



Advances in Liver Surgery for mCRC

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Disclosures

Research funding/speakers Bureau/advisory role:



- Roche
- Merck-Serono
- Bayer
- Amgen
- Servier
- Humedics
- BMS
- Olympus
- MSD
- Incyte
- Astra Zeneca
- Baxter

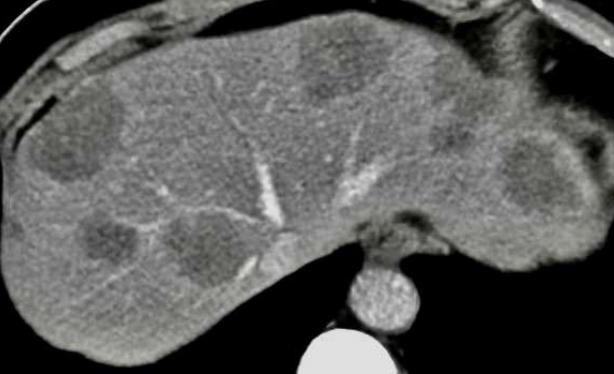




mCRC

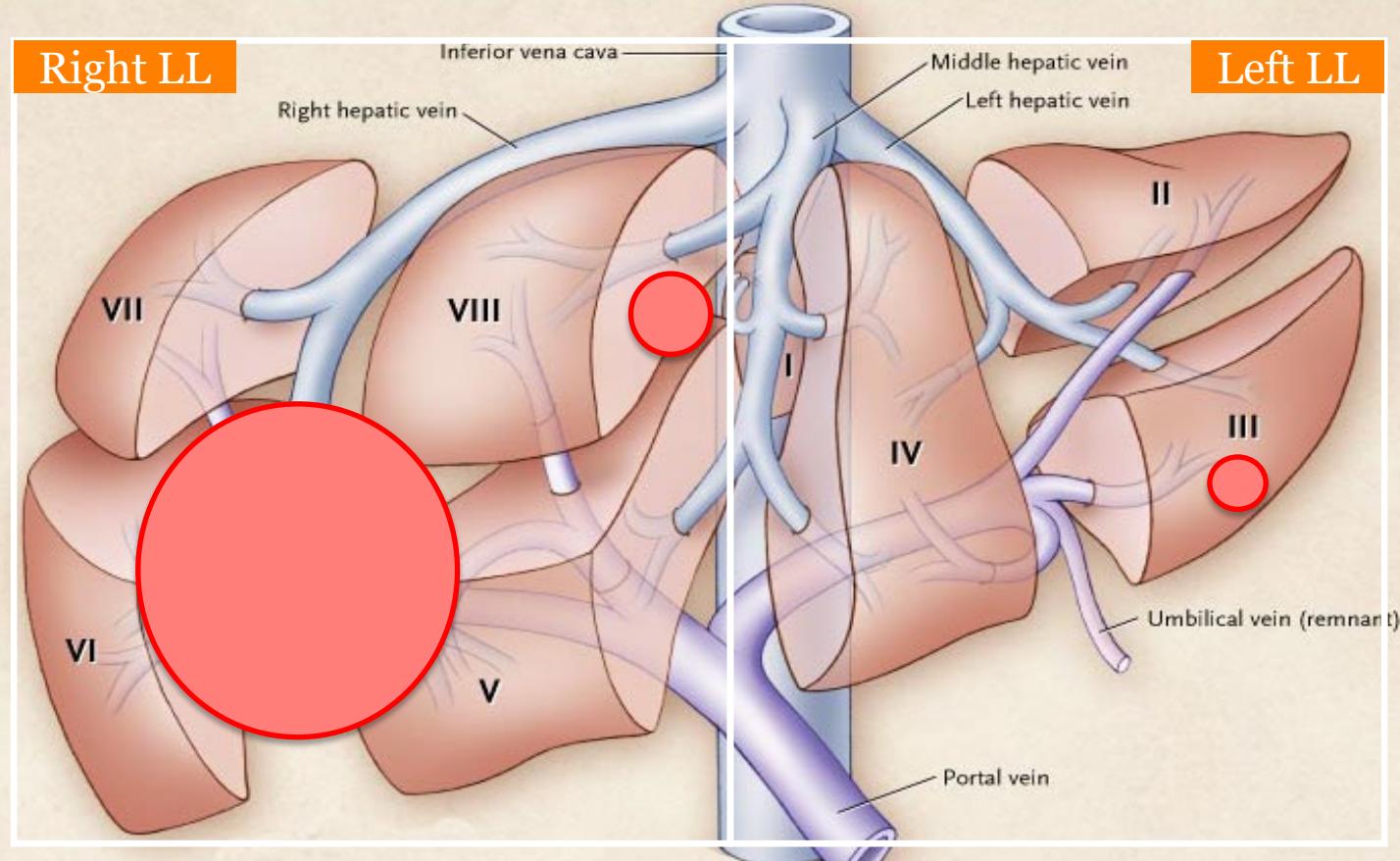


- 56 yrs lady, BMI 31
- Synchron mRC asymptomatic 05.22
- Uterus myomatosus, St.p. HIS, St.p. Sectio
- Imaging: bilob CRLM (23); RC T4, N1, EMVI; MSS, RASmt
- Lab: Leuco 13T, Thrombos 525, CRP 150, Bili 2.1, GOT 189, LDH 2876, Albumin 40; CEA 43, Ca 19-9 12



