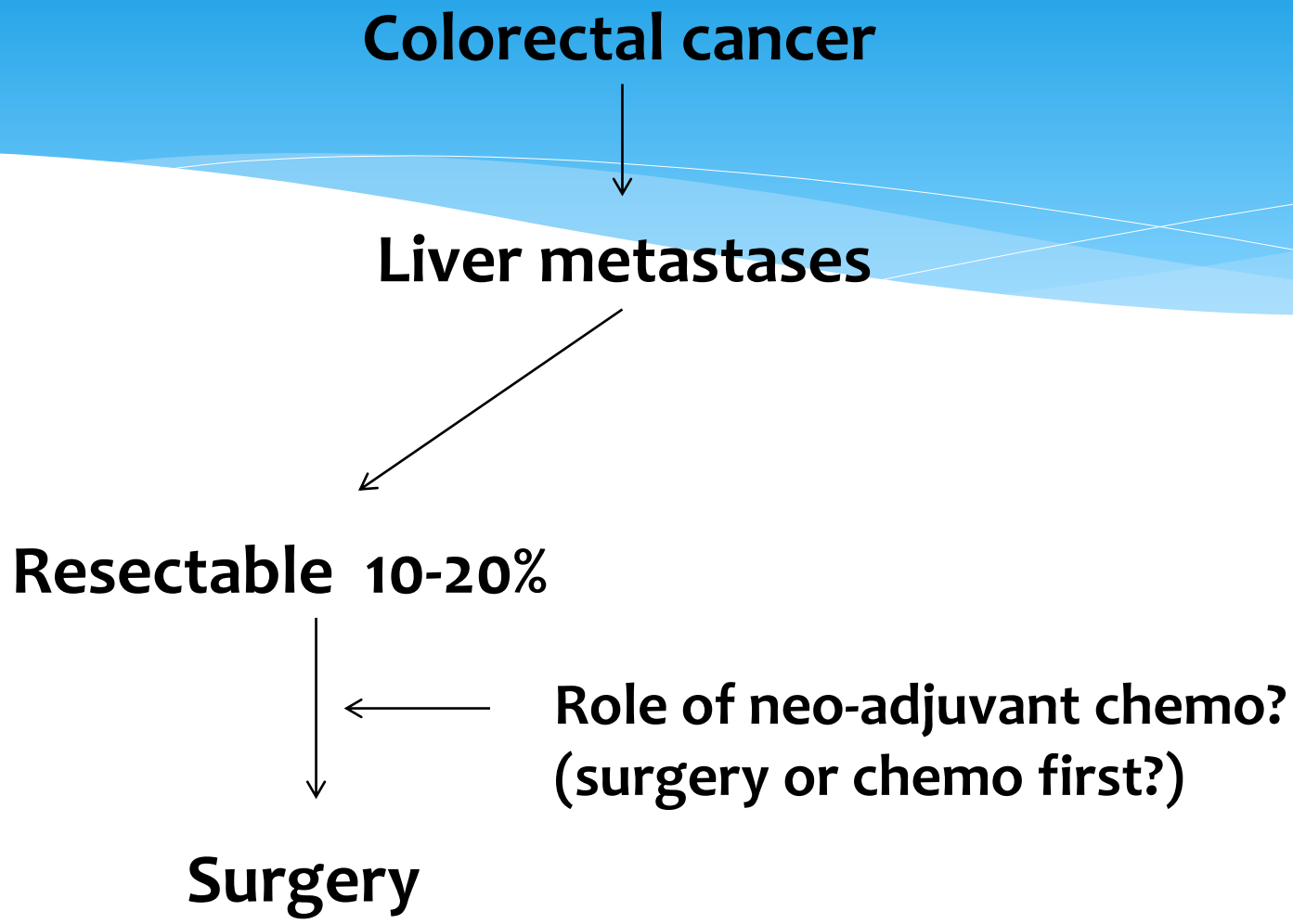
Xu et al. World J Clin Cases. 2018

* Although surgery provides encouraging OS rates, recurrence rate is still high reaching 50-75% within the first 2 years after surgery due to presence of microscopic residual disease.
* And so, improvement of results is needed.
* Increasing interest was directed to use chemotherapy combined with surgery to reduce the risk of recurrence.

Bonney et al. J Surg Oncol. 2015
Beppu et al. Hepatobiliary Surg Nutr. 2015

Treatment strategy	Arguments in support of	Arguments against
The simultaneous approach	No increase of morbidity and/or mortality in carefully selected patients	Considerable increase of morbidity and/or mortality
	Removal of all cancer in a single procedure; thereby lowering the risk of disease dissemination	No time-test approach to evaluate the biological behavior of metastasis and this may result in unnecessary liver resection in rapidly progressing disease
	Similar PFS and OS compared to those with staged resection	Higher recurrence rate and a negative impact on long-term outcome
Pre-HR chemotherapy	Decreases the magnitude of resection	Delays liver resection and may result in a unresectable state in nonresponders
	Eradicates micrometastases	May lead to liver parenchyma damage and increased postoperative morbidity
	Increases R0 resection rates	No impact on PFS and OS
	Assesses responsiveness to specific chemotherapy, thus, identifying and selecting patients with favorable tumor biology. It improves PFS	
Extensive resection for DLM	Response on imaging does not necessarily signify clinical or pathological response (in up to 83% evidence of residual disease); so resect all initial sites if possible, despite disappearance on imaging	Hence, durable clinical response is as high as 62%, resect only residual macroscopic disease leaving the disappeared lesions *in situ* or alternatively, continue systemic chemotherapy alone
The liver-first approach	It is the liver metastasis, rather than the primary tumor, that gives rise to systematic metastatic disease, so it should be addressed first	No, it is the primary tumor that produces systemic effects promoting angiogenesis in the liver, thus favoring the spread of metastatic disease
	It avoids the risk for progression of CRLM while the patient is treated for the primary tumor, especially if complications are encountered; thereby improving median survival and 3-year survival rates	Despite apparently similar treatment protocols in those few studies, the variations in survival rates of the liver-first approach are wide; so its comparison with the bowel-first approach or the combined strategy is problematic
	Option to give systemic chemotherapy as a first step early in the treatment course that may lead to an effective response in the primary tumor and avoids resection	

Kassahun. WJSO, 2015


Colorectal cancer
Liver metastases
Resectable 10-20%
Role of neo-adjuvant chemo?
(surgery or chemo first?)
Surgery

Rational of neo-adjuvant chemotherapy (NAC)

- **Advantages of NAC:**

1- Test of time: better selection of patients

2- Test of efficacy (chemo responsiveness): guide for postoperative chemo.

3- Downsizing of metastases.

4- It may induce complete pathological response

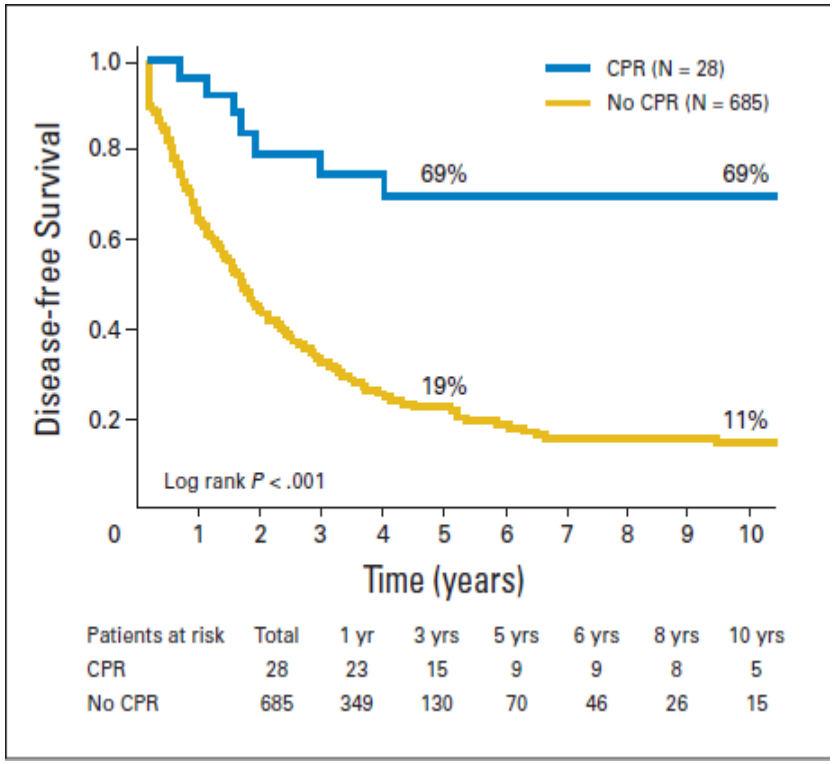
5- Elimination of the micrometastasis that is not treated by surgery

