Sequence of treatment in colorectal cancer with synchronous metastases

Gunnar Folprecht · Bernard Nordlinger

Disclosures

- Gunnar Folprecht:
  - Honoraria for lectures or advisory boards: Merck KGaA, Roche, Sanofi-Aventis, Lilly, Celgene
  - Study grant: Meck KGaA
- Bernard Nordlinger:
  - Honoraria for lectures: Merck, Roche, Amgen

Patient, 57 years old

Sigmoid cancer (adenocarcinoma G2)

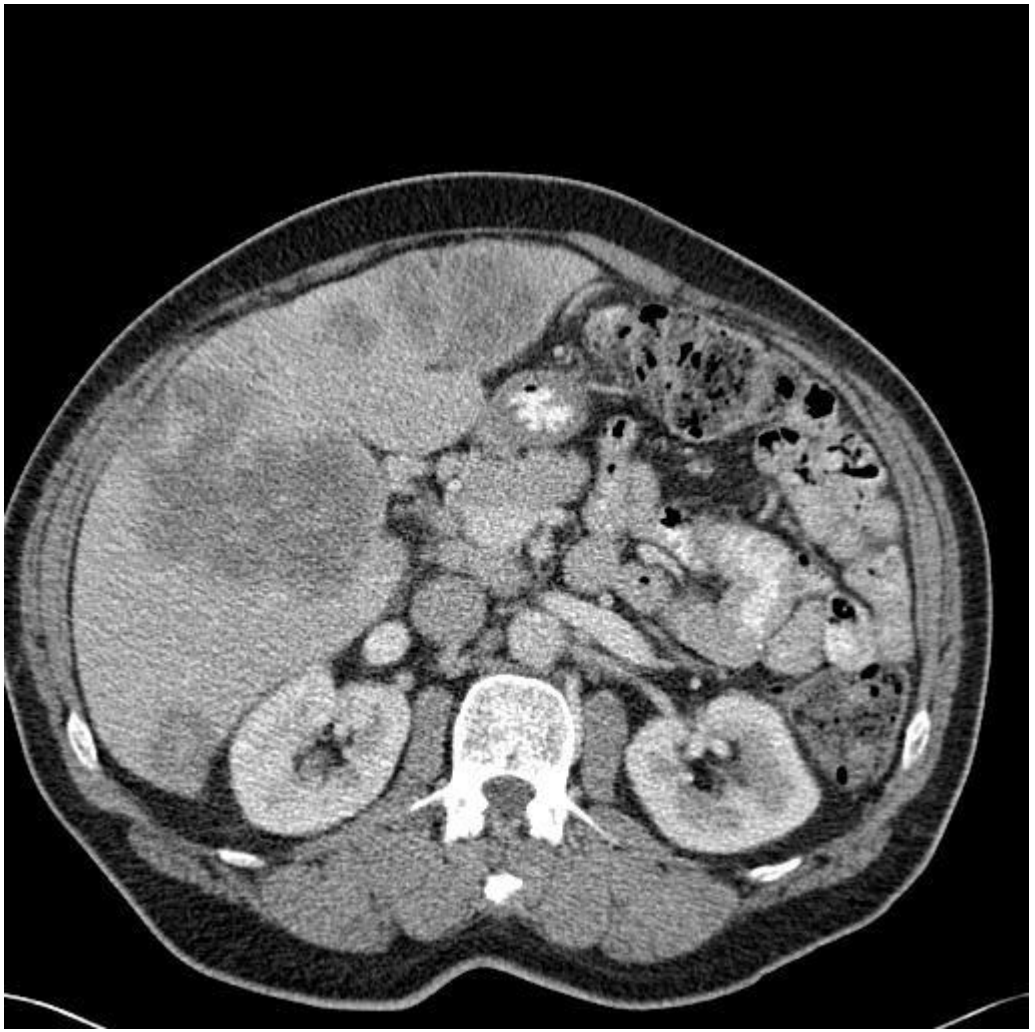
Liver metastases

CEA: 812

CA19-9: 8040

Co-morbidity:

Arterial hypertension



Tumorboards

Questions?