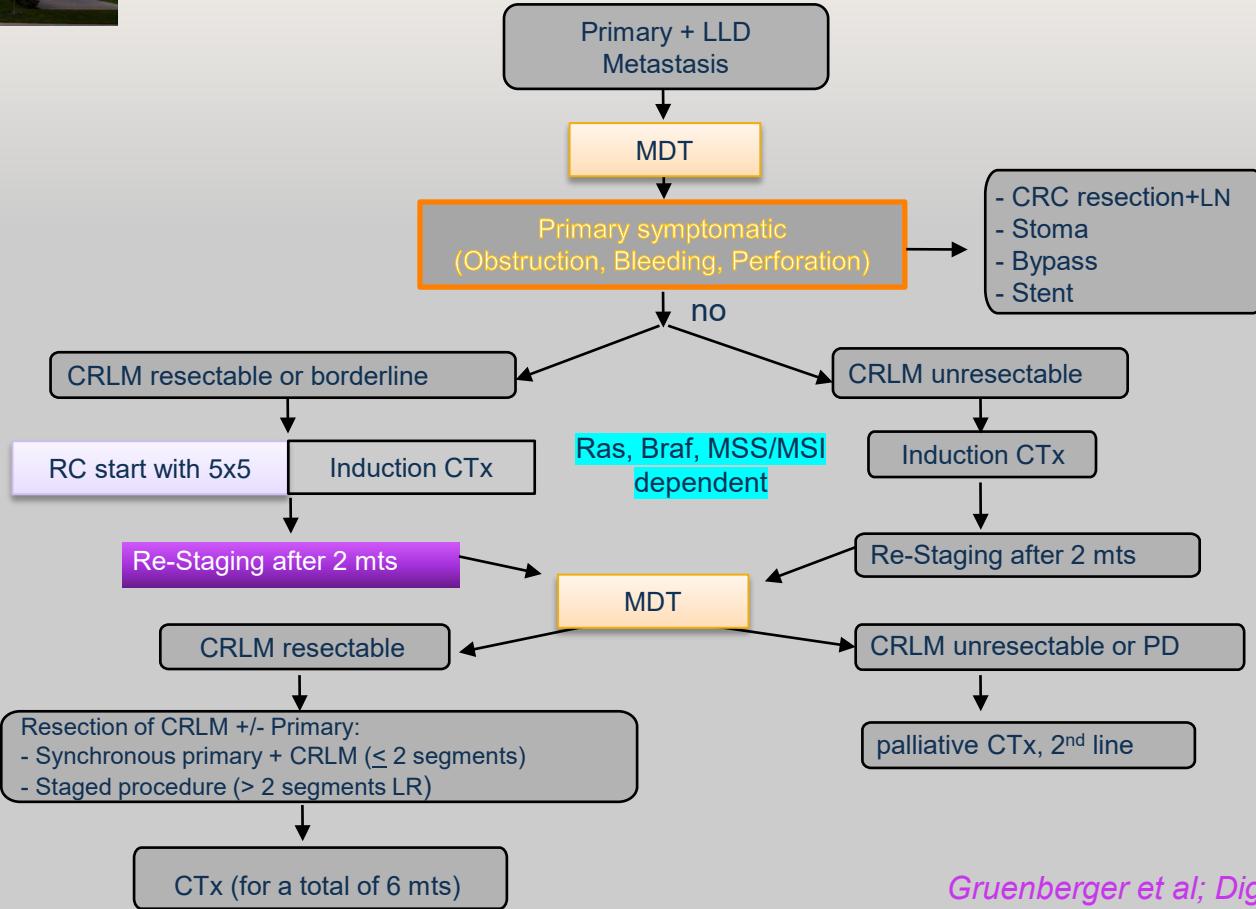


Liver anatomy





SOP synchronous mCRC

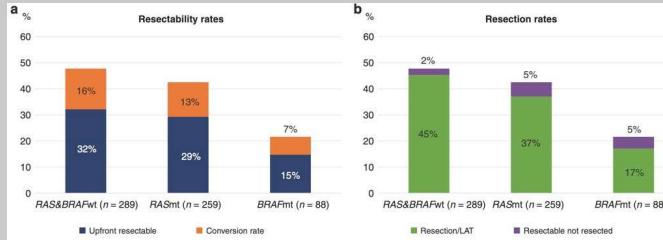
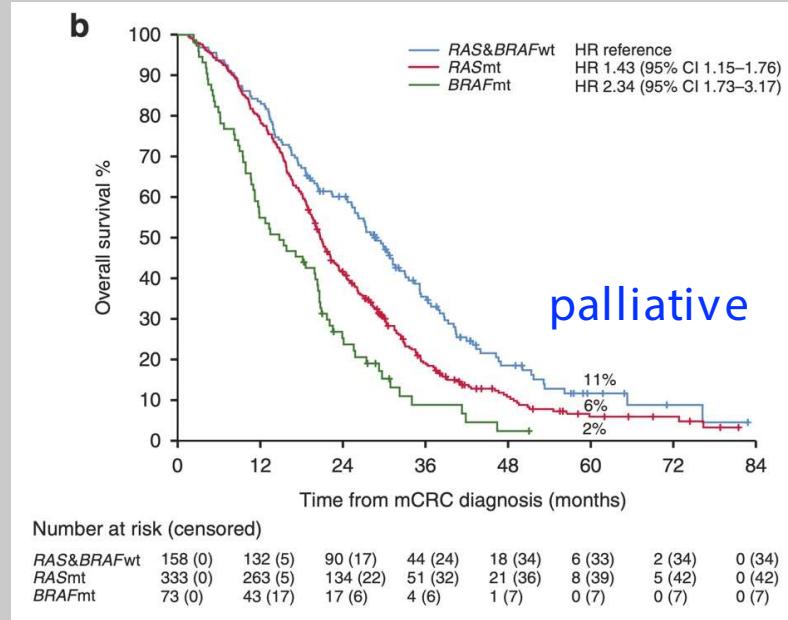
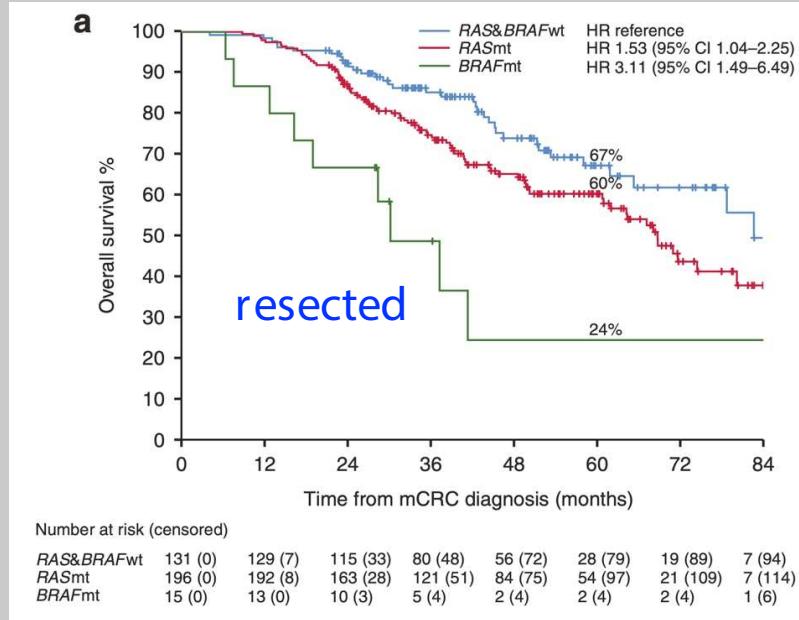