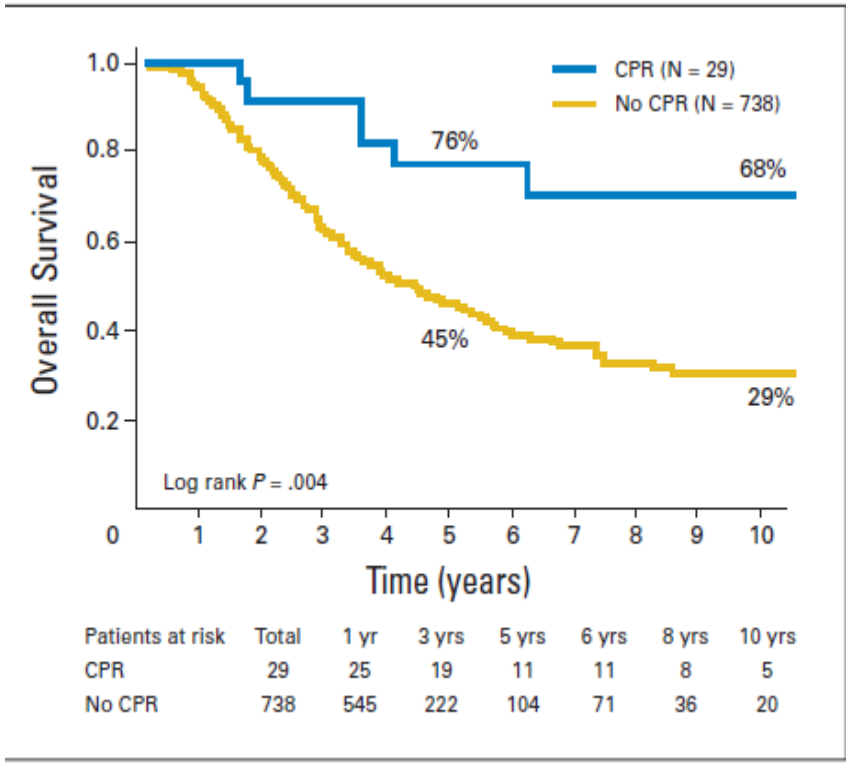
6- Avoid losing the entire regimen of CT due to PO complications.

Clinical Trial > J Clin Oncol. 2008 Apr 1;26(10):1635-41. doi: 10.1200/JCO.2007.13.7471.

Complete Pathologic Response After Preoperative Chemotherapy for Colorectal Liver Metastases: Myth or Reality?

René Adam [1], Dennis A Wicherts, Robbert J de Haas, Thomas Aloia, Francis Lévi, Bernard Paule, Catherine Guettier, Francis Kunstlinger, Valérie Delvart, Daniel Azoulay, Denis Castaing





Disadvantages of NAC:

1- Progression while on chemotherapy:

a- it could render liver metastases unresectable (uncommon).

b- liver resection during progression provides poor survival outcome.

2- Disappearing liver metastases (complete radiological response)

3- Hepatotoxic effect which increases the postoperative morbidity and mortality

* The aim of NAC is to achieve the resectability only not the complete radiological response.

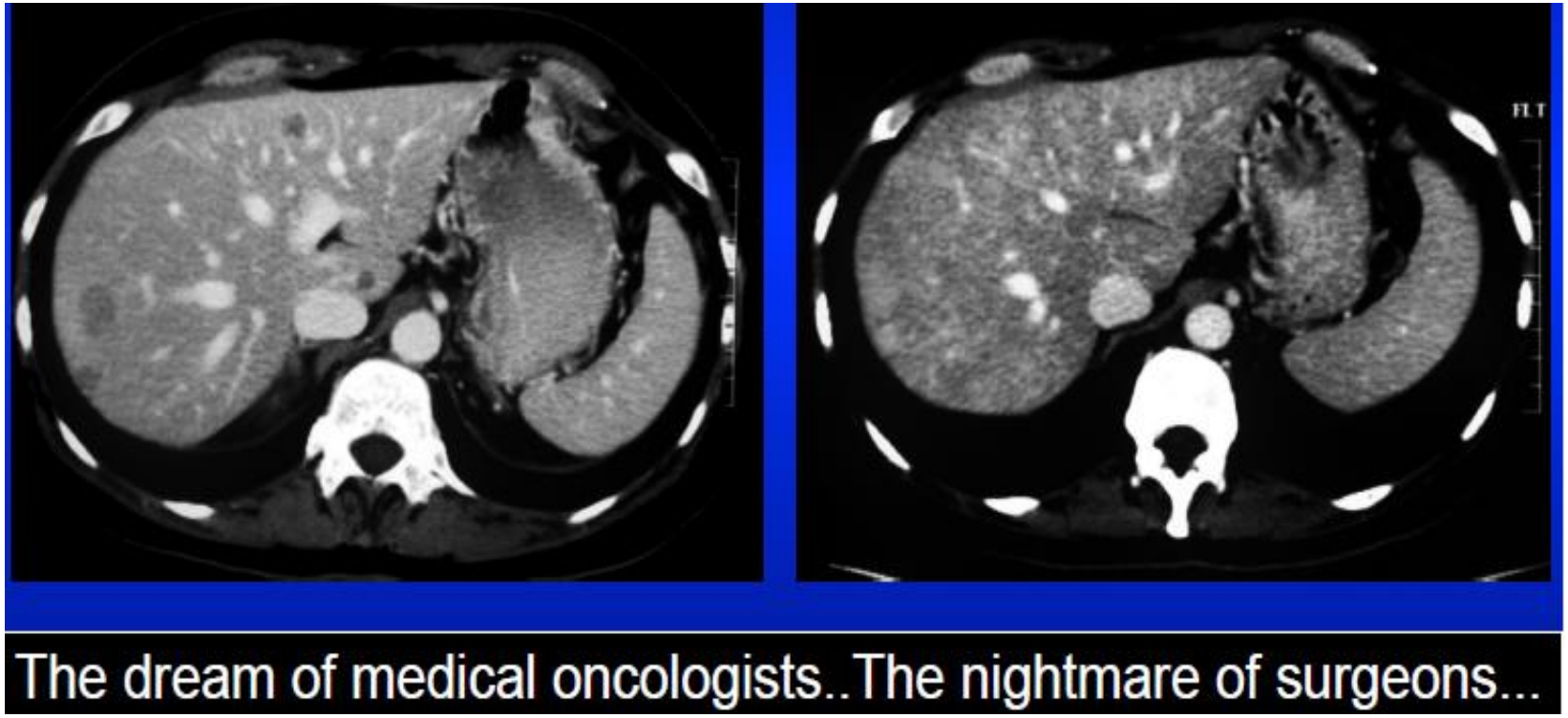
* So, it is recommended to give short course (3-4 cycles) of first-line chemotherapy to avoid liver toxicity and the optimal timing for the assessment of the response is every 2 months.

* Surgery should be avoided during the progression of the disease with chemotherapy.

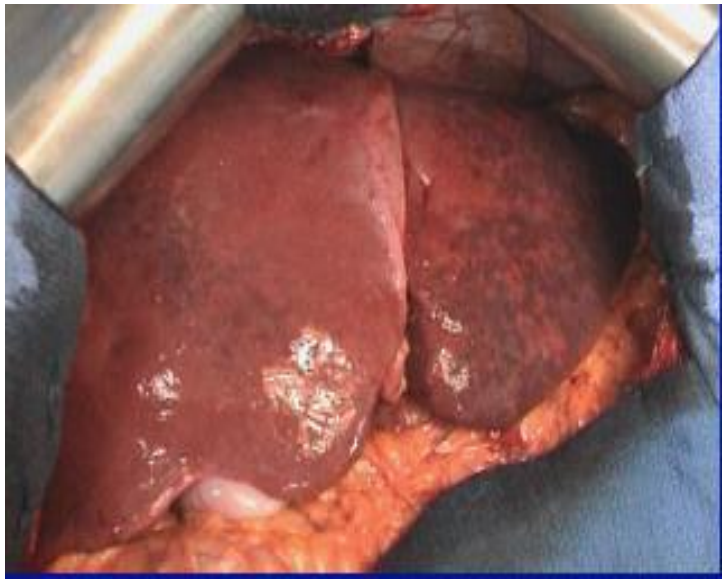
Complete radiological response

Before chemo

After chemo



Effect of chemotherapy on the liver



Blue liver
(oxaliplatin)