1. **Are all findings resectable:**
    a. **Technically?**

Criteria for resectability

Complete resection (± ablation) of tumour

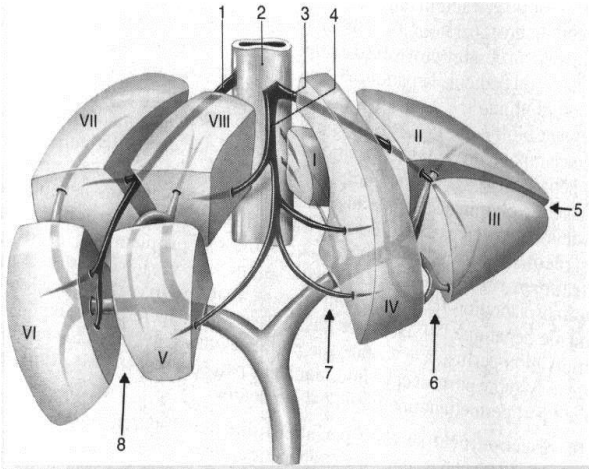
Free resection clearance

Preservation of at least 1 of 3 hepatic veins

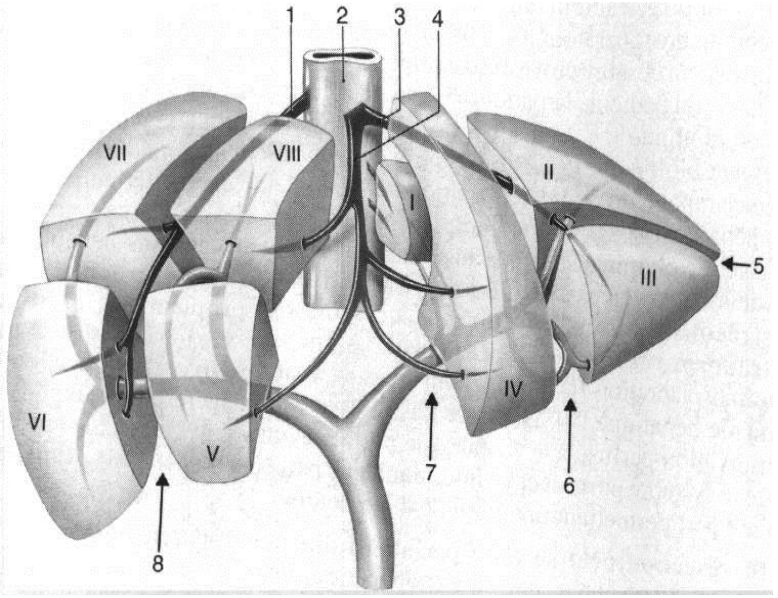
Homolateral portal pedicle

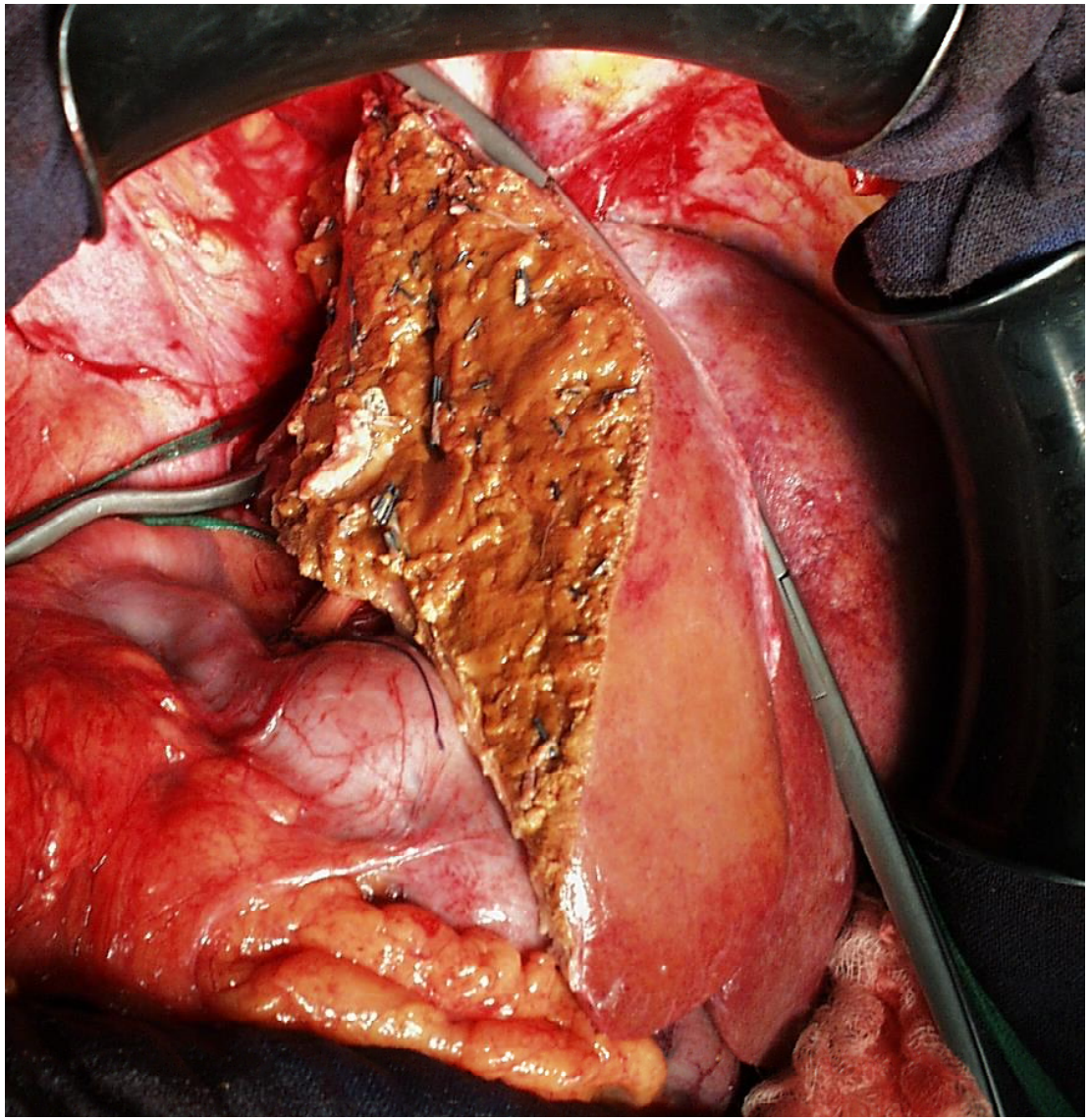
Future remnant liver parenchyma ≥25 %

Resectability does not depend on the number of metastases

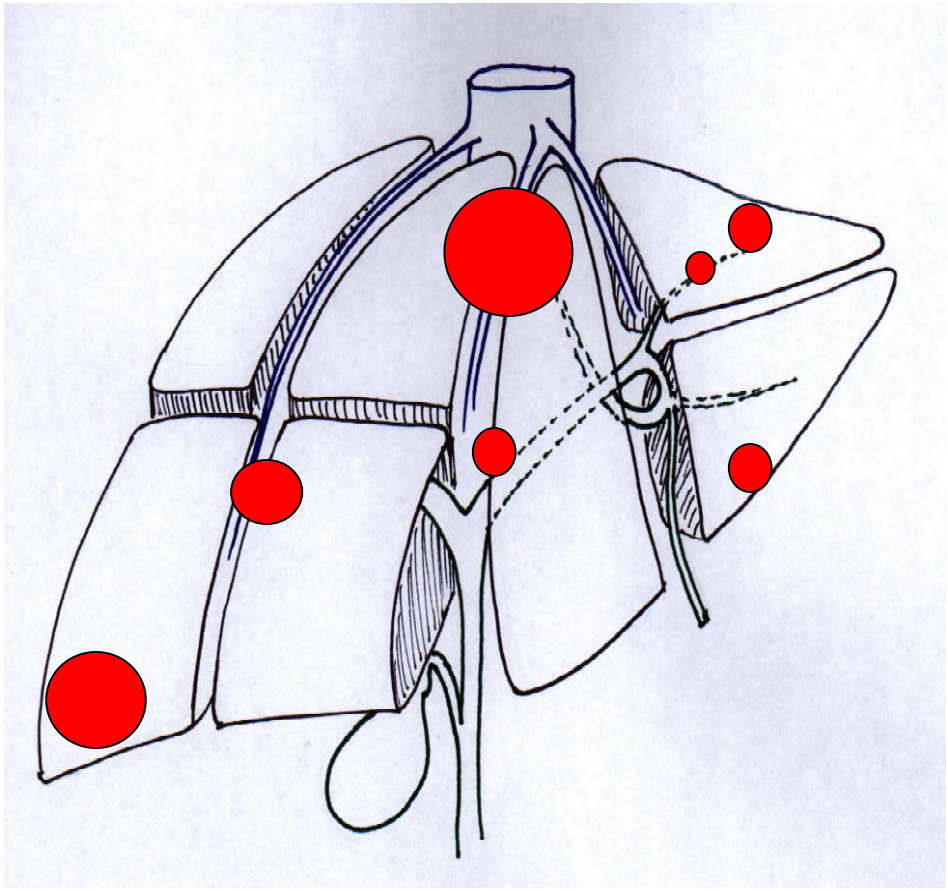


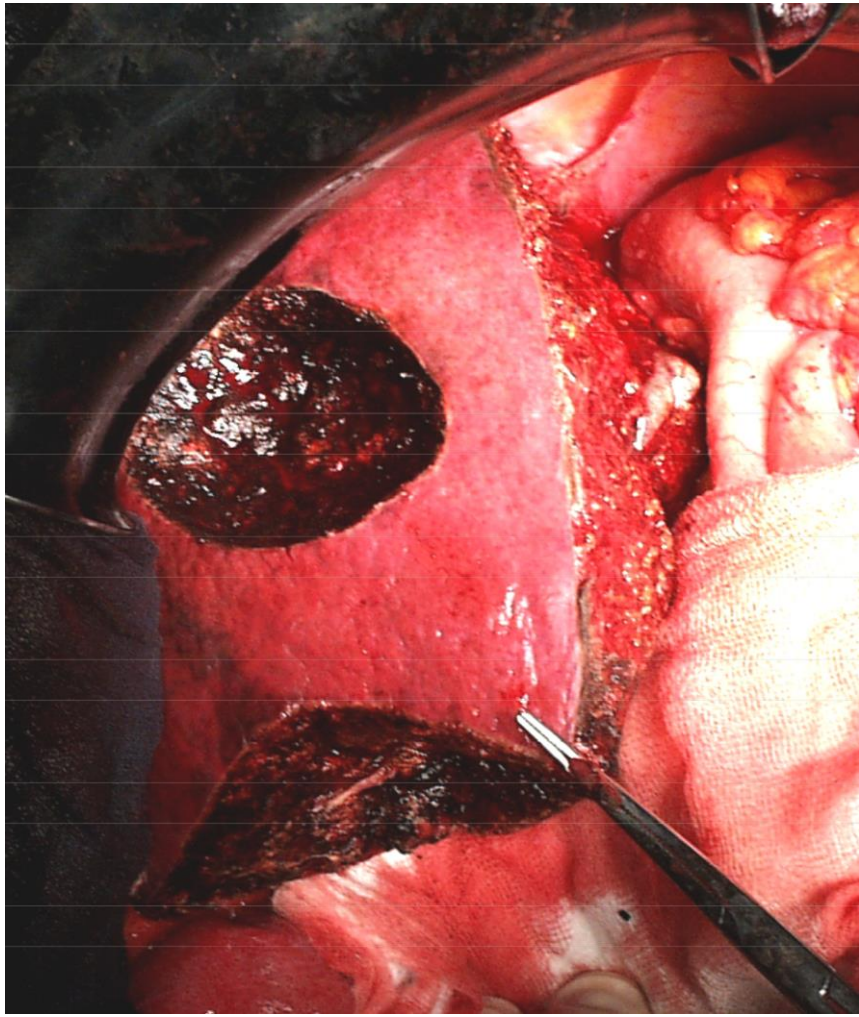
Right lobectomy





Multiple wedge resections





Questions?

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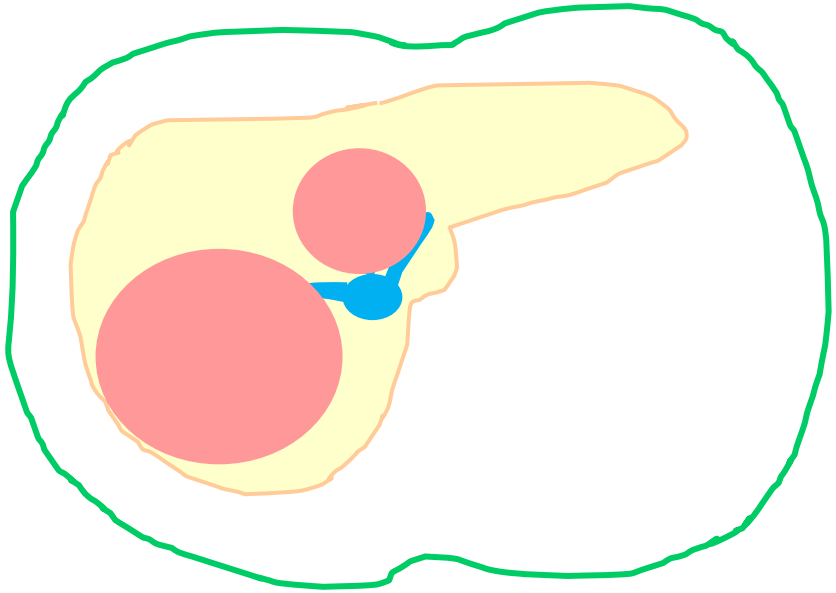
   a. **Technically?**
   b. **Would you consider prognostic factors/scores in daily decision making? Which?**

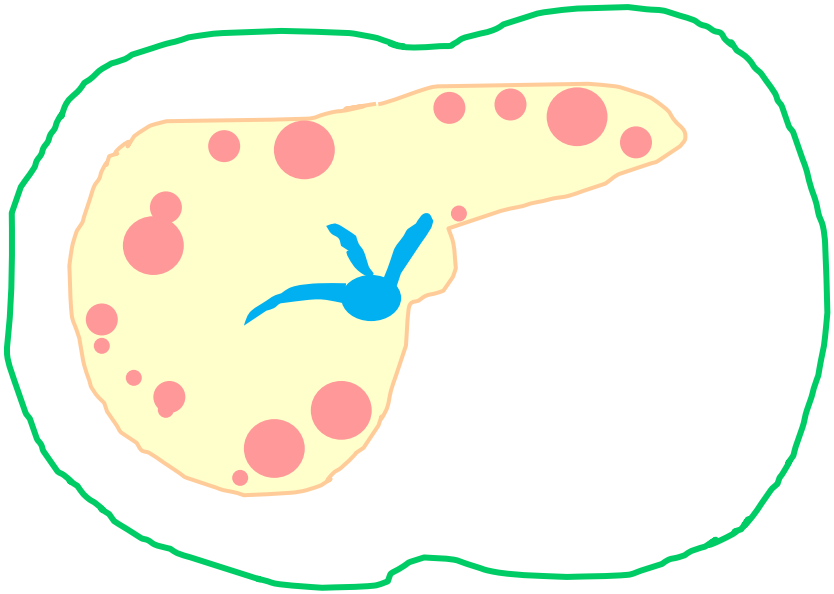


Resectability

Remaining functional
liver tissue
Invaded structures/segments

Prognostic factors

- Disease free interval
- Number / size of metastases
- Tumor markers
- Nodal status



Technical Resectability

Remaining functional liver tissue
Invaded structures/segments

Prognostic factors

- Disease free interval
- Number / size of metastases
- Tumor markers
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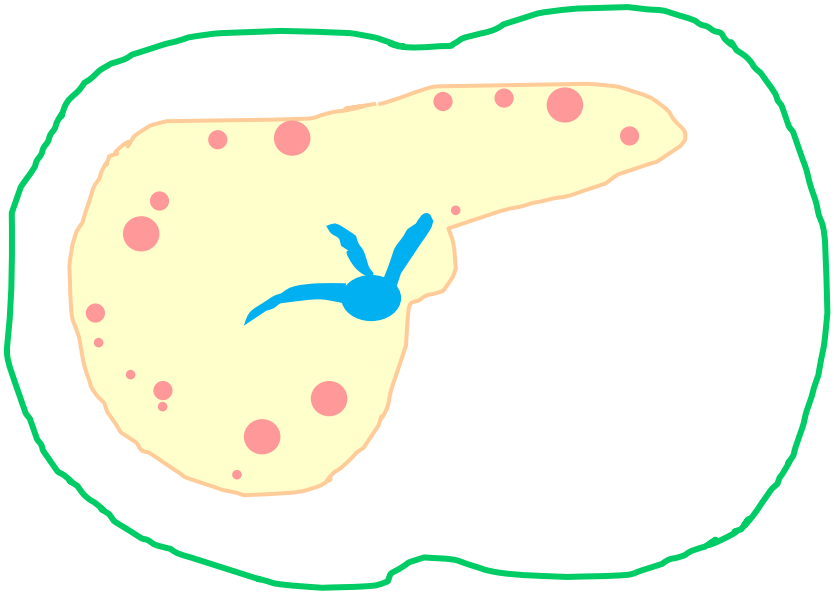