Gruenberger et al; *DigLiverDisease* 16





Outcome dependent upon molecular markers



RAXO Study 1086pts 2012-18 in
5 University + 16 regional hospitals

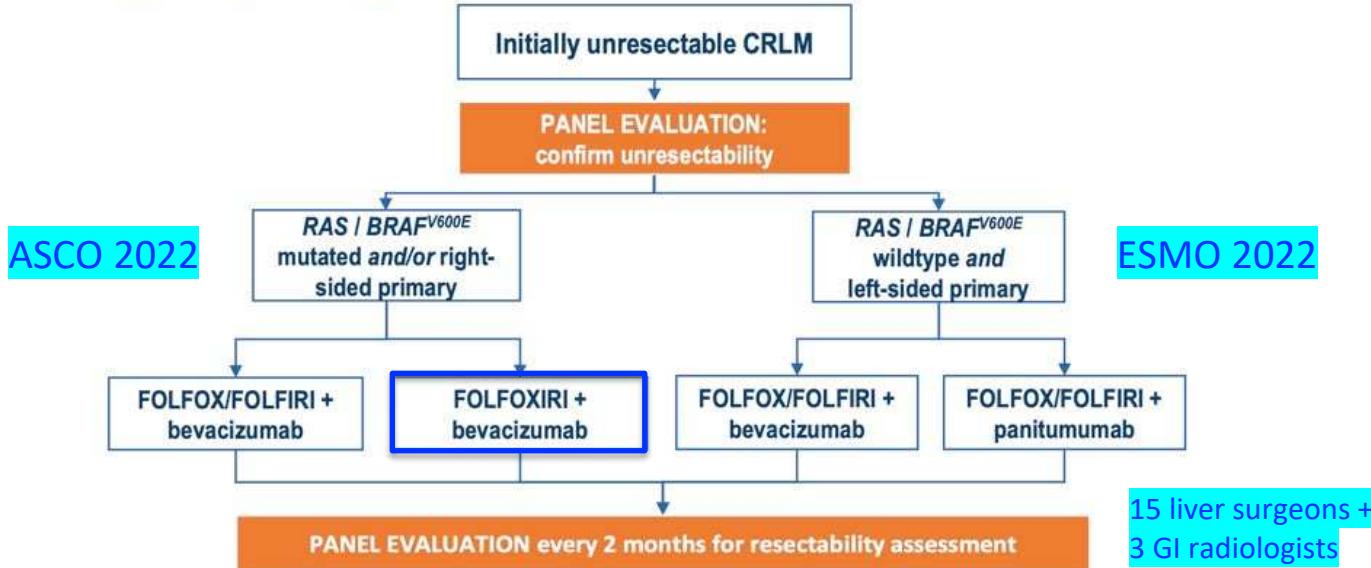
A. Uutela, H. Isoniemi, P. Osterlund et al,
BrJ Cancer 2022



mCRC, unresCRLM only



CAIRO5: prospective randomised comparison of currently most active systemic regimens in defined subgroups of patients with initially unresectable CRLM



2014-2021: 530 pts randomised in 43 Dutch + 1 Belgian sites



mCRC, unresCRLM only

DCCG CAIRO5 – patient characteristics

	FOLFOX/FOLFIRI + bevacizumab	FOLFOX/FOLFIRI + panitumumab
n	114	116
Male gender	61%	63%
Age (median, range)	59 (53-67)	60 (52-69)
WHO PS 0	65%	59%
Right-sided primary	4%	5%
<i>BRAF^{V600E}</i> mutation	4%	3%
Synchronous metastases	88%	92%
Prior adjuvant chemotherapy	4%	3%
Median number of CRLM	12 (8-18)	12 (8-22)
Normal serum LDH	46%	45%
Preference for oxaliplatin	89%	92%
Potentially resectable CRLM (panel)	82%	83%

PARIS 2022 ESMO congress
Marinde J.G. Bond, MD
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Marinde Bond

FOLFOX/FOLFIRI plus either bevacizumab or panitumumab in patients with initially unresectable colorectal liver metastases (CRLM) and left-sided and RAS/BRAFV600E wild-type mCRC. Phase III CAIRO5 study of the Dutch Colorectal Cancer Group.



Bond et al; Ann Oncol 2022; 33(suppl_7): S808



mCRC, CRLM only



CAIRO5 – local treatment

	FOLFOX/FOLFIRI + bevacizumab	FOLFOX/FOLFIRI + panitumumab	
n	114	116	
Resection +/- ablation rate	68%	67%	p=1
postoperative complications	42%	41%	p=1
Clavien Dindo grade ≥3	21%	14%	p=0.30
grade 5 (death) ¹	0.9% (n=1)	0.9% (n=1)	
Number of induction cycles (median, IQR)	6 (5-8)	6 (5-9)	
Adjuvant chemotherapy	36%	42%	
R0/1 resection +/- ablation rate	58%	56%	p=0.79

¹ Cause of death: arm C multi-organ failure, arm D abdominal sepsis.