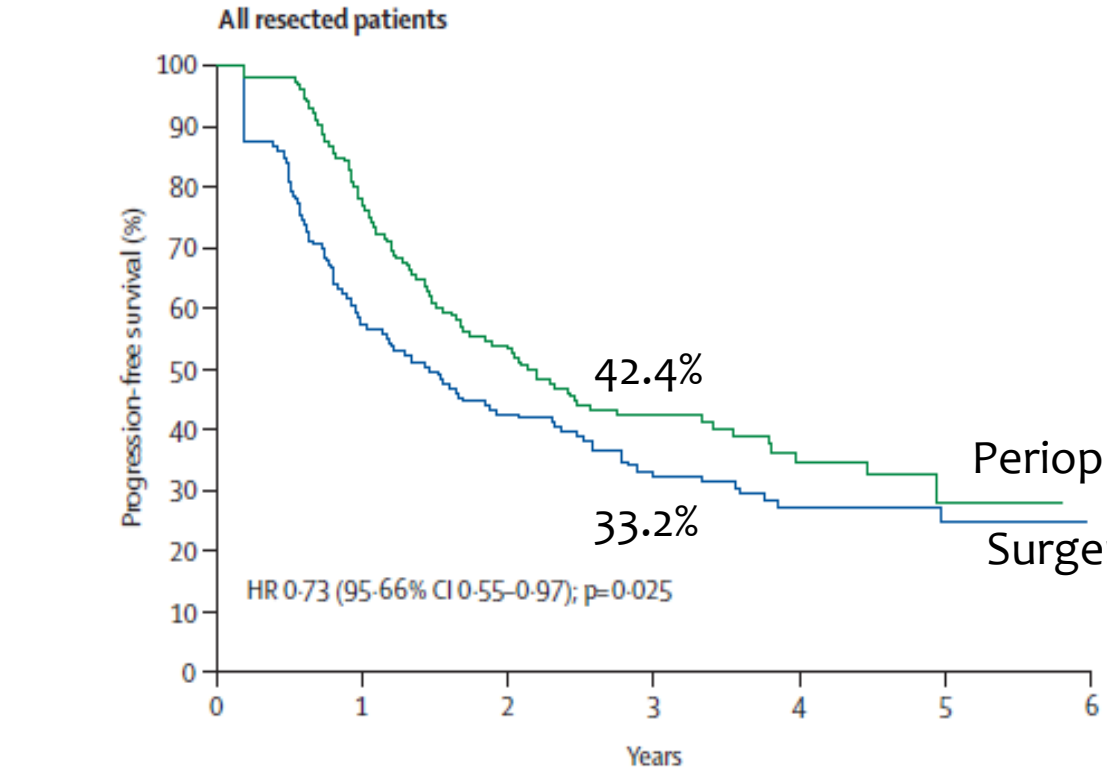
Yellow liver
(irinotecan)

Resectable CRLM : surgery or chemotherapy first?

Lancet. 2008 Mar 22; 371(9617): 1007–1016.
doi: 10.1016/S0140-6736(08)60455-9
PMCID: PMC2277487

Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial

Bernard Nordlinger,[a,*] Halfdan Sorbye,[b] Bengt Glimelius,[c,d] Graeme J Poston,[e] Peter M Schlag,[f] Philippe Rougier,[a] Wolf O Bechstein,[g] John N Primrose,[h] Euan T Walpole,[i] Meg Finch-Jones,[j] Daniel Jaeck,[k] Darius Mirza,[l] Rowan W Parks,[m] Laurence Collette,[n] Michel Praet,[n] Ullrich Bethe,[n] Eric Van Cutsem,[o] Werner Scheithauer,[p] Thomas



Total No of patients= 364

No of LM ≤4

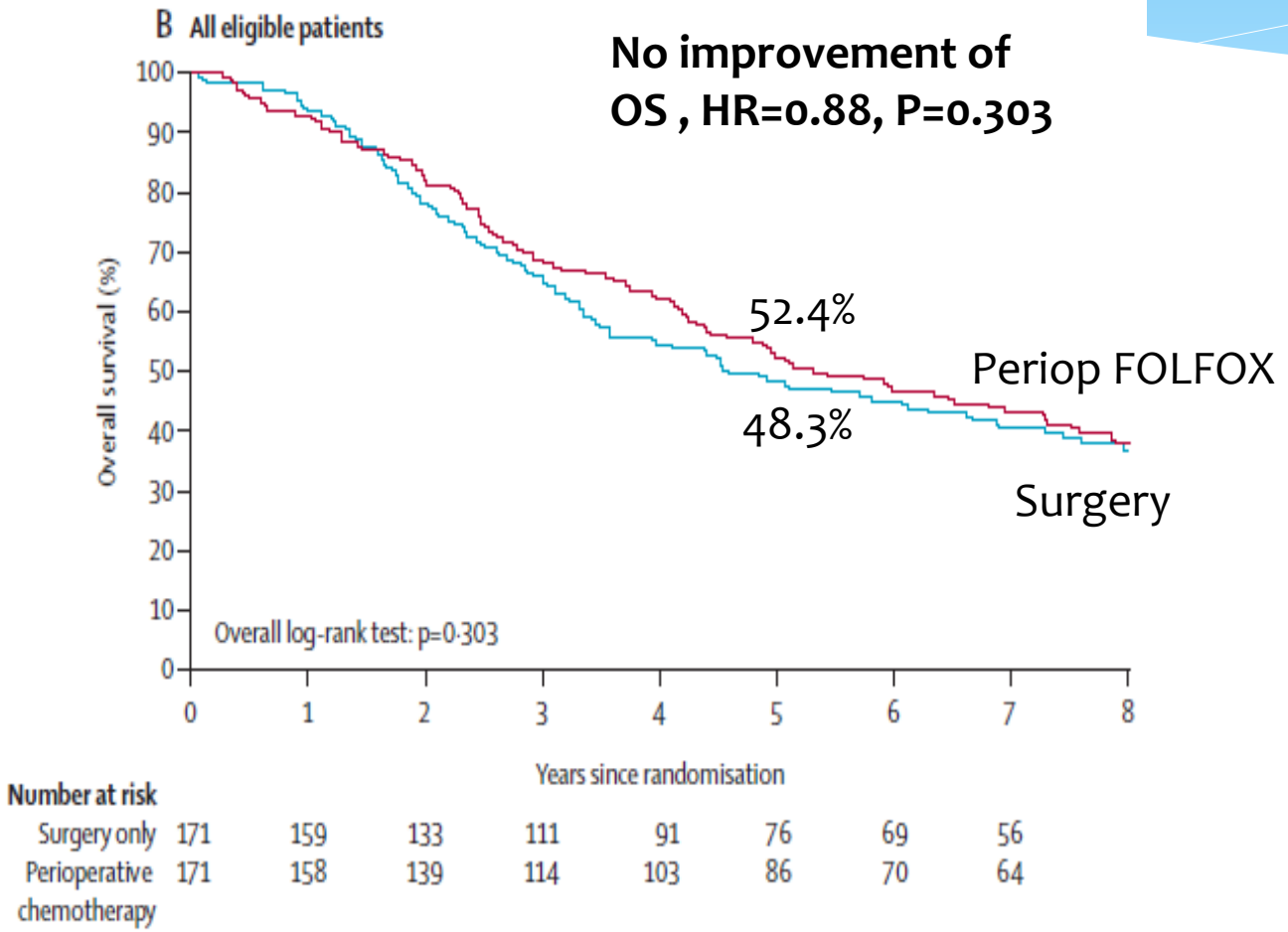
No EHM

++ PFS at 3 years by 9.2%

Lancet Oncol. 2013 Nov;14(12):1208-15. doi: 10.1016/S1470-2045(13)70447-9. Epub 2013 Oct 11.

Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial.

Nordlinger B[1], Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Mauer M, Tanis E, Van Cutsem E, Scheithauer W, Gruenberger T; EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe



No improvement of OS , HR=0.88, P=0.303

Predictive factors for the benefit of the use periop FOLFOX:

1- high CEA

2- PS=0

3- BMI <30

Regardless the No of LM

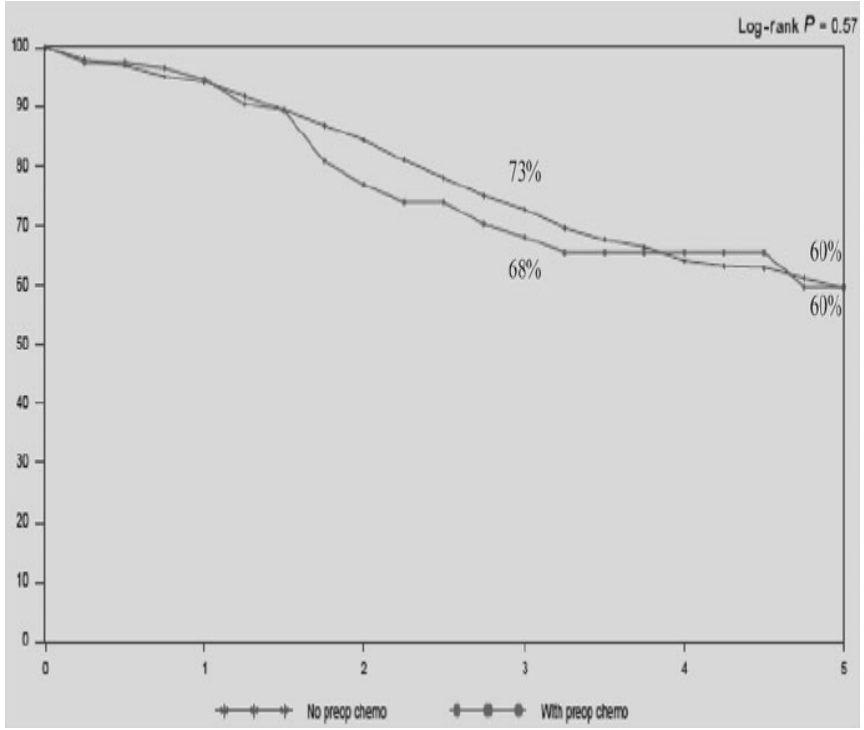
Sorbye et al. Ann Surg. 2012

Multicenter Study > Ann Surg. 2010 Nov;252(5):774-87. doi: 10.1097/SLA.0b013e3181fcf3e3.