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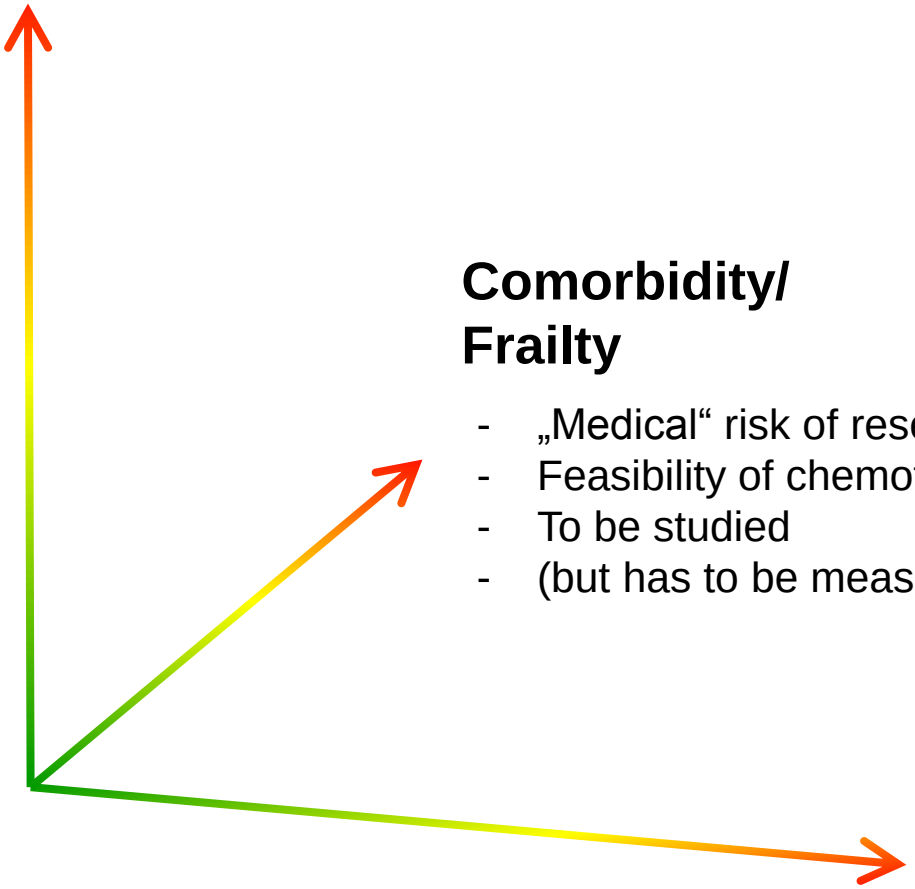


Comorbidity/ Frailty

- „Medical“ risk of resection
- Feasibility of chemotherapy
- To be studied
- (but has to be measured first…)

Technical Resectability

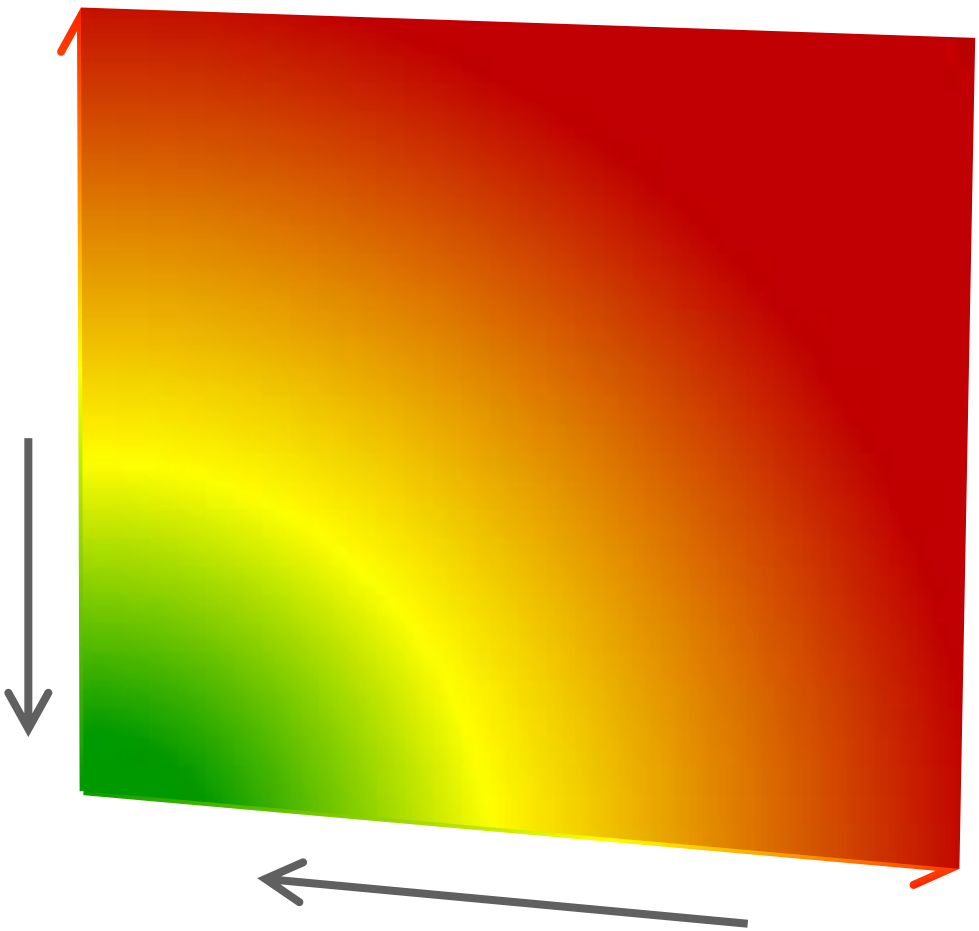
Remaining functional liver tissue
Invaded structures/segments

Prognostic factors

Molecular markers?

Probability of:
- recurrences
- overlooked metastases

– Conversion chemotherapy („adjuvant“)



– Staged resections
– Portal vein embolisation
– Combination with ablation
– Conversion chemotherapy (tumour shrinkage)

Technical Resectability

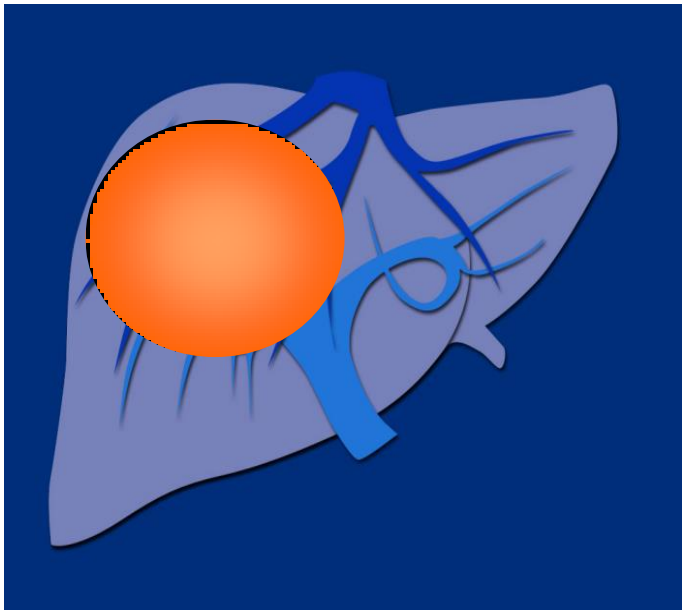
Mobidity
Risk of complications
No of resections

Questions?

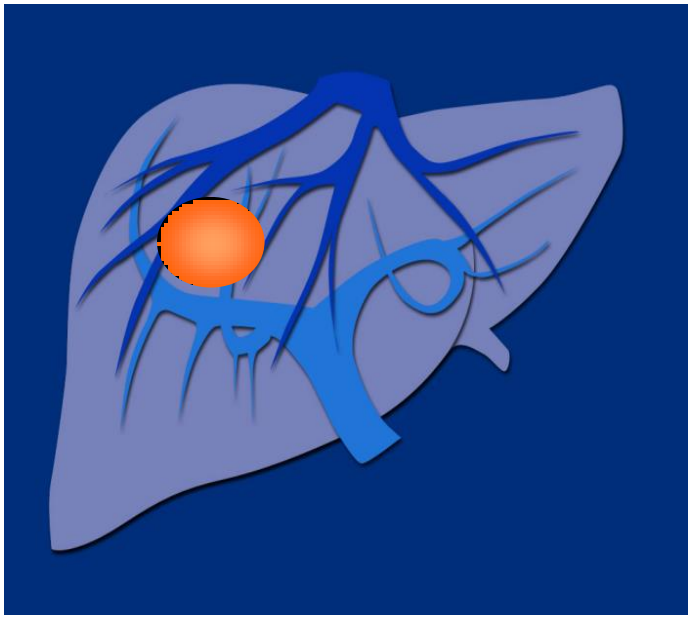
1. **Are all findings resectable:**
   a. **Technically?**
   b. **Would you consider prognostic factors/scores in daily decision making? Which?**
   c. **We proposed „intensive“ chemotherapy. Will the metastases become resectable?**