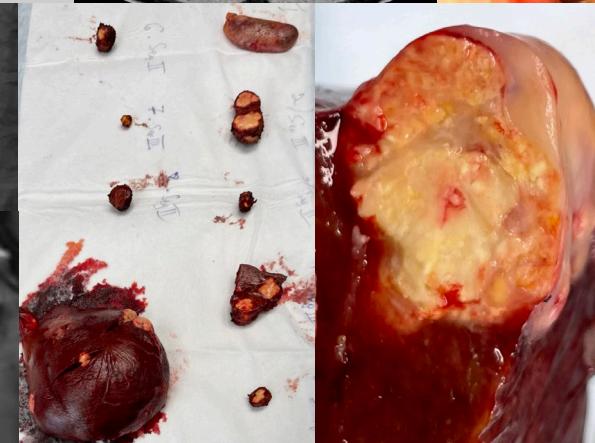
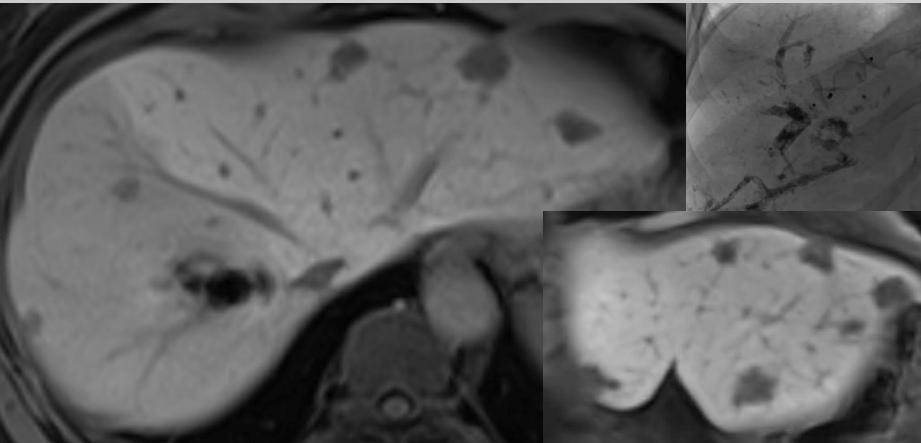
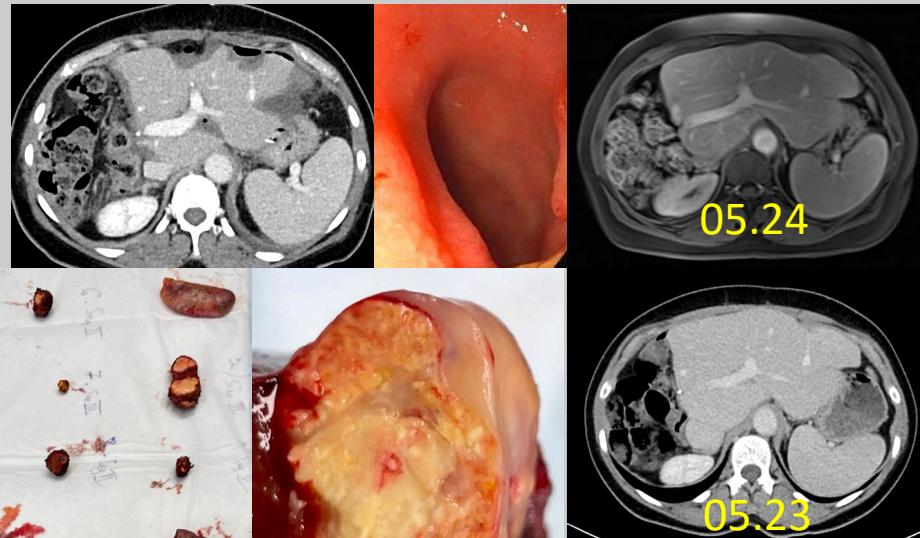
Bond et al; Lancet Oncol 2023





mCRC

- FOLFOXIRI+Bev 4mts (MDT after 2mts: insufficient rPR): sufficient rPR
- MDT: bilob LR after PVE+HVO (12d interval); 5x5 Gy in between
- No SAE under CTx; Liver starving postCTx (BMI 31 to 29)
- Limax 563; CEA 1; LOS 8d w/o M&M
- Pathology: **pCR of ALL CRLM**
- TVR 5 weeks later: near complete Response
- FU 24 mts: NED





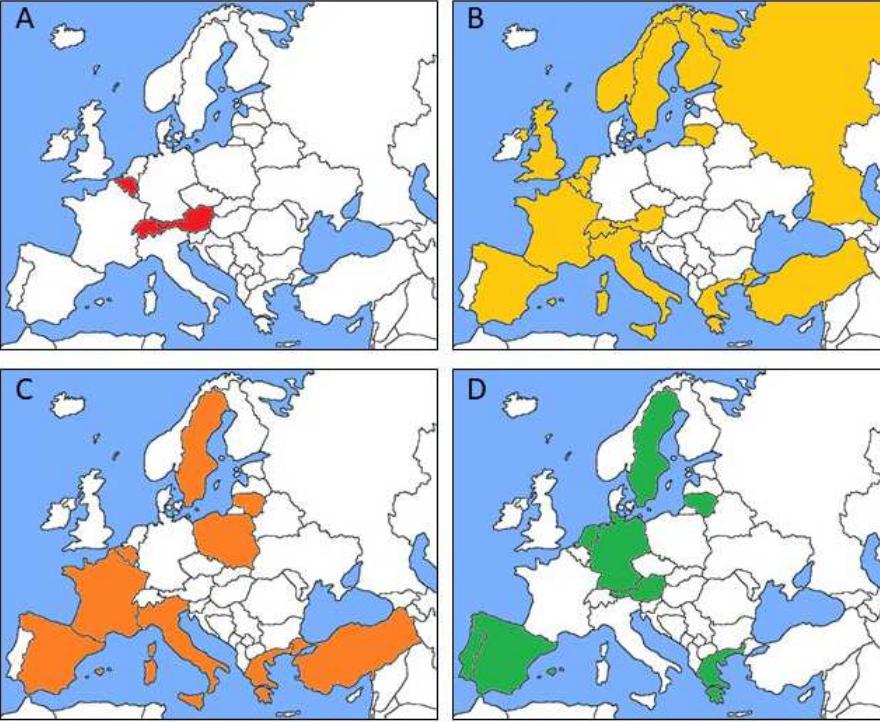
Resectable CRLM

EORTC 40983

- 364pts, 2/3 metachron,
- 50% single CRLM
- periOP Folfox vs LRalone
- ORR: 42%
- sig 3yrs RFS (35 vs 28mts)
- n.s. OS (64 vs 55mts)

newEPOC

- 257pts, 2/3 synchr
- 75% one-three CI
- periOP Folfox vs C
- ORR: 62% vs 70%
- sig RFS disadv 20%
- sig OS disadv 81%



E-AHPBA survey 2022

- A. neoadjuvant chemotherapy and local treatment
- B. perioperative chemotherapy and local treatment
- C. adjuvant chemotherapy and local treatment
- D. local treatment without chemotherapy



