

Is there an optimal strategy for (neo)-adjuvant treatment in metastatic colorectal cancer ?

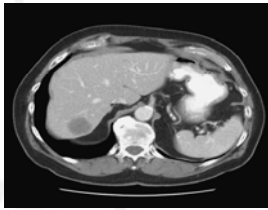
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 The Netherlands Cancer Institute
 Amsterdam



Optimal strategy for neo-adjuvant treatment in metastatic colorectal cancer

- Neo-adjuvant chemotherapy for resectable CRC liver metastases
- Neo-adjuvant therapy for unresectable CRC liver metastases
- Treatment strategy in pts primarily diagnosed with metastatic CRC

Part 1
 Neo-adjuvant therapy for resectable CRC liver metastases

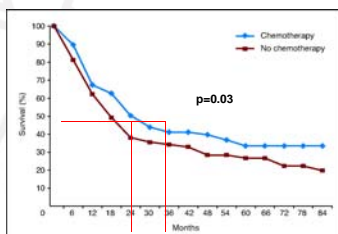


(Neo)- Adjuvant chemotherapy resectable disease

- Hepatic arterial infusion (Lorenz 1998, M Kemeny 2002)
- Systemic chemotherapy (Portier 2006, Mitry pooled analysis 2008)
- Peri-operative chemotherapy (Nordlinger 2008)



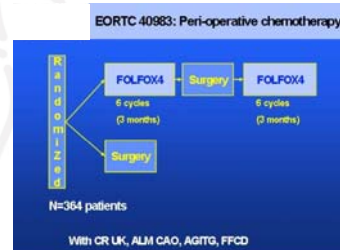
DFS after hepatic resection and adjuvant 5FU/LV



Portier 2006



EORTC intergroup study 40983



Nordlinger 2008



EORTC intergroup study 40983

EORTC Surgery		
	Peri-op CT (N=182)	Surgery (N=182)
Operated	159 (87.4)	170 (93.4)
Resected	151 (83.0)	152 (83.5)
Not resected	8 (4.3)	18 (9.9)
Not operated	22 (12.1)	8 (4.4)
more advanced disease	10	7
refusal	4	0
poor condition/death	3	0
other reason	5	1
Unknown	1 (0.5)	4 (2.2)
Median time to surgery	16.5 w	2 w

Nordlinger 2008

NKI-AVL



EORTC intergroup study 40983

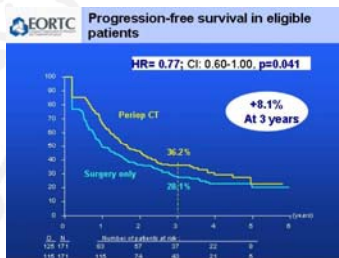
EORTC Results					
	N pts CT	N pts Surgery	% absolute difference in 3-year PFS	Hazard Ratio (Confidence Interval)	P-value
All patients	182	182	+7.2% (0.1% to 13.4%)	0.79 (0.62-1.02)	P=0.058
All eligible Patients	171	171	+8.1% (0.1% to 16.2%)	0.77 (0.60-1.00)	P=0.041
All resected Patients	151	152	+9.2% (3.2% to 14.4%)	0.73 (0.55-0.97)	P=0.025

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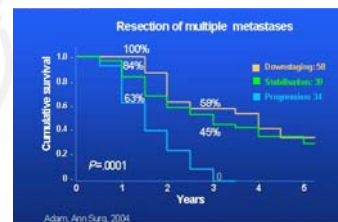


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Response to chemotherapy related to survival



Adams, Ann Surg, 2004

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Part 2 Neo-adjuvant chemo in unresectable disease

- Down-staging to resectable disease

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Down-staging to resectable disease

“Myth” ? OR “Reality” ?

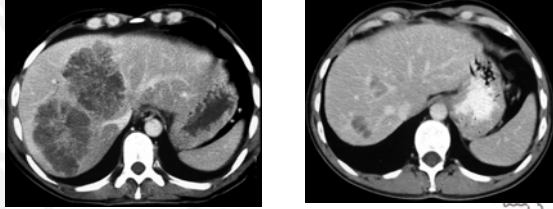
- Resection rates after neo-adjuvant chemo up to 40%
- 80% with Complete Clinical Response shows persistent cancer**
- Complete pR after chemo < 5%*

* Adam ASCO 2008, ** Benoit JCO 2007

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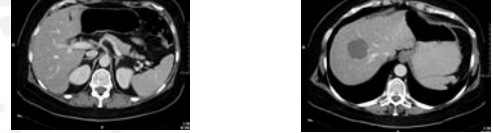


Conversion unresectable to resectable



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 Institut für Lebertumoren, Erlangen

Conversion unresectable → resectable ?



After 3 months CAPOX + Avastin

according to same pre-defined criteria ?