Initially unresectable metastases

Before



After chemotherapy



Initially unresectable metastases

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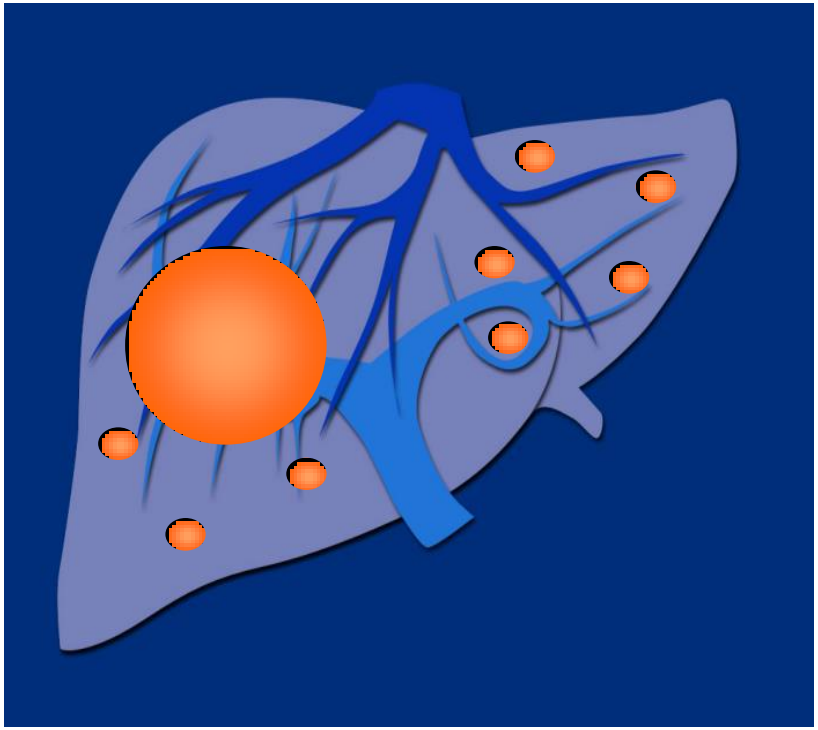
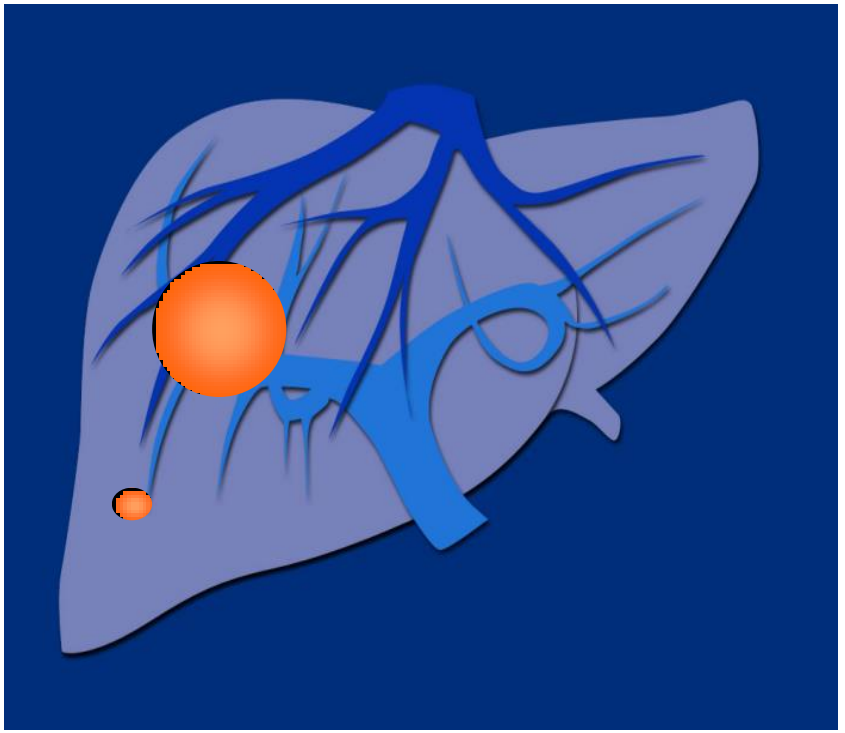


After chemotherapy



„Complete response“

66 LM disappeared on imaging after chemotherapy

Surgery: Macroscopic cancer : 20 LM

No lesion : 46 LM

15 sites resected

31 sites left in place

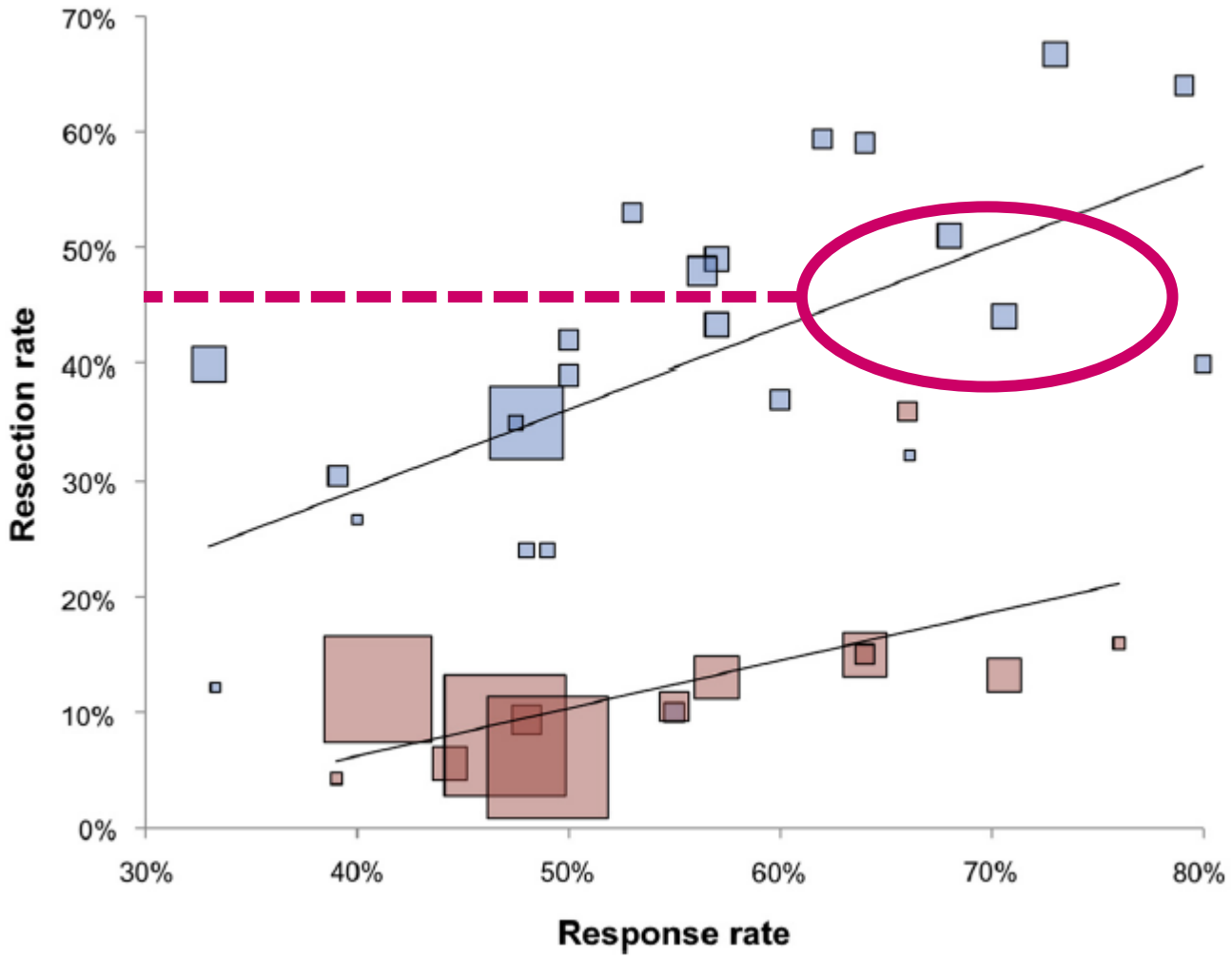
Viable tumor cells : 12

***In situ* recurrence *:* 23**

55/66 (83%) of metastases were not "cured"

Benoist, Nordlinger et al , JCO 2006

Response and resection rates within the trials



Jones, Folprecht Eur J Cancer 2014

Questions?

1. Are all findings resectable:
   a. Technically?
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   c. We propose „intensive“ chemotherapy. Will we achieve resectability?
2. **When metastases are unresectable, should the primary be resected (first)?**

Treatment options for synchronous initially ***unresectable*** CRC liver metastases

- **Up-front treatment is controversial**
- **Chemotherapy : which timing ? before or after surgery**
- **Surgery of the primary tumor +/- radiation or chemoradiation**
- **Surgery of the metastases if they become resectable**

Up-front primary tumor resection in ***symptomatic*** patients

- **In symptomatic patients (bleeding, obstruction, perforation) the primary tumor should be resected first.**

- **Alternatively: stoma, bypass, stent…**

Up-front primary tumor resection: ***non symptomatic*** patients

Goals:

- **avoid complications related to the primary tumor in place (bleeding, obstruction, tumor perforation) during chemotherapy particularly with bevacizumab**
- **cure (if metastases become resectable)**

The majority of patients in the US used to undergo primary tumor resection

Chang et al, JCO 2012
Hapani et al,Lancet Oncol, 2009
Costi et al. Ann Surg Oncol 2007

Up-front primary tumor resection

- **Up-front primary tumor resection delays administration of chemotherapy for several weeks.**
- **Complications of surgery can further delay or even preclude administration of chemotherapy.**
- **Complication rates for primary resection in patients with unresectable distant metastases was 11.8% (major complications) and 20.6% (minor complications)**

Scheer et al. Ann Oncol 2008

Up-front systemic chemotherapy

- **Median survival of patients with unresectable metastases increased to more than 24 months with modern treatments.**

- **Systemic chemotherapy is active on liver metastases but also on the primary tumor and can even induce complete response in some cases .**

Karoui et al. DCR, 2011; Schrag et al. JCO 2010;
Grothey et al. JCO 2008;
FOxTROT collaboration Group et al. Lancet 2012

Up-front systemic chemotherapy

- **Retrospective studies have observed low rates of primary tumor–related complications during treatment in patients with initially asymptomatic disease.**

Poultsides et al, JCO, 2009

NSABP C-10:

Ph. II prospective study primary CT (mFOLFOX6 + bev) for patients (n=86) with asymptomatic primary intact unresectable stage IV colon cancer

The majority of patients could be managed without primary tumor (PT) intervention

- **86% of patients - no major morbidity due to PT**
- **Median overall survival :19.9 months**

The investigators conclude that avoiding resection of the asymptomatic PT did not result in an unacceptable rate of PT-related complications and did not compromise survival

73.3% of the patients had not required PT resection at the time of death or last follow-up.

McCahill LE,et al. JCO.2012

Can primary tumor resection improve survival ?