Nordlinger et al
Lancet 08
LancetOncol 13

Primrose et al
LancetOncol 14
LancetOncol 20

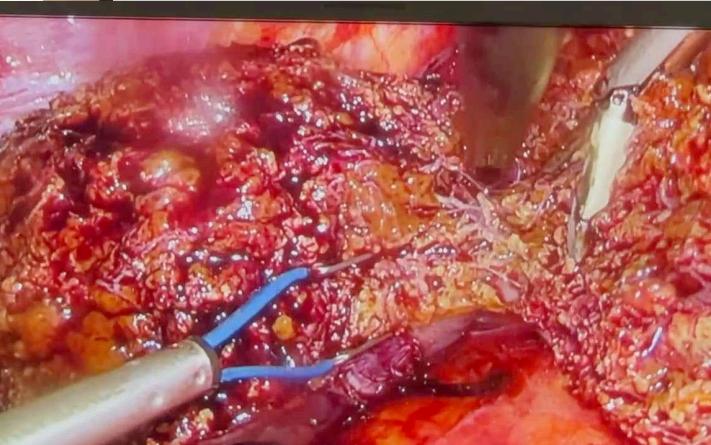
Kuiper et al HPB 24

Gruenberger et al
JCO 08, AnnOn 12
Cancers 24





MIS – laparoscopic LR





MIS – robotic approach





Interventional CRLM destruction MWA, RFA, IRE; SBRT



Puijk et al. BMC Cancer (2018) 18:821
<https://doi.org/10.1186/s12885-018-4716-8>



BMC Cancer

STUDY PROTOCOL

Open Access



Colorectal liver metastases: surgery versus thermal ablation (COLLISION) – a phase III single-blind prospective randomized controlled trial

Robbert S. Puijk^{1*}, Alette H. Ruurds¹, Laurien G. P. H. Vroomen¹, Aukje A. J. M. van Tilborg¹, Hester J. Scheffer¹, Karin Nielsen², Marcus C. de Jong¹, Jan J. J. de Vries¹, Babs M. Zonderhuis², Hasan H. Eker², Geert Kazemier², Henk Verheul³, Bram B. van der Meij¹, Laura van Dam¹, Natasha Sorgedrager¹, Veerle M. H. Coupe⁴, Petrousjka M. P. van den Tol², Martijn R. Meijerink¹ and COLLISION Trial Group

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UGENT



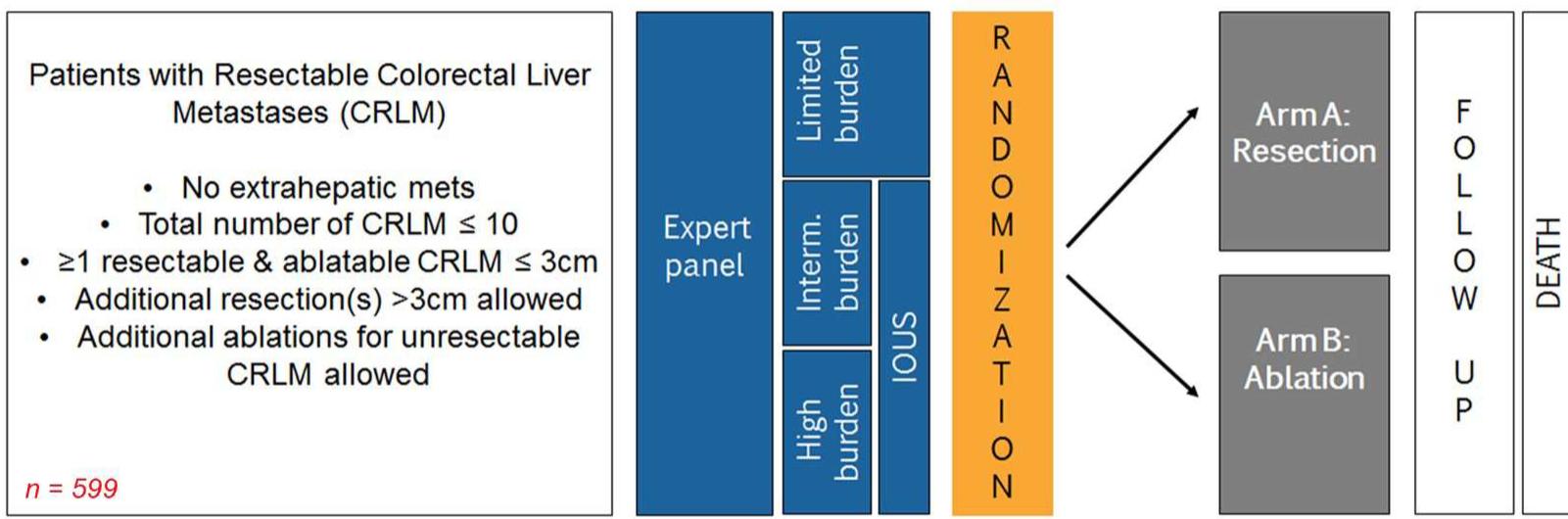
2024 ASCO
ANNUAL MEETING

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KNOWLEDGE CONQUERS CANCER



Phase III international multicenter randomized controlled trial to prove / disprove hypothesis of non-inferiority of thermal ablation compared to surgical resection for small-size colorectal liver metastases (CRLM)

- Approach (percutaneous, laparoscopic or open) according to local expertise
- If limited disease burden (max 3 CRLM $\leq 3\text{cm}$) consider percutaneous / laparoscopic approach
- If intermediate or high disease burden randomize after eligibility check (after IOUS) during OR (single-blind)

RESULTS

BASELINE CHARACTERISTICS

	Resection	Ablation		
Procedure-related characteristics	N = 148	N = 148		
Subgroup				
A low disease burden	89 (60.1%)	94 (64.2%)	0.469	
B intermediate disease burden	50 (33.8%)	41 (27.7%)		
C high disease burden	9 (6.1%)	12 (8.1%)		
Preprocedural systemic therapy				
No	112 (75.7%)	118 (79.7%)	0.485	
Yes	36 (24.3%)	30 (20.3%)		
Capecitabine	2 (1.4%)	2 (1.4%)		
CAPOX	2 (1.4%)	3 (2.0%)		
CAPOX-B	23 (15.6%)	21 (14.2%)		
FOLFOX-B	2 (1.4%)	2 (1.4%)		
FOLFIRI-B	2 (1.4%)	1 (0.7%)		
FOLFOXIRI-B	4 (2.7%)	1 (0.7%)		
Missing	1 (0.7%)	0 (0%)		
Procedures				
Resection alone	90 (60.8%)	0 (0%)		
Ablation alone	1 (0.72.0%) *	118 (79.7%)		
Resection + ablation	52 (35.1%)	27 (18.2%)		
No local treatment	5 (3.4%)	3 (2.1%)		
Cycles of systemic therapy	Median (range)	5.5 (2 – 10)	6 (3 – 12)	0.420
Approach °				
Percutaneous	2 (1.4%)	84 (56.8%)		
Laparoscopic	68 (46.6%)	10 (6.8%)		
Open	76 (52.1%)	54 (36.5%)		
Anesthesia °				
General	146 (100%)	111 (75.0%)		
Propofol	0 (0.0%)	37 (25.0%)		
Number of CRLM	Median number CRLM (range)	2 (1 – 10)	2 (1 – 12)	0.964
Tumor-related characteristics	N = 446	N = 447		
CRLM °				
Target	304 (68.2%)	349 (78.1%)		
Non-target (unresectable / unablatable)	142 (31.8%)	98 (21.9%)		
Size CRLM randomization (mm)	Mean size target CRLM (range)	14 (2 – 34)	13 (3 – 34)	0.457
Size CRLM treatment (mm)	Mean size target CRLM (range)	14 (2 – 40)	14 (2 – 50)	0.459