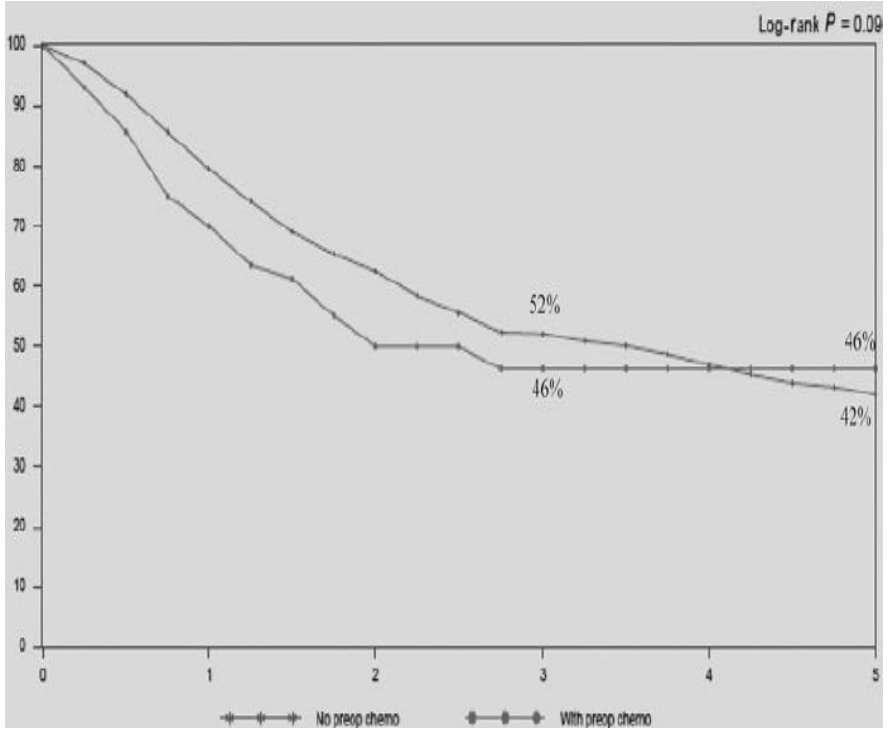
Is Perioperative Chemotherapy Useful for Solitary, Metachronous, Colorectal Liver Metastases?

Rene Adam [1], Prashant Bhangui, Graeme Poston, Darius Mirza, Gennaro Nuzzo, Eduardo Barroso, Jan Ijzermans, Catherine Hubert, Theo Ruers, Lorenzo Capussotti, Jean-Francois Ouellet, Christophe Laurent, Esteban Cugat, Pierre Emmanuel Colombo, Miroslav Milicevic

Total no of patients =1471, no EHM



OS



DFS

J Surg Oncol. 2015 May;111(6):716-24. doi: 10.1002/jso.23899. Epub 2015 Apr 9.

Role of neoadjuvant chemotherapy in resectable synchronous colorectal liver metastasis; An international multi-center data analysis using LiverMetSurvey.

Bonney GK[1], Coldham C, Adam R, Kaiser G, Barroso E, Capussotti L, Laurent C, Verhoef C, Nuzzo G, Elias D, Lapointe R, Hubert C, Lopez-Ben S, Krawczyk M, Mirza DF; LiverMetSurvey International Registry Working Group.

Study period 2000 – 2011
Total number of patients = 1301
No EHM
NAC at least 3 cycles

Conclusion: We present an analysis of a large multi-center series of the role of neo-adjuvant chemotherapy in resectable CLM and demonstrate no survival advantage in this setting.

Summary of the recent studies about the role of pre-operative chemotherapy

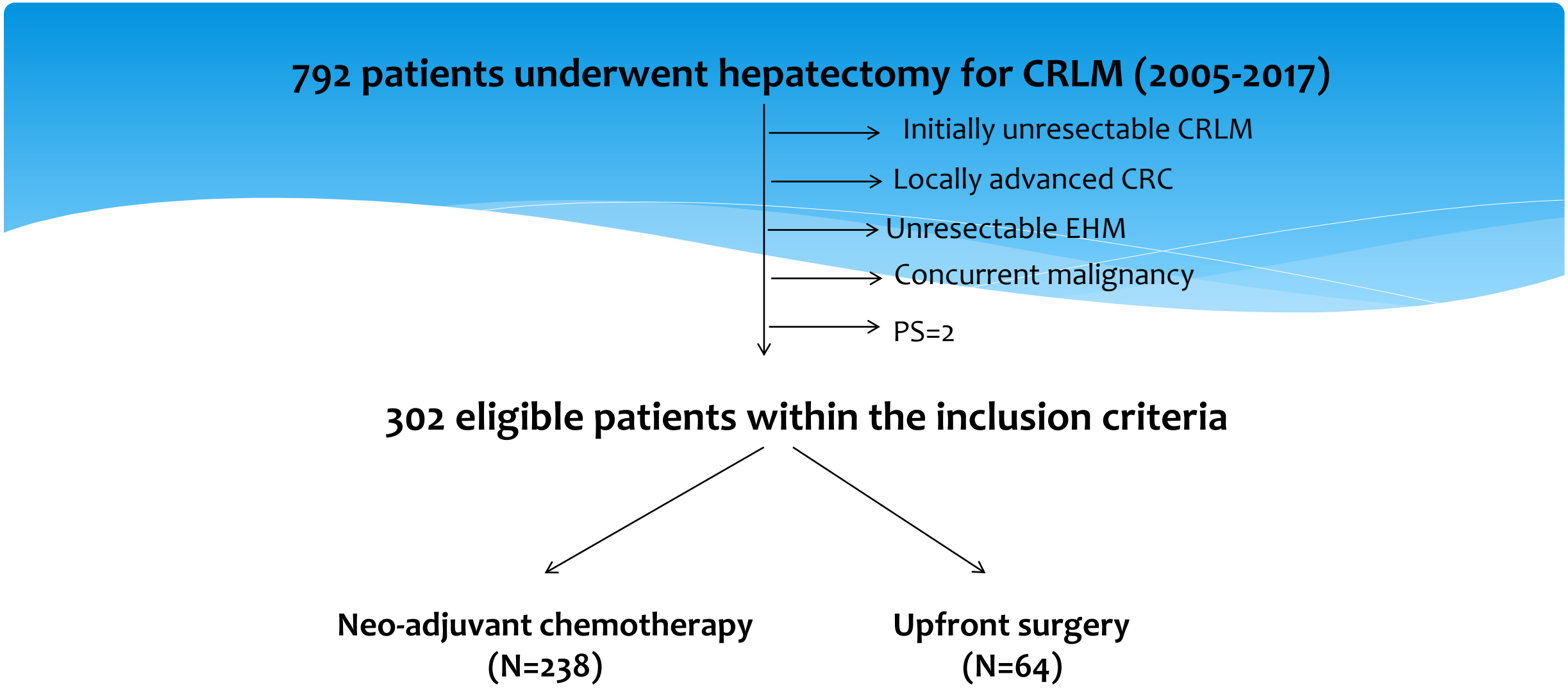
Author	Year	Journal	Study	No Pts	Benefit	
Kataoka	2017	Ann Surg Oncol	Phase 2	47	No	PFS
Nagayama	2017	Int J Clin Oncol	Phase 2	61	No	Feasible
Mukai Y	2017	Jpn J Clin Oncol	Phase 2	61	No	
Kawaguchi	2016	Anticancer Res	PSM stud	70	Yes Transf	Hosp Stay
Nigri	2015	Surgeon	Review	1785	No	OS
Sasaki	2015	Anticancer Res	Retrosp	32	Possible	
Wang	2015	Eur Surg Oncol	Review	1896	No (periop)	OS
Ayez	2015	Eur J Surg Oncol	Retrosp	363	No (OS)	Yes CRS ↗
Bonney	2015	J Surg Oncol	Retrosp	1211	No	Yes Multi
Faron	2014	J Gastroint Cancer	Retrosp	179	No	Yes Postop
Zhu	2014	Plos One	Retrosp	466	No	Yes CRS ↗

* The potential role of NAC for resectable CRLM is still a matter of debate.