- **Survival benefit suggested with prior resection of primary**
  - **Multi-institutional retrospective analysis**
  - **Population based studies**
  - **Retrospective analysis of randomized trials**

- **Analysis are retrospective and potentially biased**
  (Patients selected for resection being better fit and with more limited metastatic disease)

- **New prospective trials:**
  - **CLIMAT-PRODIGE 30 (France),**
  - **CAIRO 4 (The Netherlands),**
  - **SYNCHRONOUS (Germany)**

Karoui et al. DCR, 2011
Gresham et al, Ann. Surg. Oncol.2014
Temple et al. JCO 2004
Ferrand F et al, Eur J Cancer 2013
Venderbosch et al, Ann. Surg. Oncol.2011

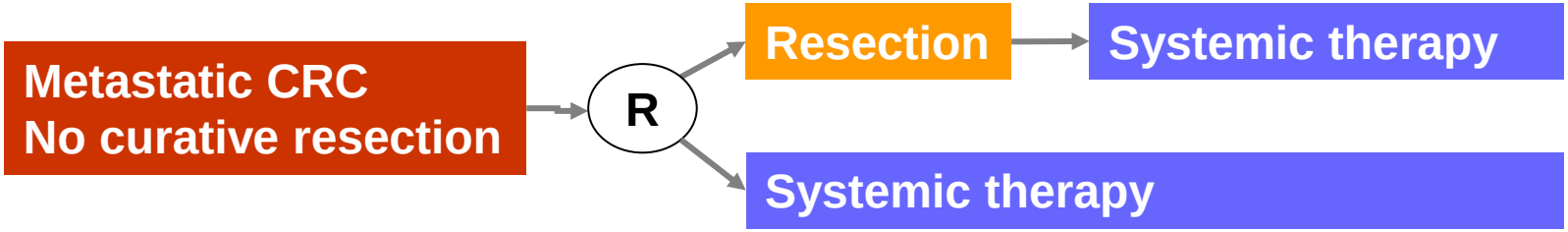
SYNCHRONOUS

Resection of the primary tumor versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV)

-

A randomized controlled multicenter trial (SYNCHRONOUS-Trial)

SYNC-03/2011



800 pts (180 pts recruited)
Primary endpoint: Overall survival

Trials with similar design:
CAIRO4 (NL), CLIMAT-PRODIGE (F)

Need for resection of the intact primary after chemotherapy for synchronous metastases?

- **Progression of metastases and asymptomatic primary: NO**
- **Tumor response: YES in particular if resection of metastases is considered**
- **Complete tumor response on primary tumor: discuss in MDM**

Patient, 57 years old

Sigmoid cancer (adenocarcinoma G2)

Liver metastases

CEA: 812

CA19-9: 8040

KRAS/NRAS/B-RAF: wild type

FOLFOXIRI combinations in first line therapy

	n	RR	PFS	OS
FOLFOXIRI/Bev	252	**65%**	**12.1**	**31.0**
FOLFIRI/Bev	256	**53%**	**9.7**	**25.8**
Falcone, ASCO 2013		**p<0.01**	**HR 0.77 p<0.01**	**HR 0.83**
FOLFOXIRI	122	**60%**	**9.8**	**22.6**
FOLFIRI	122	**34%**	**6.9**	**16.7**
Falcone, JCO 2007		**p<0.0001**	**HR 0.63; p<0.01**	**HR 0.80;p=0.032**
FOLFOXIRI/Bev	41	**81%**	**18.8**	
FOLFOX/Bev	39	**62%**	**12.0**	
Bridgewater, ECC 2013		p=0.061	**p<0.01**	

EGFR vs. VEGF plus chemo
k-ras exon 2 wt (not approved)

	n	RR	PFS	OS
FOLFIRI/Cetux	295	62%	10.0	28.7
FOLFIRI/Beva	297	58%	10.3	25.0
Heinemann, Lancet Oncol 2014		p=0.18	HR 1.06	HR 0.77 p=0.017
FOLFOX/Pani	142	58%	10.9	34.2
FOLFOX/Beva	143	54%	10.1	24.3
Schwartzberg, JCO 2014			HR 0.84	HR 0.62 p=0.009
Chemo/Cetux	578	64%	10.4	29.9
Chemo/Beva	559	58%	10.8	29.0
Venook, ASCO 2014			HR 1.04	HR 0.93

See discussion in room Madrid after this session

Patient, 57 years old

Sigmoid cancer (adenocarcinoma G2)

Liver metastases

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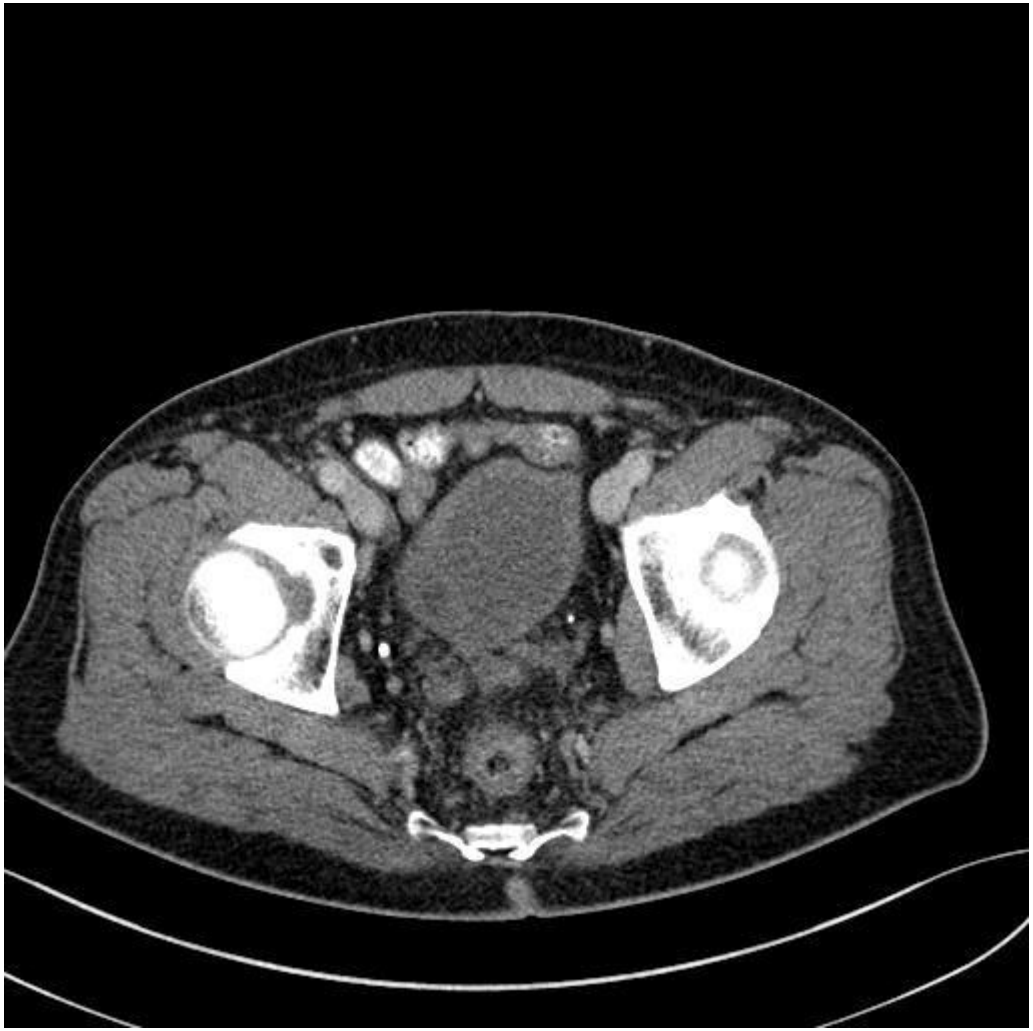
KRAS/NRAS/B-RAF: wild type

Treatment:

6 cycles

FOLFOXIRI / Cetuximab



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2. If unresectable: Should we resect the primary (first)?
3. Did the metastases become the resectable?
   a. Which order for resection of primary and metastases?

Surgical options if synchronous metastases become resectable after response to chemotherapy

- **Resection of the primary tumor (+/- radiation or CRT for rectal cancer)**
- **Surgery of the liver**
- **Which order?**
  - **“Classical” primary tumor first?**
  - **Combined?**
  - **Reverse: liver first?**

Surgical strategy: the primary first

- **Resection of primary tumor → Resection of metastases**
- **No risk of primary related complications**
- **Risk of progression of CLM which may become unresectable during the treatment of primary**

Surgical strategy:
Simultaneous resections of primary and metastases

Advantages:

- **Only one operation**
- **Resection of metastases not delayed by the treatment of the primary**

Limitations

- **Increased morbidity (major liver resection + major colorectal surgery)**
- **Requires double surgical expertise**
- **Depends on surgical access (open +/- laparoscopy)**

Reddy et al. Ann Surg Oncol 2007
De Santibanes et al. J Am Coll Surg 2003
Fujita et al, Jpn J Clin Oncol 2000
Tocchi et al, Int J Colorectal Dis 2004
Adam et al. Br J Surg 2010

Surgical Strategy: the combined approach

	Combined resection	Staged resection	P value
Major Hepatectomy			
n	36	51	
Mortality	3 (8.3%)	0	0.07
Severe morbidity	13 (36.1%)	9 (17.6)	0.05
Minor Hepatectomy			
n	99	19	
Mortality	1 (1%)	0	0.83
Severe morbidity	14 (14.1%)	2 (10.5%)	0.73

Reddy et al. Ann Surg Oncol 2007

Surgical Strategy: the combined approach

	Combined resection	Staged resection	P value
Major Hepatectomy			
Mortality	**6.1%**	**2.4%**	**0.009**
Minor Hepatectomy			
Mortality	**2.2%**	**0.5%**	**0.11**

Nordlinger, Jaeck , Cancer 1996

Surgical Strategy:
the reverse approach - liver surgery first

Preoperative chemotherapy → Resection of metastases →Resection of the Primary Tumor

Rationale:

- **Survival depends on progression of metastases rather than of the primary tumor**
- **Prevents the risk of progression of CLM which could become unresectable during treatment of primary**
- **Primary related complications during treatment of CLM are rare**

Mentha G et al. Br J Surg 2006

Surgery for synchronous colorectal liver metastases and primary: experience of M. D. Anderson

Approach	No Pts	Tumors No.	Mortality %	Cumulative Morbidity %	5y OS
Classic	72	3	3	51	48%
Combined	43	1	5	47	55%
Reverse	27	4	0	31	39%
P value		0.01, 0.001	NS	NS	NS

Provided adequate patient selection, the different approaches appear similar for postoperative morbidity and control of cancer