Metastases confined to the liver: "initial selected series"

Phase II studies	No of patients	Response Rate	R0 resection	Pt selection criteria
Albers 2004 FOLF-FOX	43	51%	33% (14pt)	Not well defined
Pizzo 2004 Irinotecan, LV5 FU	40	48%	33% (13pt)	Defined but pre and post chemo not identical
De la Camara 2004 Oxaliplatin/Irinotecan/SFU	22	64%	43% (9pt)	Not well defined
Quenert 2004 Folfirinax	26	73%	35% (9pt)	Well defined
Folprecht 2009	111	75%	35%	Well defined

30 – 40%

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Unselected pts with mCRC: chemo

Unselected series	Study	Chemotherapy	Response Rate	R0 resection	Median Overall survival mo
Tomasevic JCO 2004	Randomised Phase III, N=220 mCRC	A: Folfiri → Folfox 6	56%	A: 8 pt 7%	A: 21.5
		B: Folfox 6 → Folfiri	54%	B: 14 pt 13%	B: 20.6
Tomasevic JCO 2006	Randomised Phase III, N = 620 mCRC	A: Folfox 4	59%	A: 35 pt 11%	A: 19.3
		B: Folfox 7 stop and go	59%	B: 29 pt 9%	B: 21.2
Goldberg, Delaunoy 2005 Ann Oncol	Randomised Phase III, N=795 mCRC	A: Irinotecan, FU, LV	37%	A: 2 pt 1%	A: 15
		B: oxaliplatin, FU, LV	54%	B: 11 pt 4%	B: 19.5
		C: oxaliplatin/Irinotecan	39%	C: 11 pt 4%	C: 17.4
Falcone 2007, JCO	Randomised Phase III, N = 244 mCRC	A: Folfiri	34%	A: 7 pt 6%	A: 16.7
		B: Folfixiri	60%	B: 18 pt 15% Liver only 36%	B: 22.6

10%- 15%

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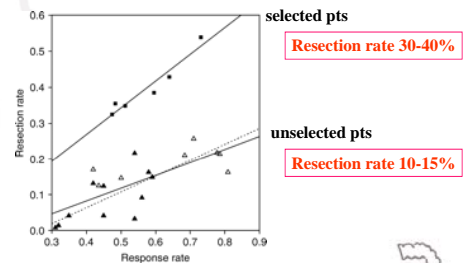
Unselected pts with mCRC: Chemo + targeted therapy

Unselected series	Study	Chemotherapy	Response Rate	R0 resection	Median Overall survival mo
Herritz NEJM 2004	Randomised Phase III, N=402 mCRC	A: IFL B: IFL + bevacizumab	45% 35%	A: < 2% B: 2 pt < 2%	A: 15.6 B: 20.3
Garra Alfonso ASCO GI 2008	Retrospective N=35 mCRC	Xeliri + bevacizumab	68%	17%	Not reported
Diaz Rubio ASCO 2005	Phase II N= 42	Folfox + cetuximab	72%	19%	Not reported
Folprecht Ann Oncol 2006	Phase II N=21 mCRC	FOLFIRI + cetuximab	67%	19% 33	
Gammighan ASCO GI 2008	First BEAT N=1965 mCRC	CT + bevacizumab	ng	9% 11.5% (Liver only)	Not reported

10% - 15%

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Relation: response – resection rate



Folprecht Ann Oncol 2005

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Survival after resection:

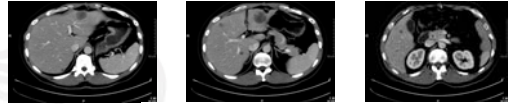
		3 yr	
		DFS	OS
• Primarily resectable	n=116	51%	63%
• After neo-adjuvant chemo	n= 34	21%	63%

Selecting responders

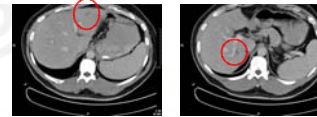


Capusotti Br J Surg 2006

Take care; the other "Reality"



After 5 months
CAPOX + Avastin

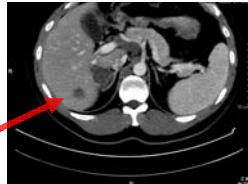


Take care; the other "Reality"

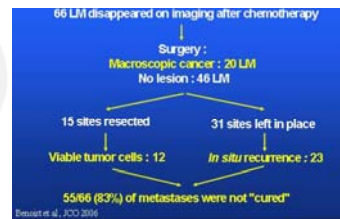
RFA: 6 weeks after
discontinuation avastin