* There is still a need for clear evidence for the benefit of NAC combined with surgery in patients with resectable CRLM in terms of DFS and OS.

Study design and population:

This was **retrospective study** which included all patients who underwent hepatectomy for initially resectable CRLM from January 2005 to December 2017 in Hepatobiliary tertiary center, Paul Brousse Hospital, France.


792 patients underwent hepatectomy for CRLM (2005-2017)
Initially unresectable CRLM
Locally advanced CRC
Unresectable EHM
Concurrent malignancy
PS=2
302 eligible patients within the inclusion criteria
Neo-adjuvant chemotherapy
(N=238)
Upfront surgery
(N=64)

* **Primary outcome**
* The overall survival (OS) of patients in the two groups.

* **secondary outcomes**
* The secondary outcomes were the response to chemotherapy, postoperative complications, recurrence rate, disease free survival and predictors of disease free survival (DFS) and OS.

Table (1): Demographic data

Variable[¥]	Neoadjuvant chemotherapy (n=238)	Upfront surgery (n=64)	P value
Age (mean±SD)	62.2 (±11.5)	65.9 (±11.4)	0.021
Age group			
- <70	171 (71.8%)	39 (60.9%)	0.092
- ≥70	67 (28.2%)	25 (39.1%)	
Sex			
- Male	152 (63.9%)	38 (59.4%)	0.509
- Female	86 (36.1%)	26 (40.6%)	
Comorbidities	161 (67.6%)	42 (65.6%)	0.760
BMI (mean±SD)	26.2 (±5.1)	26.2 (±4)	0.940
BMI group (n=297)			
- <30	188 (79.7%)	49 (80.3%)	0.908
- ≥30	48 (20.3%)	12 (19.7%)	
PS (n=289)			
- 0	174 (77.3%)	50 (78.1%)	0.894
- 1	51 (22.7%)	14 (21.9%)	

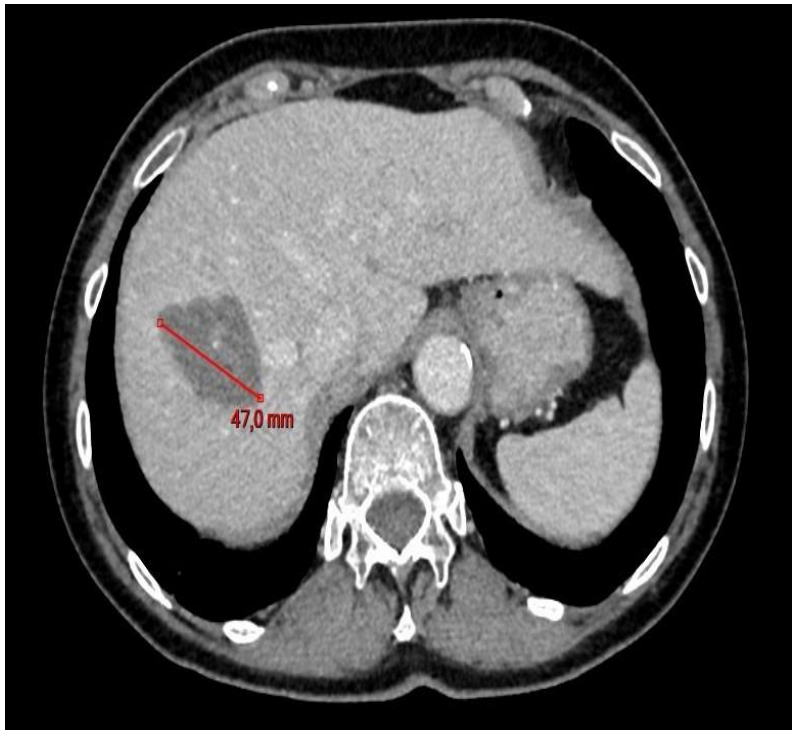
Table (2): Data of primary colorectal cancer.

Variable¥	Neoadjuvant chemotherapy (n=238)	Upfront surgery (n=64)	P value
Tumour site			
- Colon	188 (79%)	51 (79.7%)	0.871
- Rectum	50 (21%)	13 (20.3%)	
Tumour side**			
- Right colon (n=68)	46 (25.6%)	22 (45.8%)	0.006
- Left colon (n=160)	134 (74.4%)	26 (54.2%)	
T group (n=280)			
- T1-2	22 (10%)	11 (18%)	0.061
- T3-4	194 (88.6%)	50 (82%)	
- PCR	3 (1.4%)	0 (0%)	
N group (n=280)			
- Nx	1 (0.5%)	2 (3.3%)	0.110
- N0	71 (32.4%)	23 (37.7%)	
- N1-2	147 (67.1%)	36 (59%)	
PO complications	36 (16.1%)	10 (16.4%)	0.416
Adjuvant chemotherapy#	54 (22.7%)	28 (43.8%)	0.001
Genetic mutation (n=80)			
- KRAS	66 (34%)	19 (34.5%)	0.942
- NRAS	4 (2.9%)	1 (2.5%)	0.893
- BRAF	3 (2.1%)	2 (5%)	0.316
- PIK3C	7 (5%)	2 (5%)	0.993

Table (3): Preoperative data of colorectal liver metastasis.

Variable ¥	Neoadjuvant chemotherapy (n=238)	Upfront surgery (n=64)	P value
Timing of diagnosis			
- Synchronous	148 (62.2%)	22 (34.4%)	<0.001
- Metachronous	90 (37.8%)	42 (65.6%)	
Metachronous LM			
- Early (< 1y)	34 (37.8%)	15 (35.7%)	0.083
- Late (≥1y)	56 (62.2%)	27 (64.3%)	
CEA (µg/L)	40 (14 – 109)	14 (5.5-56.5)	0.048
CA19-9 (kU/L)	69 (20-304)	35 (4.8-79.5)	0.043
LM number (median-range)	2 (1-15)	1 (1-3)	<0.001
LM size (cm)	3 (2-4.1)	2.3 (2-3.2)	0.003
LM number group (n=300)			
- ≤ 2	123 (51.9%)	61 (96.8%)	<0.001
- >2	114(48.1%)	2 (3.2%)	
Tumour burden score (TBS)	4.5 (3.3-6.5)	2.7 (2.2-3.6)	<0.001
TBS group (n=299)			
- <3	48 (20.3%)	37 (59.7%)	
- 3-9	163 (68.8%)	24 (38.7%)	<0.001
- ≥9	26 (10.9%)	1 (1.6%)	
Distribution of LM			
- Unilobar	121(50.8%)	60 (93.8%)	<0.001
- Bilobar	117 (49.2%)	4 (6.2%)	
Associated EHM	56 (23.8%)	5 (7.9%)	0.007

Partial response after neo-adjuvant chemotherapy



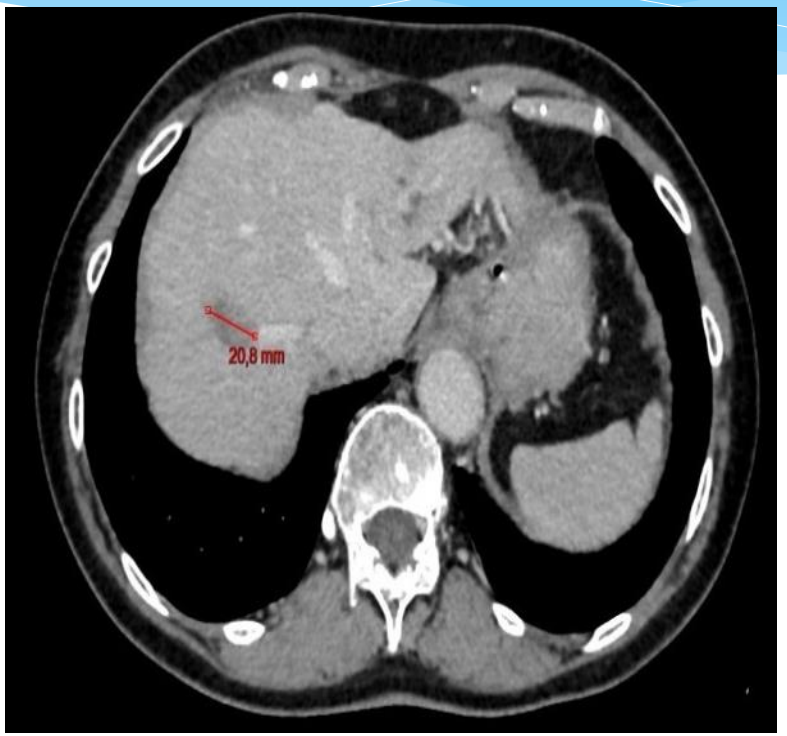


Table (5): Operative data.