Brouquet et al. J Am Coll Surg 2010

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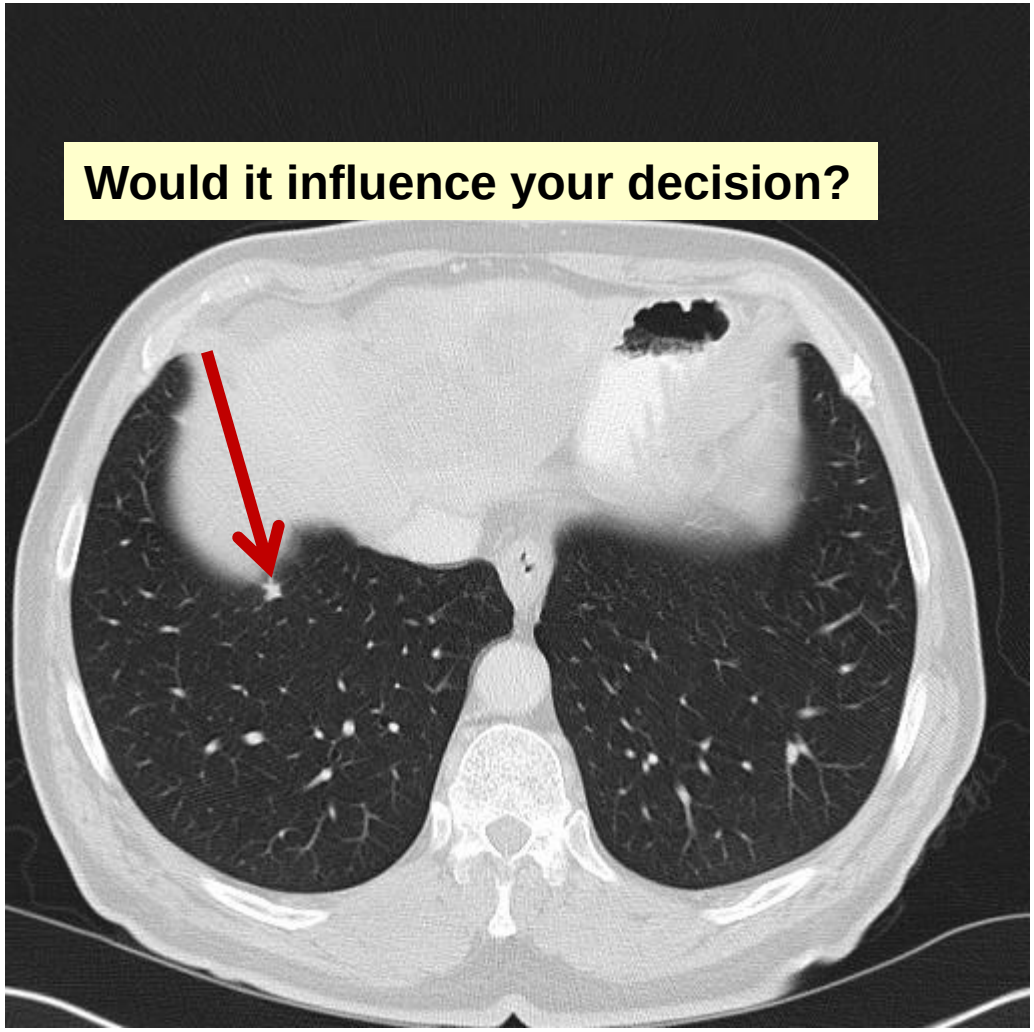
Treatment:

6 cycles

FOLFOXIRI / Cetuximab



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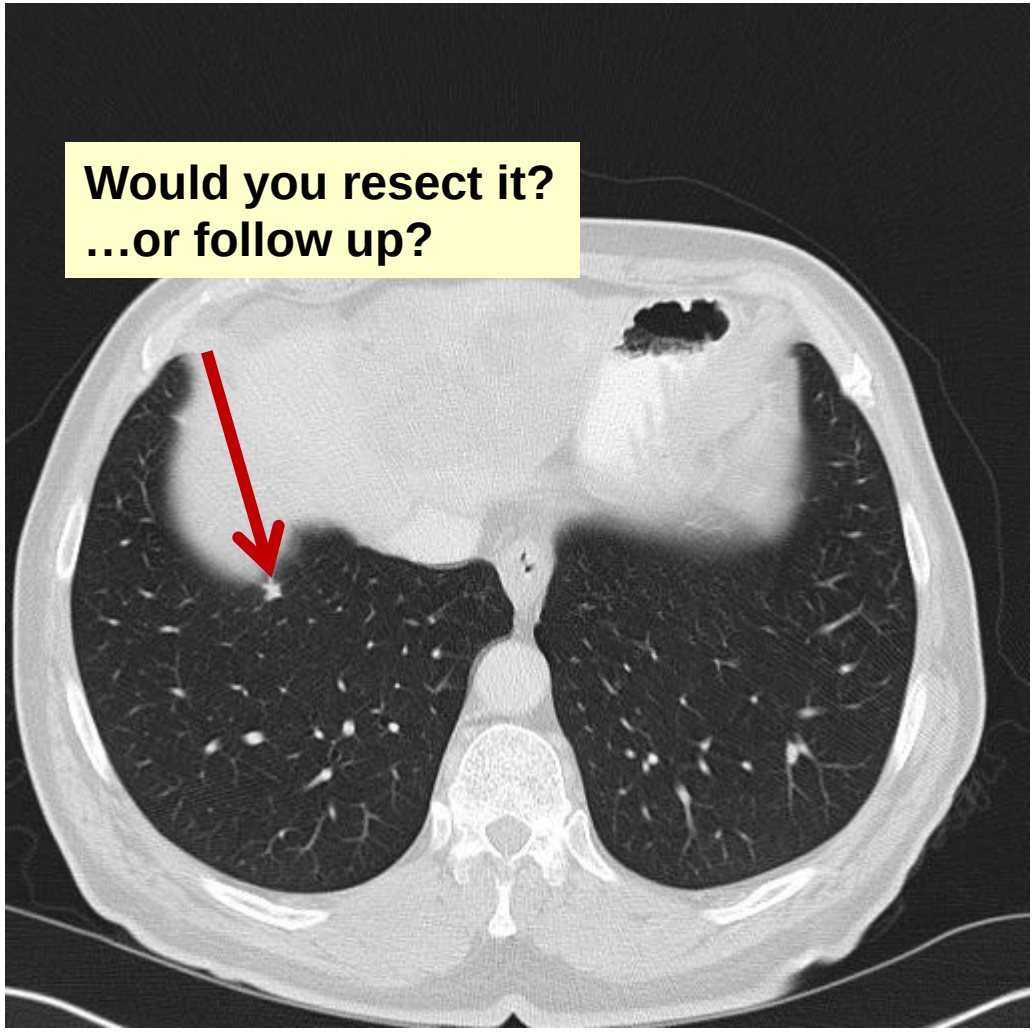

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Treatment:

6 cycles FOLFOXIRI / Cetuximab

Extended left hemihepatectomy, atypical resection

Histology: Good regression, TRG II (Rubbia-Brandt 2007)

Margin: ≥ 3 mm margin

No CASH, no SOS

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2. If unresectable: Should we resect the primary (first)?
   a. Which order for resection of primary and metastases?
3. Did the metastases become the resectable?
4. **Do you think the patient will be cured?**

Prognostic factors

	Rees	Malik	Minagawa	Konopke	Nordlinger	Fong	Zakaria	Yamaguchi	Iwatsuki	Tan	Schindl	Tanaka	Lise	Ueno	Nagashima
Number of met‘s	+	+	+	+	+	+	-	+	+	-	+	-	+	+	+
Nodal status	+	-	+		+	+	-	+	-	+	+	-	+	+	+
Max. size of met‘s	+	-	-	-	+	+	-	+	+	-	-	-	-	-	+
Interval primary-met‘s		-	-		+	+	-		+					+	+
CEA at resection: 2.6	+	-	+	+	-	+	-			-	+		-	-	-
Extrahep. spread	+		-			+		+	+			-			+
Positive margins	+	-				+	-		+						
Poorly diff. tumour	+		-						-	+	-	+		-	
Serosal invasion					+							-		-	+
Hepat. lymph nodes			+				+								
Bilobar spread	-		-		-	-	-		+	-	-	+		-	-

Spelt, Eur J Surg Oncol 2012

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   What do you communicate?

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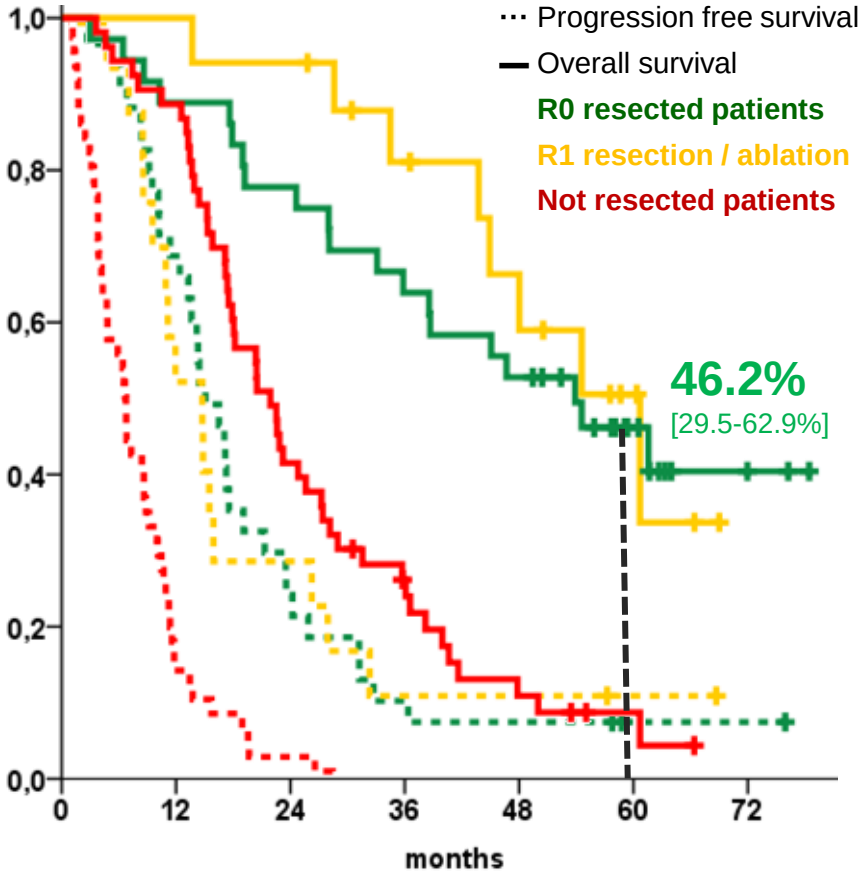
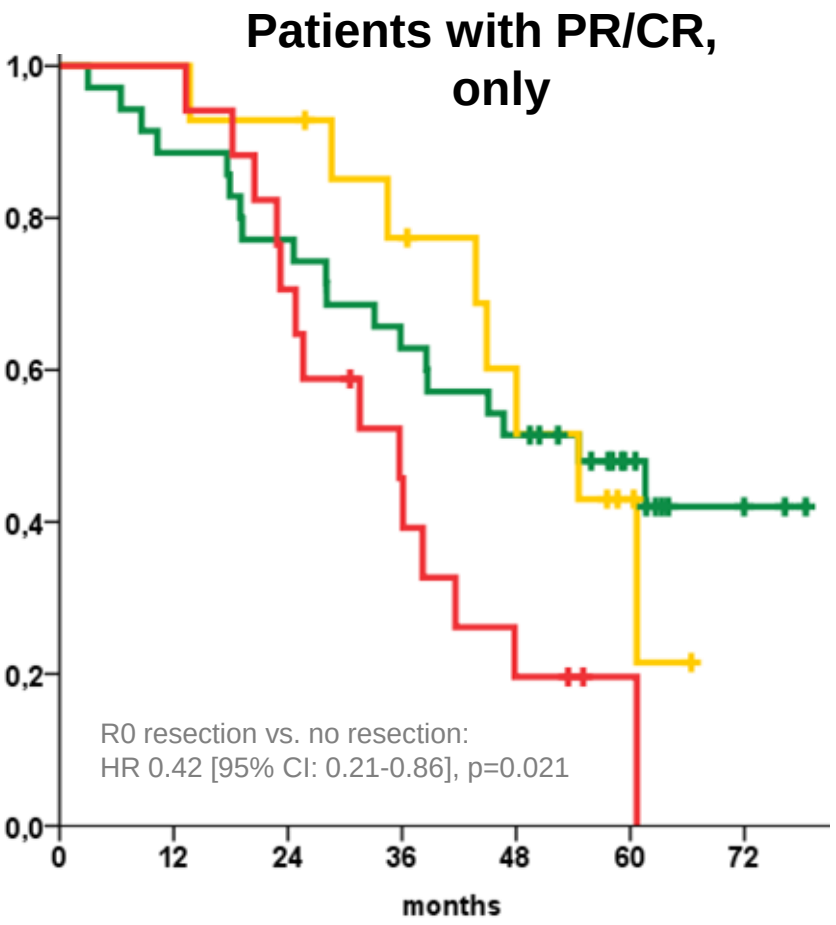
4. Do you think the patient will be cured?
   What do you communicate?
5. **Do you think the patient benefited from the combined approach?**