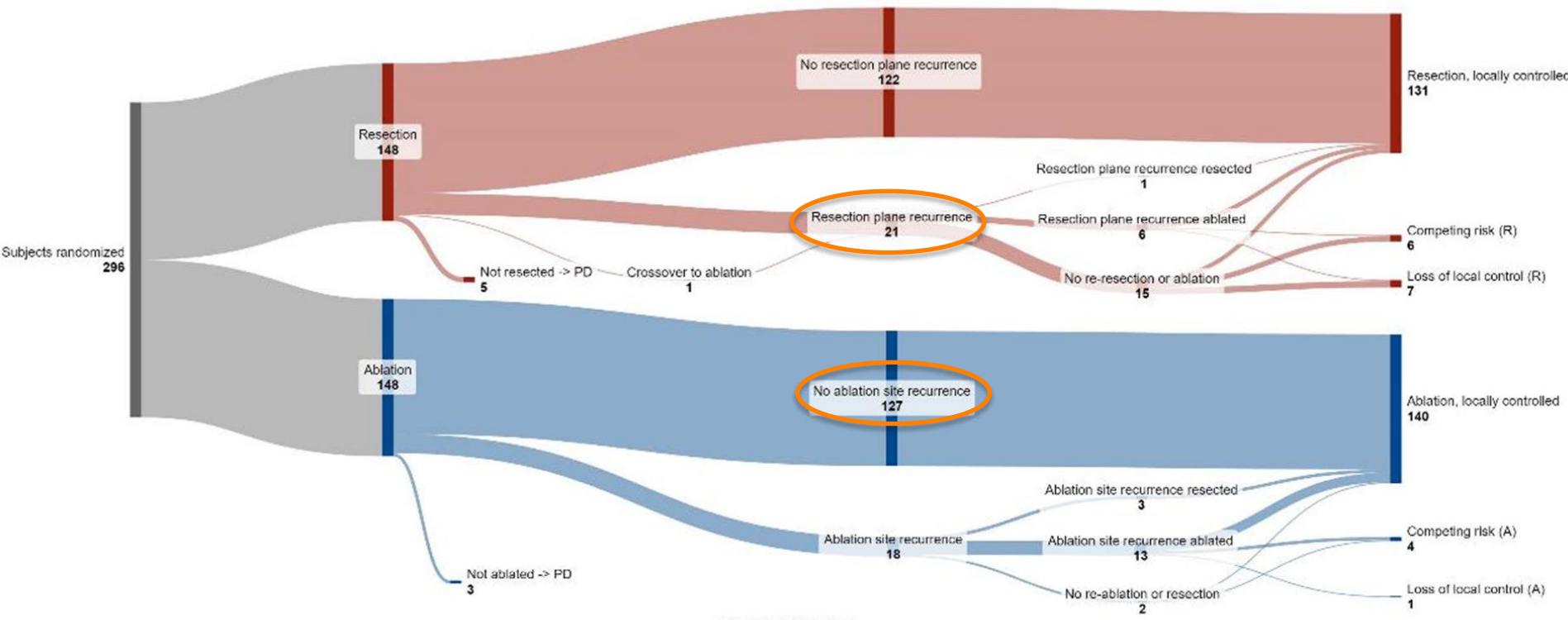
- 62% low disease burden
- **22% chemo first**
- median number CRLM = 2
- mean-size CRLM 14mm

- ***64% of resections in low disease burden group performed using (robot) laparoscopy***

- ***83% of ablations in low disease burden group performed percutaneously***

RESULTS

SANKEY FLOWCHART



- **COLLISION stopped at halftime based on predefined stopping rules for**
 - Showing benefit of the experimental arm (ablation) over standard-of-care (resection)
- **For patients with small-size colorectal liver metastases, thermal ablation compared to standard-of-care surgical resection**
 - Substantially reduced morbidity and mortality
 - treatment related mortality 2.1% (resection) → 0.0% (ablation)
 - all-cause 90-day mortality 2.1% (resection) → 0.7% (ablation)
 - AEs rate 56% (resection) → 19% (ablation) and SAE rate 20% (resection) → 7% (ablation)
 - Was at least as good as surgical resection in locally controlling CRLM
 - no difference in *per-patient* local control: HR 0.131 (95% CI 0.016-1.064; p = 0.057)
 - superior *per-tumor* local control: HR 0.092 (95% CI 0.011-0.735; p = 0.024)
 - Showed no difference in local & distant tumor progression-free survival
 - Did not compromise overall survival (OS)

Liver Transplantation and Chemotherapy versus Chemotherapy alone in patients with definitively unresectable colorectal liver metastases : results from a prospective, multicentre, randomised trial (TransMet)

R Adam, C Piedvache, L Chiche, E Salamé, O Scatton, V Granger, M Ducreux, U Cillo, F Cauchy, JY Mabrut, C Verslype, L Coubeau, J Hardwigsen, E Boleslawski, F Muscari, J Lerut, L Grimaldi, F Levi, M Lewin, M Gelli