Variable ¥	Neoadjuvant chemotherapy (N=238)	Upfront surgery (N=64)	P value
Approach :			
- Open	203 (85.3%)	54 (84.4%)	
- Laparoscopic	30 (12.6%)	8 (12.5%)	0.981
- Converted	5 (2.1%)	2 (3.1%)	
Timing to colorectal resection:			
- Colorectal	202 (84.9%)	48 (75%)	<0.001
- Liver first	19 (8%)	1 (1.6%)	
- Simultaneous	17 (7.1%)	15 (23.4%)	
Type of resection			
- Anatomical	84 (35.3%)	28 (43.8%)	
- Non-anatomical	69 (29%)	27 (42.2%)	0.003
- Both	85 (35.7%)	9 (14.1%)	
Extent of hepatectomy			
- Major (≥ 3 segments)	79 (33.2%)	8 (12.5%)	0.001
- Minor	159 (66.8%)	56 (87.5%)	
Concomitant ablative therapy (RFA/MWA)	19 (8%)	3 (4.7%)	0.368
Blood loss (ml)*	425 (250-850)	300 (130-700)	0.023
Blood transfusion	28 (11.8%)	3 (4.7%)	0.041
Operative time (min)	325.5 (±90)	282.3 (±93.3)	0.003

Table (6): Postoperative data

Variable	Neoadjuvant chemotherapy (N=238)	Upfront surgery (N=64)	P value
Postoperative complications	77 (32.4%)	16 (25%)	0.258
Hepatic complications	41(17.2%)	9 (14.1%)	0.545
- Bile leak	7 (2.9%)	2 (3.1%)	0.939
- Collection	24 (10.1%)	8 (12.5%)	0.577
- Internal haemorrhage	2 (0.8%)	0 (0%)	0.462
- Liver failure	3 (1.3%)	0 (0%)	0.367
- Vascular thrombosis	5 (2.1%)	1 (1.6%)	0.784
- Ascites	4 (1.7%)	0 (0%)	0.563
General complications	55 (23.1%)	13 (20.3%)	0.634
Major complications (≥IIIa)	26 (10.9%)	6 (9.4%)	0.721
Management:			
- Reintervention	10 (4.2%)	1 (1.6%)	0.317
- Percutaneous	14 (5.9%)	5 (7.8%)	0.572
- Endoscopic	1 (0.4%)	0 (0%)	0.603
Hospital stay, median (IQR)	8 (3 - 56)	8 (4 – 42)	0.474
Mortality (90 days)	3 (1.3%)	0 (0%)	0.367
Adjuvant chemotherapy	188 (79%)	50 (78%)	0.736
Resection margin (mm)	1 (0-5)	3 (0-5)	0.038
Safety margin (n=284)			
- R0	128 (56.1%)	41 (73.2%)	0.020
- R1	100 (43.9%)	15 (26.8%)	

Table (7): Risk factors of disease-free survival in the whole cohort (n=302)

Risk factor	Univariate analysis			Multivariate analysis		
	P	HR	95% CI	*P*	HR	95% CI
Age ≥70 y	0.081	1.331	0.965 – 1.834	-	-	-
Sex	0.748	1.049	0.783 – 1.406	-	-	-
BMI ≥30	0.584	1.100	0.782 – 1.548	-	-	-
CRC site (colon vs rectum)	0.698	1.070	0.761 – 1.505	-	-	-
T stage (T3-T4)	0.002	2.029	1.297 – 3.176	0.003	2.250	1.311 – 3.861
N stage (N1-2)	<0.001	2.185	1.543 – 3.094	0.001	1.855	1.299 – 2.650
KRAS status	0.496	1.116	0.814 – 1.530	-	-	-
Timing of diagnosis*	0.179	0.823	0.619 – 1.094	-	-	-
CEA ≥30 µg/L	0.422	1.212	0.758 – 1.940	-	-	-
Size ≥ 3cm	0.921	1.014	0.765 – 1.345	-	-	-
Number ≥3	<0.001	1.925	1.449 – 2.557	0.005	1.873	1.204 – 2.912
Bilobar disease	0.025	1.381	1.042 – 1.831	0.493	0.871	0.587 – 1.292
EHM	0.388	1.162	0.826 – 1.635	-	-	-
NAC	0.247	0.816	0.578 – 1.151	-	-	-
No CT	0.019	2.076	1.128 – 3.819	0.011	2.271	1.208 – 4.268

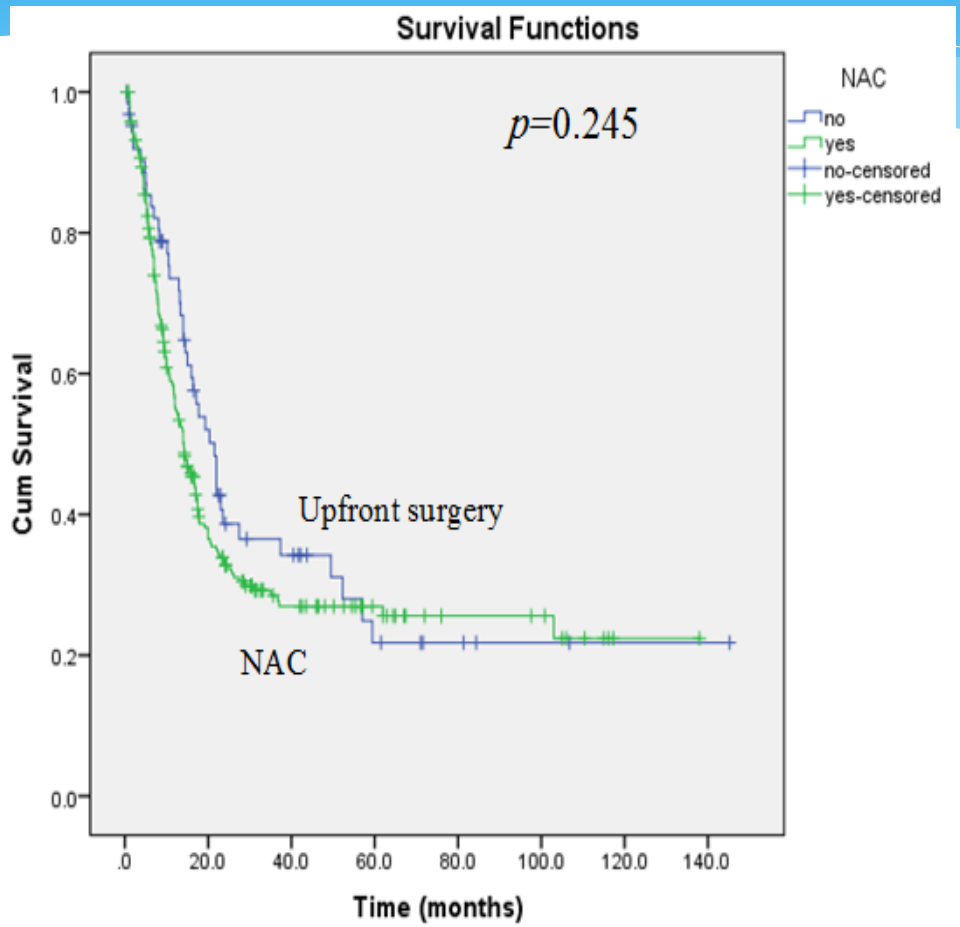
Table (8): Predictors of early recurrence (≤1y) after first hepatectomy.