Survival according to metastasectomy



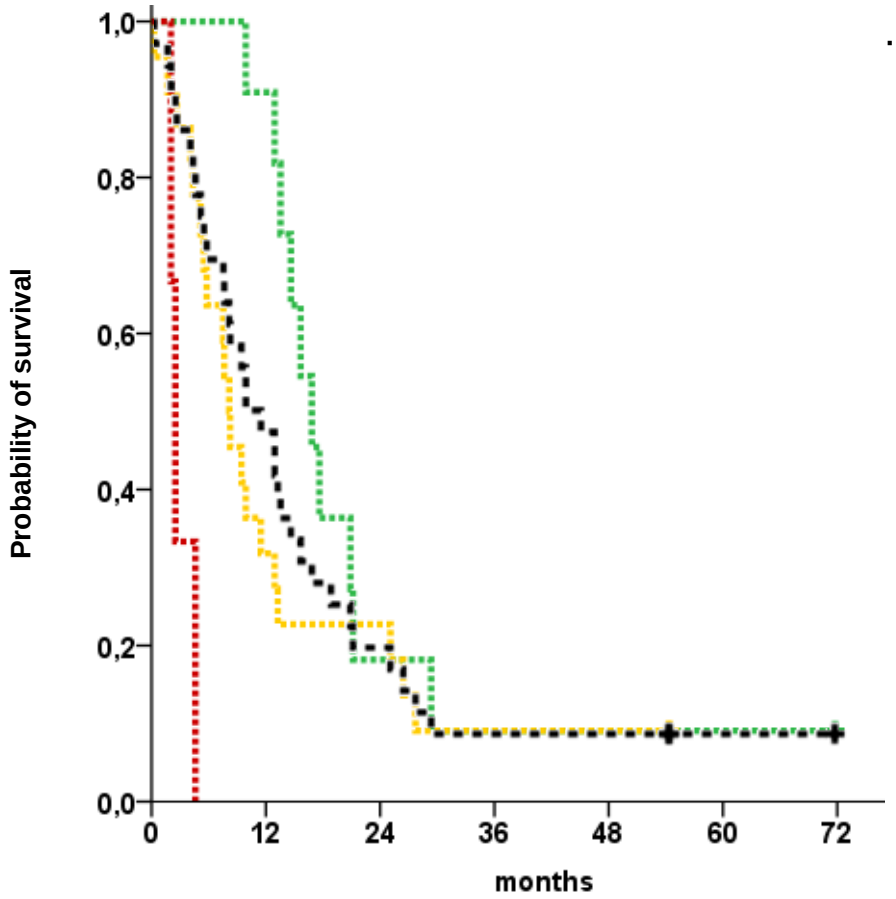


OS **R0 resected** 53.9 mo. [95% CI: 35.9-71.9]
not resected 21.9 mo. [95% CI: 17.1-26.7]
HR 0.29 [0.17-0.50], p < 0.001

PFS **R0 resected** 15.4 mo. [95% CI: 11.4-19.5]
not resected 6.9 mo. [95% CI: 5.9-8.0]
HR 0.31 [0.19-0.50]p < 0.001

Folprecht et al, Ann Oncol 2014

DFS after R0 resection



⋯ Disease free survival after resection

All patients

< 5 metastases

5-10 metastases

> 10 metastases

DFS 9.9 [95% CI: 5.8-14.0] months

Comparison between groups:
$p < 0.001$

Folprecht et al, Ann Oncol 2014

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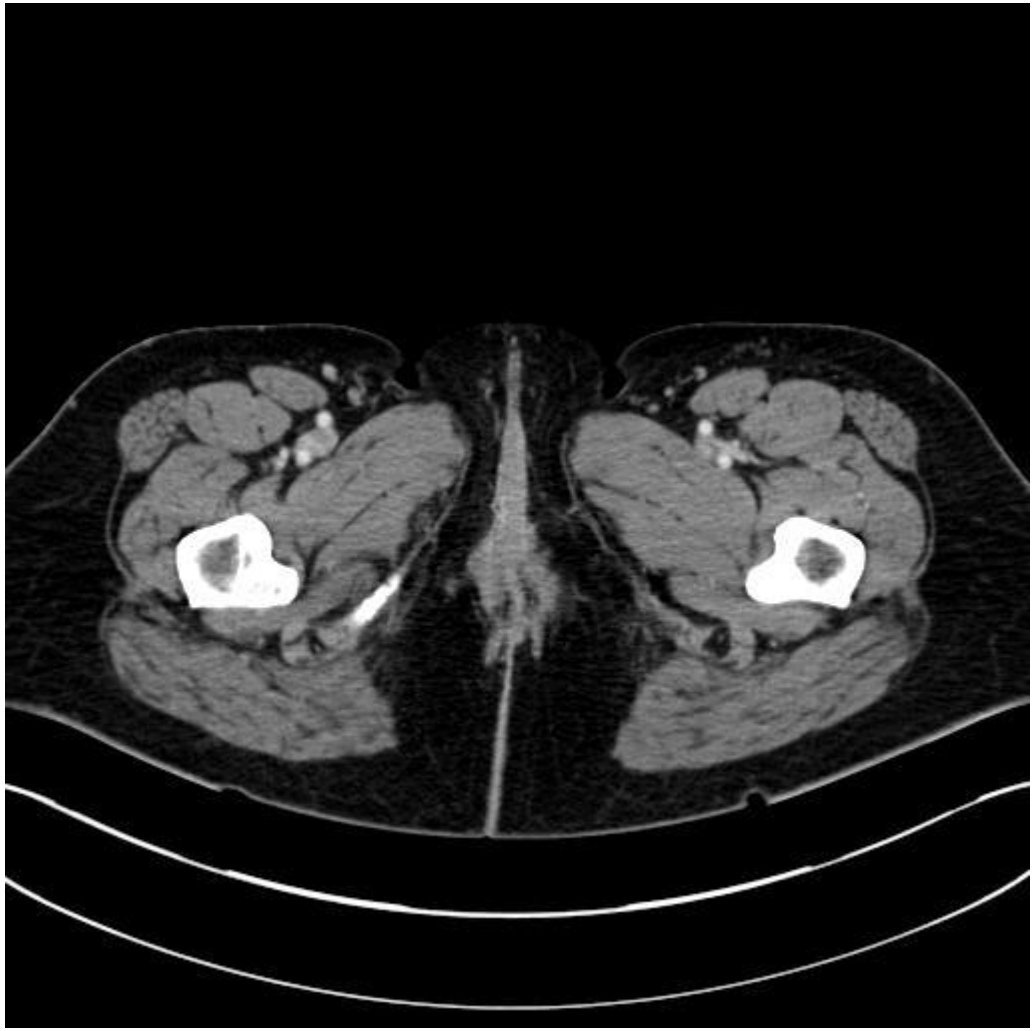
Female Patient, 54 years