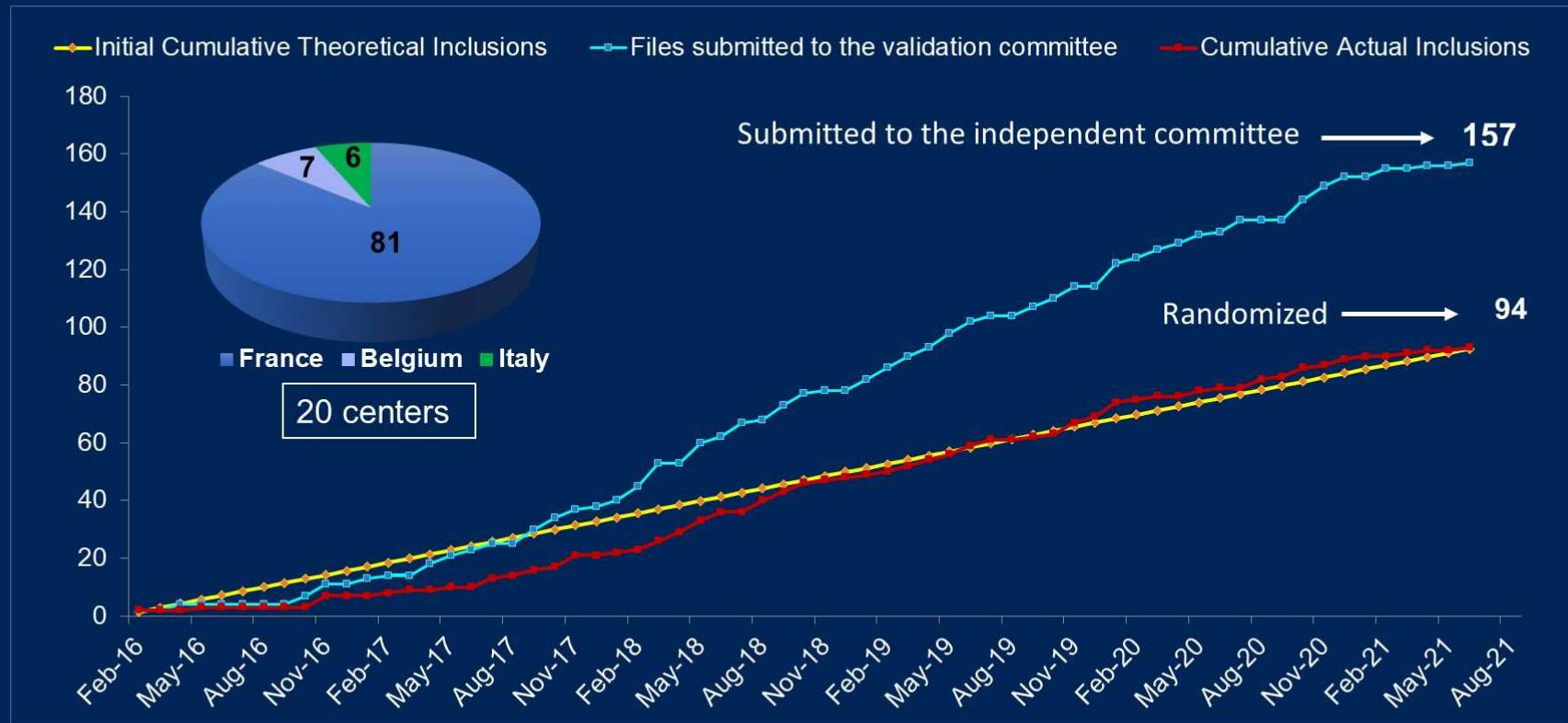
Paris-Saclay – Villejuif – Kremlin Bicêtre (France), Bordeaux (France), Tours (France), Paris (France), Grenoble (France), Villejuif (France), Padova (Italy), Clichy (France), Lyon (France), Leuven (Belgium), Louvain (Belgium), Marseille (France), Lille (France), Toulouse (France), Bruxelles (Belgium)



TransMet Trial : Eligibility criteria

- ≤ 65 years
- Good performance status (ECOG 0 or 1)
- Confirmed unresectability of CLM by expert surgeons
- Gold standard Resection of the primary
- No extrahepatic disease
- Partial Response or Stability with Chemo : ≥ 3 months, ≤ 3 lines
- No BRAF mutation
- CEA < 80 ng/ml or 50% decrease from baseline
- Platelets count > 80.000 and white blood cell count > 2500

TransMet Trial : Inclusion progression (Feb 2016 - July 2021)