Risk factor	Univariate analysis			Multivariate analysis		
	P	OR	95% CI	*P*	OR	95% CI
Age ≥70 y	0.447	1.285	0.673 – 2.452	-	-	-
Sex	0.633	0.865	0.476 – 1.570	-	-	-
BMI ≥30	0.583	1.212	0.609 – 2.413	-	-	-
CRC site (colon vs rectum)	0.342	0.705	0.342 – 1.451	-	-	-
T stage (T3-T4)	0.536	0.708	0.238 – 2.113	-	-	-
N stage (N1-2)	0.977	0.990	0.493 – 1.987	-	-	-
KRAS status	0.058	1.886	0.979 – 3.633	-	-	-
Timing of diagnosis*	0.424	0.789	0.441 – 1.410	-	-	-
CEA at diagnosis	0.462	0.999	0.997 – 1.001	-	-	-
Size ≥ 3cm	0.136	0.644	0.361 – 1.149	-	-	-
Number ≥3	0.008	2.214	1.232 – 3.981	0.527	1.854	0.523 – 1.394
Bilobar disease	0.027	1.929	1.076 – 3.458	0.922	1.024	0.636 – 1.648
EHM	0.399	1.355	0.669 – 2.746	-	-	-
NAC	0.012	0.507	0.299 – 0.861	0.078	0.567	0.302 – 1.065
Safety margin (R1)	0.033	1.951	1.055 – 3.607	0.112	1.780	0526 – 1.157

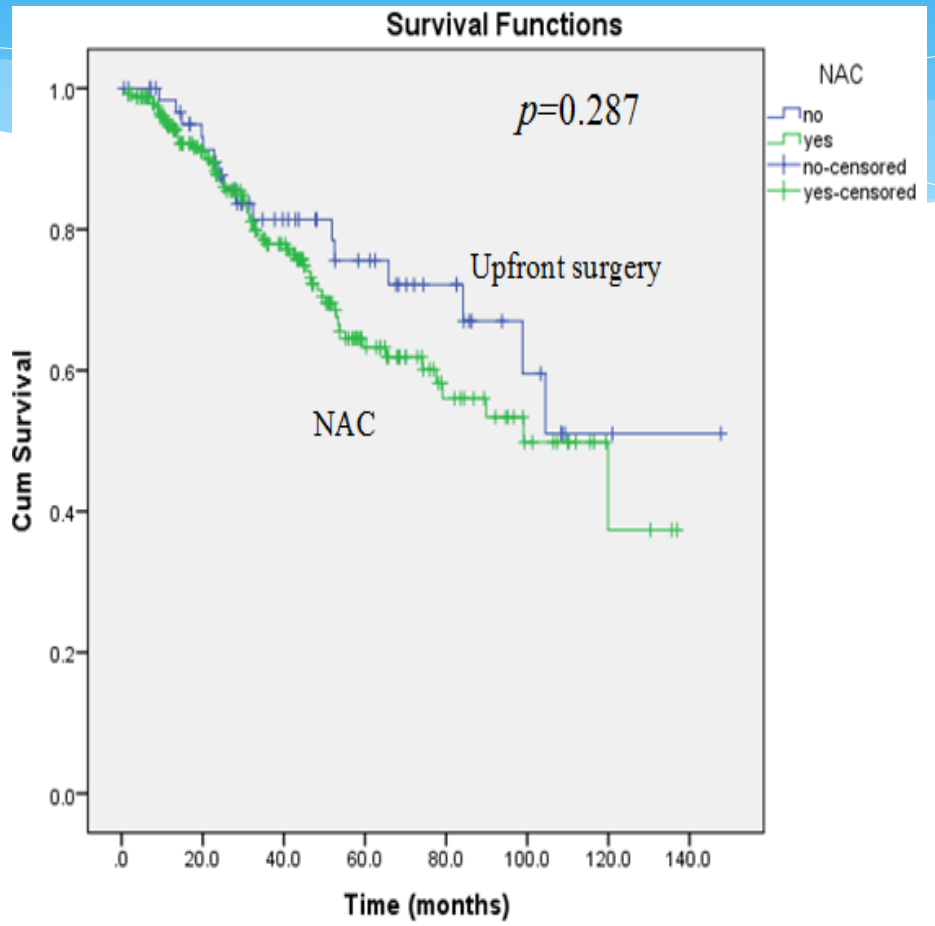
Table (9): Risk factors of overall survival in the whole cohort (n=302)

Risk factor	Univariate analysis			Multivariate analysis		
	P	HR	95% CI	*P*	HR	95% CI
Age	0.042	1.022	1.001 – 1.044	0.090	1.025	0.996 – 1.054
Sex	0.462	1.185	0.754 – 1.864	-	-	-
BMI ≥30	0.875	1.043	0.615 – 1.770	-	-	-
Right side CRC	0.007	2.055	1.220 – 3.461	0.002	2.636	1.442 – 4.818
T stage (T3-T4)	0.021	3.902	1.226 – 12.419	0.016	4.421	1.605 – 36.115
N stage (N1-2)	0.001	3.027	1.650 – 5.553	0.004	2.967	1.403 – 6.272
KRAS status	0.247	0.740	0.444 – 1.232	-	-	-
Synchronous LM	0.835	1.049	0.672 – 1.637	-	-	-
CEA at diagnosis	0.341	0.998	0.994 – 1.002	-	-	-
Size ≥ 3cm	0.913	1.025	0.656 – 1.602	-	-	-
Number ≥3	0.044	1.578	1.012 – 2.459	0.243	1.698	0.382 – 1.276
Bilobar disease	0.056	1.541	0.990 – 2.400	-	-	-
EHM	0.001	2.269	1.401 – 3.674	0.021	2.119	1.118 – 4.014
NAC	0.288	0.742	0.428 – 1.287	-	-	-
No response to CT*	0.053	1.633	0.994 – 2.683	-	-	-
Blood loss ≥500	0.061	1.606	0.979 – 2.637	-	-	-
Blood transfusion	0.005	2.328	1.294 – 4.190	0.010	2.609	1.258 – 5.412
Hepatic complications	0.037	1.739	1.034 – 2.923	0.008	2.491	1.276 – 4.864
Adjuvant CT	0.278	0.755	0.455 – 1.254	-	-	-
Early recurrence	<0.001	1.258	0.164 – 0.408	0.001	1.267	0.147 – 0.518