3 months after RFA: new
"old" lesion



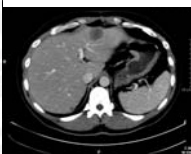
Complete radiological response



Bouzat et al., JCO 2009



Vanishing tumours



Close monitoring; resect as soon as possible



Hepatotoxic

- Sinusoidal lesions mimicing hepatic veno occlusive disease
- Steatohepatitis

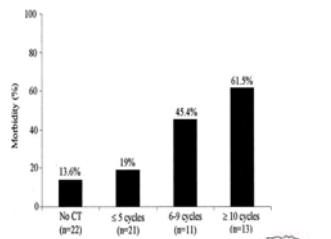


Callie ASCO 2007



Morbidity liver resection

- Mortality not increased
- Morbidity related to number of cycles
- Bevacizumab seems safe when stopped > 5wks



Karoui Ann Surg 2006, Gruenberger JCO 2006



Conclusion neo-adjuvant chemo for unresectable disease

- 10-15% of the pts will become resectable
- Complete pathological response after chemo < 5%
- In 80% of the pts active lesions will be left behind despite Clinical CR



Optimal strategy neo-adjuvant chemo:

- Use regimen with optimal response
- Perform close evaluation by CT
- Differentiate between uni or multifocal disease
- Resect as soon as possible
- Recurrence rate is high; be willing to accept re-intervention e.g. RFA

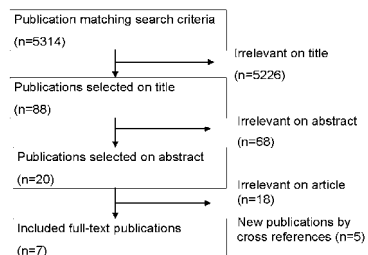


Part 3: Treatment strategy in pts primarily diagnosed with metastatic CRC

- Should resection of primary tumour be performed ?
- Should chemo be started right away, with primary tumour still in situ ?



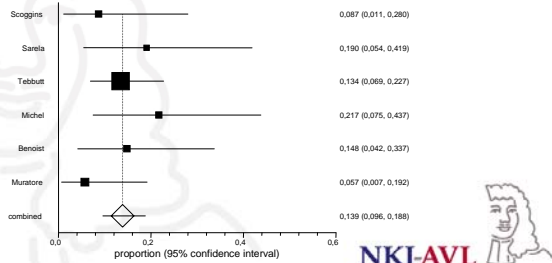
Literature search: policy in pt with synchronous CRC liver metastases



Author	Journal of publication	Year	Study quality	Methods	N 850
Scoggins	Ann Surg Oncol	1999	19	Retrospective case series	66 surgery 23 radiotherapy/ chemotherapy
Sarela	Br J Surg	2001	12	Retrospective case series	21 chemotherapy
Tebbutt	Gut	2003	20	Prospective case series	280 surgery 82 chemotherapy
Ruo	J Am Coll Surg	2003	16	Retrospective case series	127 surgery 103 chemotherapy
Michel	Gastroenterol Clin Biol	2004	18	Retrospective case series	31 surgery 23 chemotherapy
Benoist	Br J Surg	2005	21	Retrospective case-control study	32 surgery 27 chemotherapy
Muratore	Ann Surg Oncol	2006	15	Prospective case series	35 chemotherapy

Intestinal obstruction in patients initially treated with chemotherapy

Proportion meta-analysis plot [random effects]

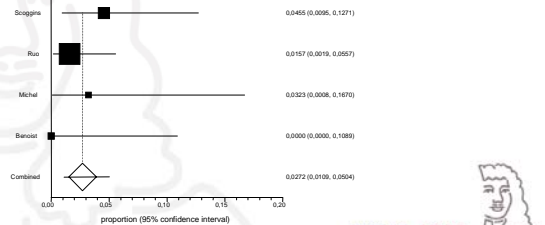


Scheer Ann Oncol 2008



Mortality after resection of primary tumor

Proportion meta-analysis plot [random effects]

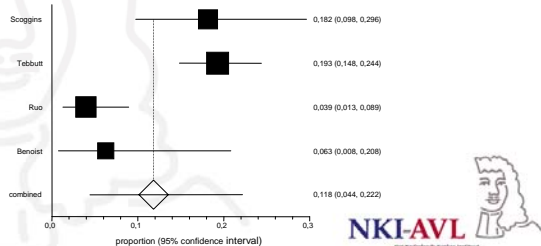


Scheer Ann Oncol 2008



Major complications after resection primary tumor

Proportion meta-analysis plot [random effects]



Scheer Ann Oncol 2008



Optimal strategy in pts with synchronous unresectable liver metastases

- In asymptomatic pts no need for resection primary tumor
- (Intestinal obstruction in 15%)



Is there an optimal strategy for (neo)-adjuvant treatment in metastatic colorectal cancer ?

- For resectable crc liver mets: YES
may also be adjuvant
- For unresectable crc liver mets: YES
but resect as soon as possible
- For synchronous unresectable liver mets + primary in situ: YES