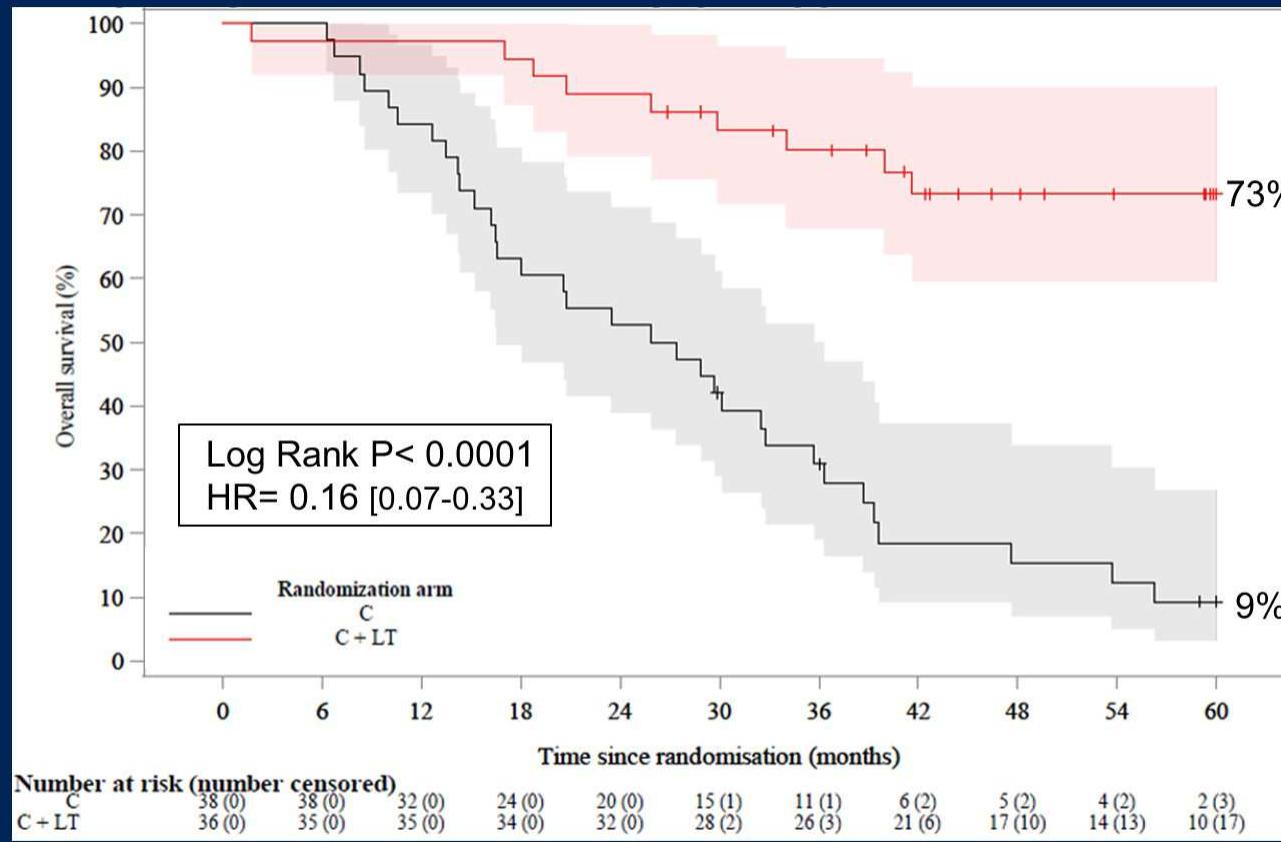


TransMet Trial : Patients Demographics at Diagnosis

	LT+C group (n=47)	C alone group (n=47)
Age (years)	52·0 (47·0, 59·0)	55·0 (47·0, 59·0)
Gender, n (%)		
Male	27 (57%)	28 (60%)
Female	20 (43%)	19 (40%)
Right sided primary tumour, n (%)	7 (15%)	7 (15%)
RAS mutation, n (%)	11 (23%)	12 (26%)
No of nodules at diagnosis (Median IQR)	20·0 (14·0, 25·0)	20·0 (12·0, 25·0)
< 10	5 (11%)	7 (15%)
Between 10 and 20	19 (40%)	18 (38%)
> 20	23 (49%)	22 (47%)
Diameter max (mm) at diagnosis (Median IQR)	55·0 (43·0, 76·0)	50·0 (27·0, 83·0)
Synchronous (0-1 Mo)	47 (100%)	45 (96%)
CEA (ng/mL) at diagnosis	305·0 (32·9, 762·0)	81·0 (20·0, 530·0)
CA 19-9 (U/mL) at diagnosis	96·0 (19·7, 800·0)	193·0 (20·9, 1949·0)
Fong's clinical risk score > 2	42 (89%)	42 (89%)

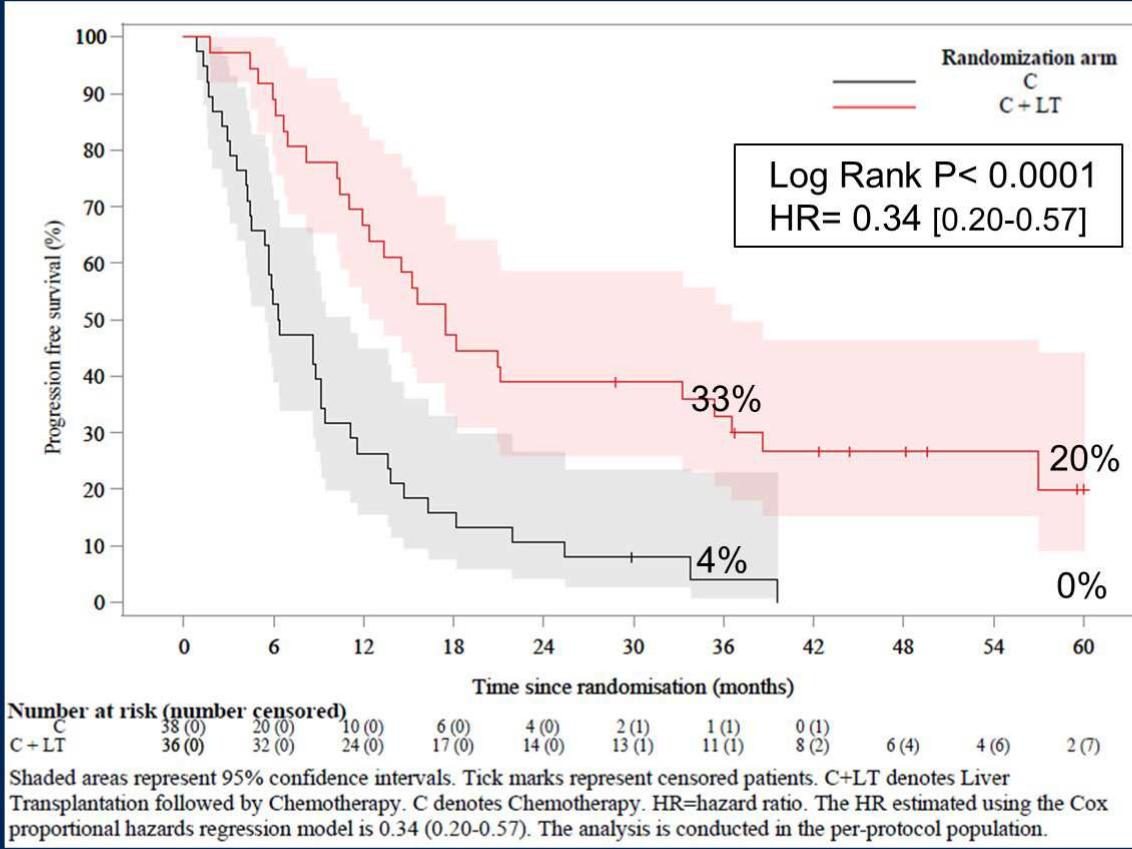
TransMet Trial : Primary Endpoint 5-Yr OS (Per Protocol)

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TransMet Trial : Secondary Endpoint 3-5-Yr PFS (Per Protocol)

16



Take Home messages from the TransMet trial

- Liver Transplantation + Chemotherapy significantly improves OS and PFS in selected patients with unresectable colorectal liver metastases compared to C alone
 - These results were obtained through a rigorous patient selection and a prioritization for organ allocation
 - Transplanted patients for CLM have similar survival (73% at 5 years) as those transplanted for established LT indications
 - LT +C offers a potential of cure to cancer patients with otherwise poor long-term outcome
-  These results support LT as a new standard option that could change our practice in treating patients with liver-only, definitively unresectable CLM.



Summary & THM

- Multidisciplinary approach prolongs survival
- Initial decision dependent upon symptoms of primary
- Basic molecular analyses prior induction CTx/ AB decision
- Regular follow-up and rediscussion (e.g. every 2 months)
- Interventional approach needs to be adapted to pts needs
- keep in mind: **TOGETHER WE CAN**