Survival analysis of the two groups

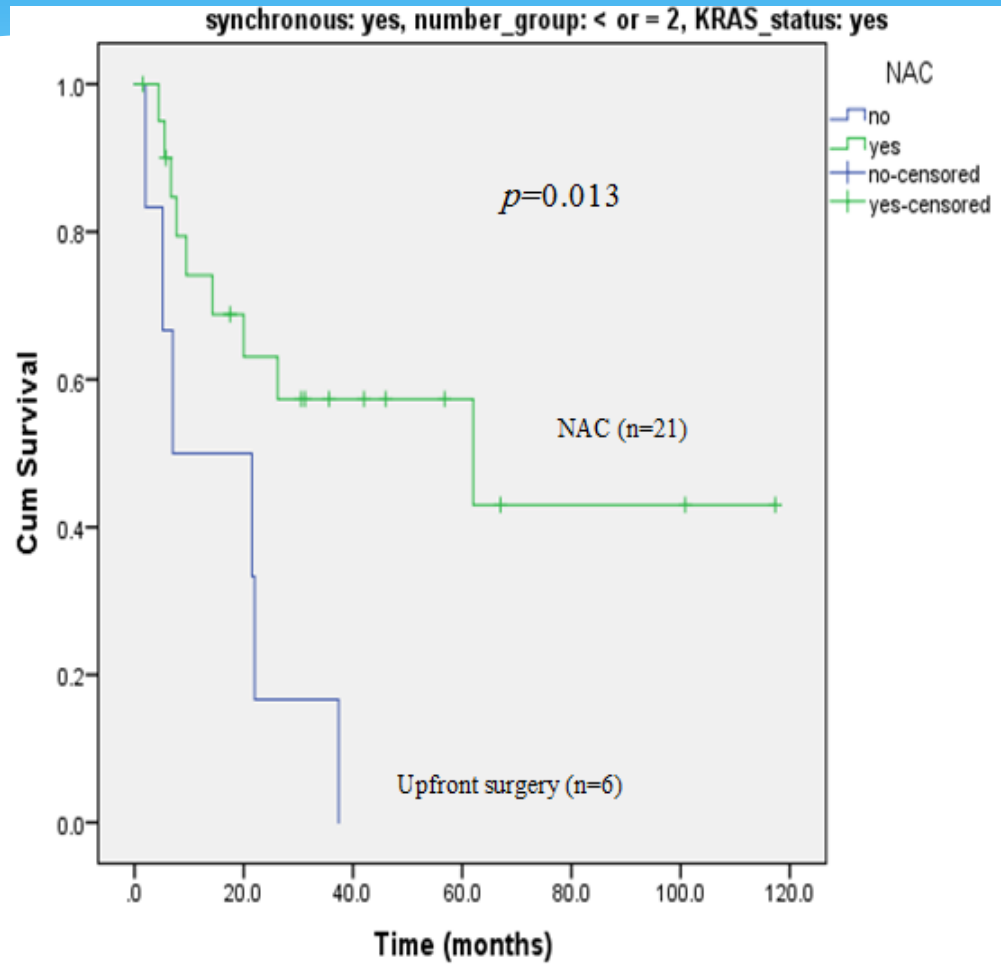


DFS



OS

Subgroup analysis of the role of NAC in high risk patients



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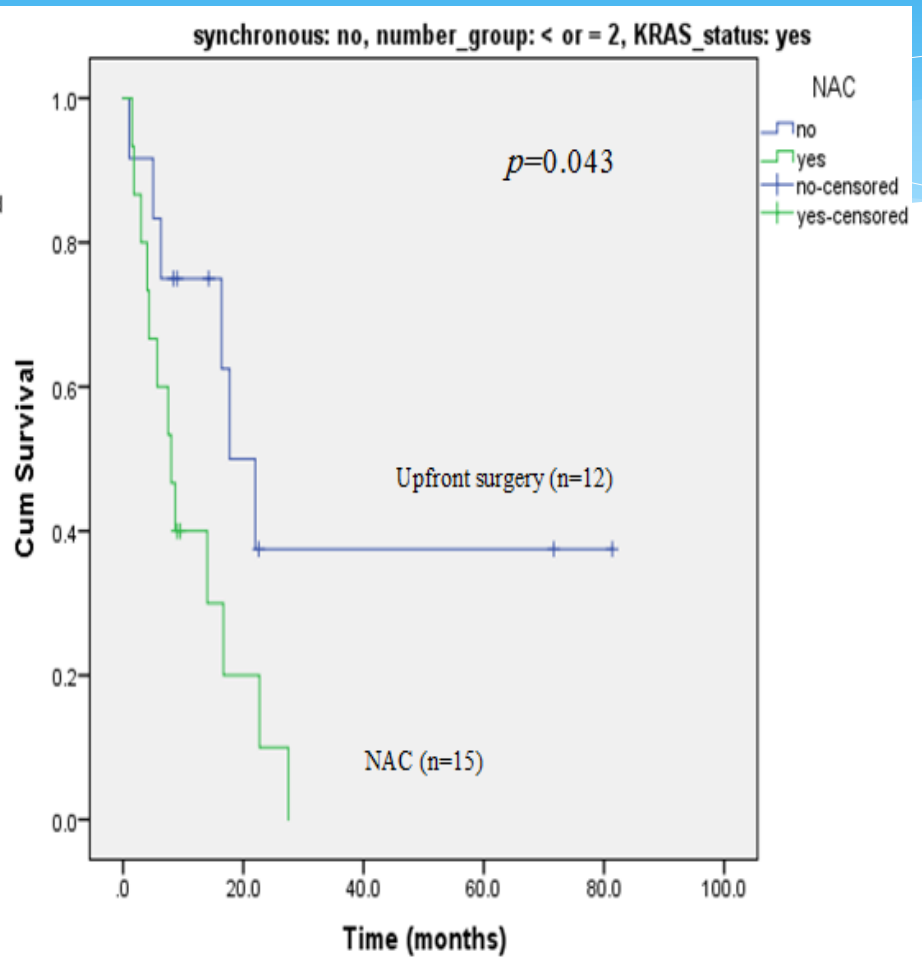
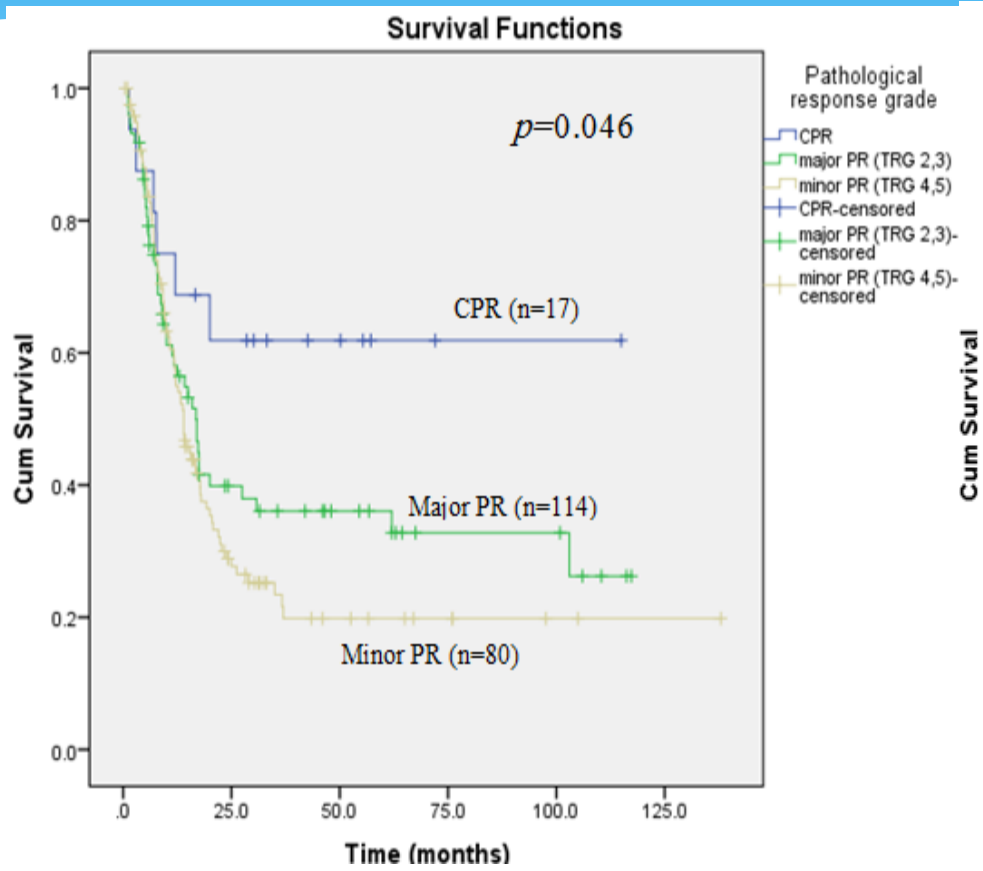


DFS

Role of the pathological response after NAC in survival



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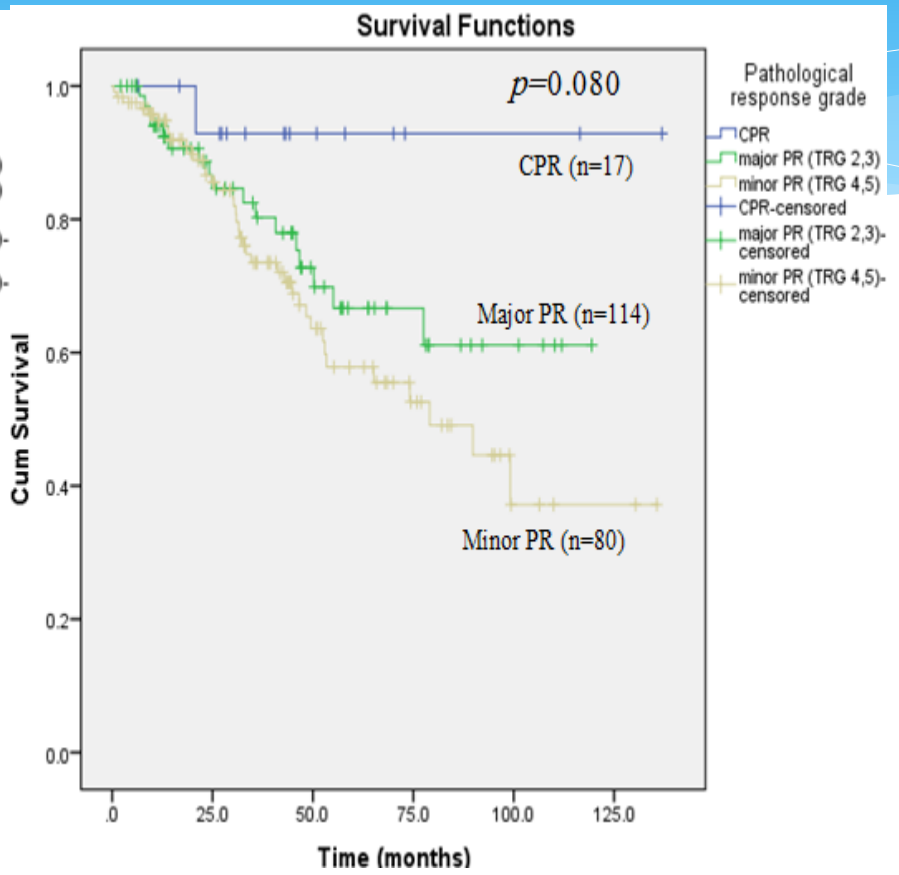

OS

* Neo-adjuvant chemotherapy had no survival benefit in patients with initially resectable CRLM in our series. However, we showed that the NAC group had significantly better DFS in well-selected high risk patients with synchronous CRLM and KRAS mutation. NAC use was associated with decreased rate of early recurrence (≤1 year).
* Prospective randomized controlled trials are highly recommended in well matched population to prove our findings.

Mansoura University Gastrointestinal Surgery center experience

* There is ongoing study started in Gastrointestinal Surgery Center in Mansoura University focusing on the single center experience in the last 10 years in management of CRLM in collaboration with Paul Brouse Hospital in France and the results will be published soon.


Thank You!