Rectal Cancer

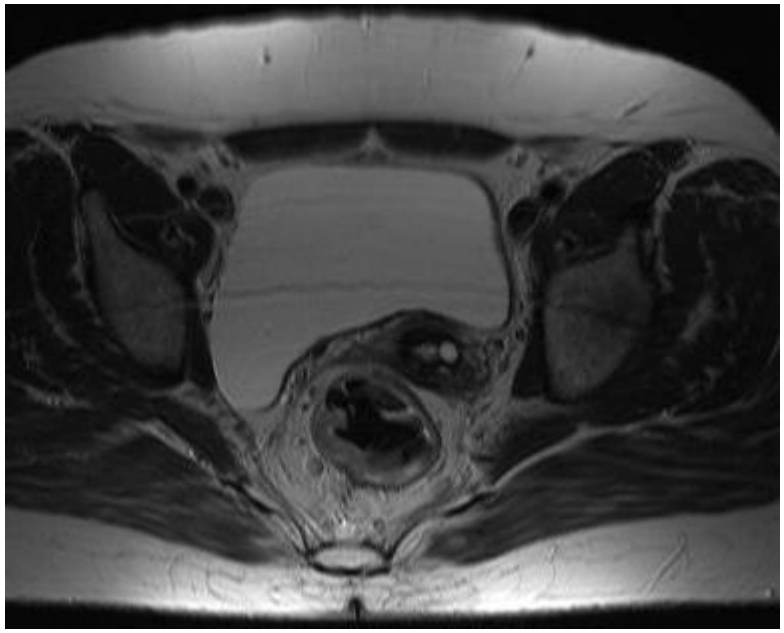
Distance to sphincter: 3 cm

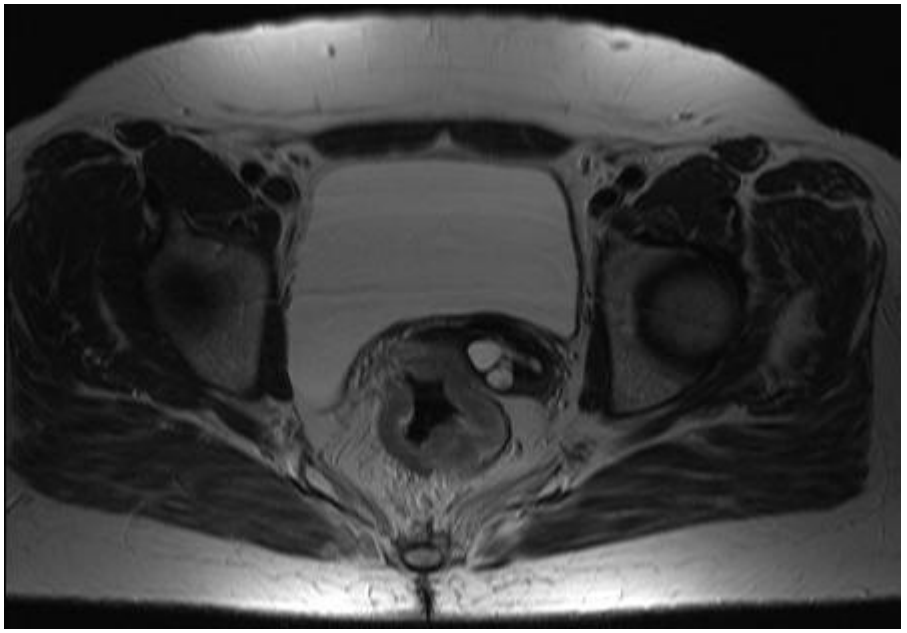


Female Patient, 54 years

Rectal Cancer

Distance to sphincter: 3 cm





Question: treatment options?

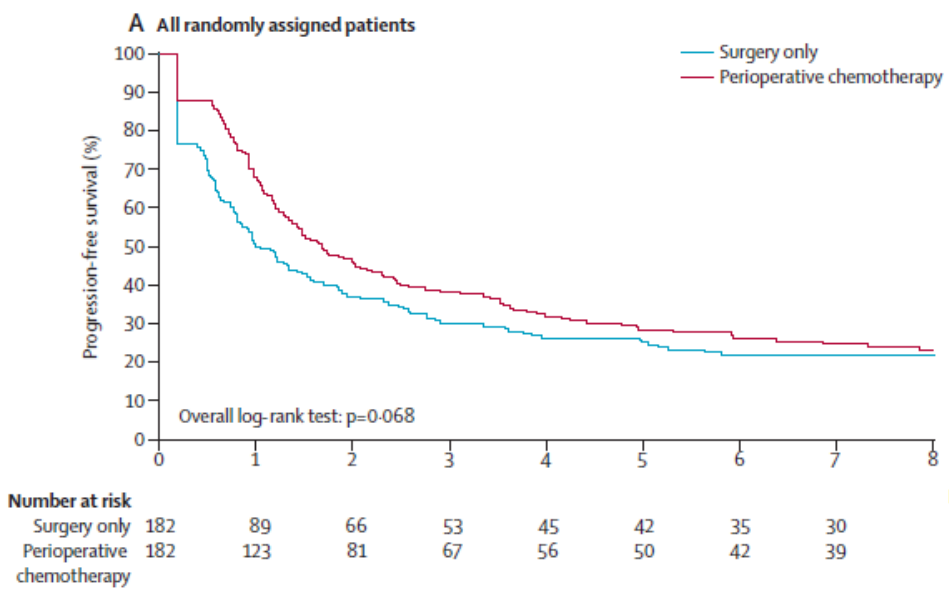
Cancer of the low rectum,T3 N+; resectable with multiple resectable liver metastases

- **Which treatment strategy?**
- **Would you recommend radiation:**
  - **5x5 → Chemo?**
  - **Chemo → 5x5?**
  - **Long course RT (which regimen)?**
- **Would you recommend chemotherapy?**
- **Would you recommend chemo-radiation?**
- **Would you recommend surgery ?**

If there were isolated/metachronous liver metastases:

EORTC 40983: Lebermet. +/- periop. FOLFOX

Progression free survival



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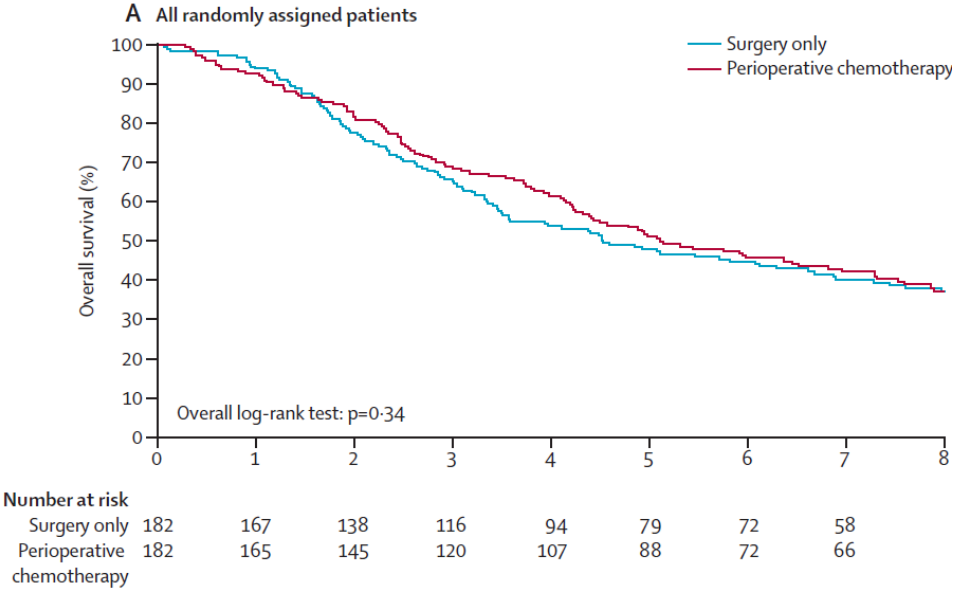
Overall survival



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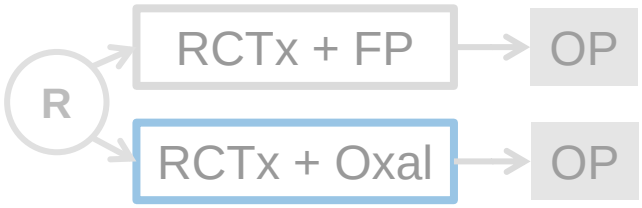
Nordlinger Lancet Oncol 2013

If there was isolated rectal cancer



Cape vs 5-FU **NSABP-R04**

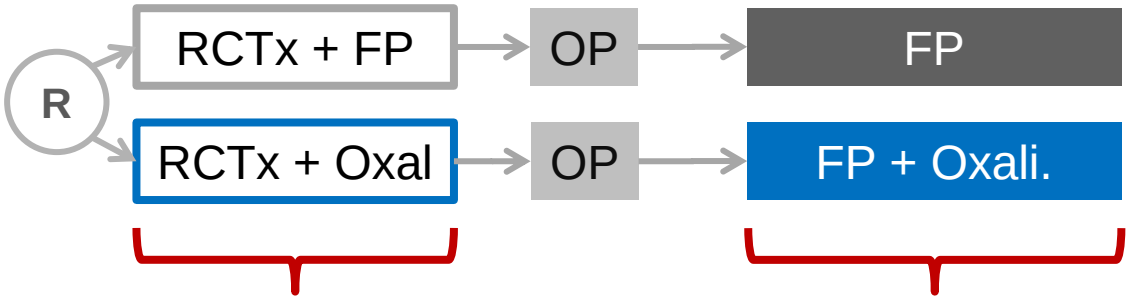
Allegra #3603, O'Conell JCO 2014,

5-FU CI **STAR-01**

Aschele JCO 2011

Cape **ACCORD 12/0405 Prodige 2**

Gerard JCO 2012



5-6 weeks **4 months**

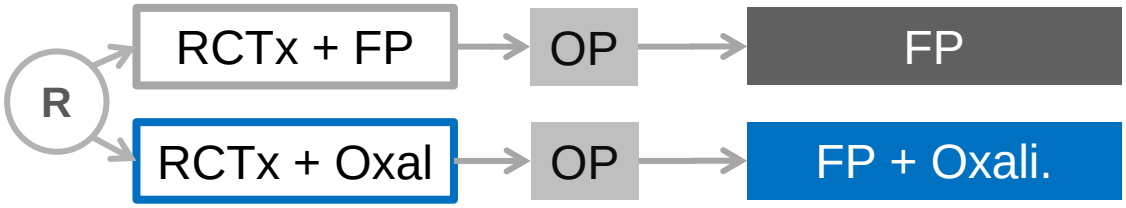
5-FU AIO/ARO/CAO04

Rödel #3500

Cape PETACC6

Schmoll #3501

Patients: cT ≥ 3 or N ≥ 1, < 12 cm

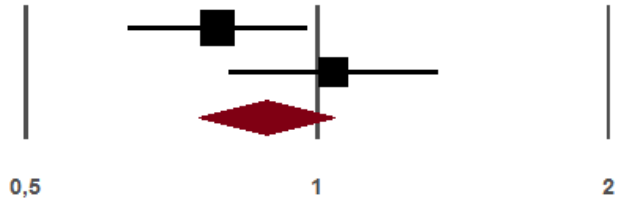


5-FU AIO/ARO/CAO04
Rödel #3500
Cape PETACC6
Schmoll #3501

Disease free survival

Study name	Comparison	Outcome	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
CAO/ARO/AIO 04	FP +/- Oxal	DFS	0,790	0,638	0,978	-2,169	0,030	57,53
PETACC 6	FP +/- Oxal	DFS	1,040	0,812	1,333	0,310	0,757	42,47
			0,888	0,755	1,044	-1,443	0,149	

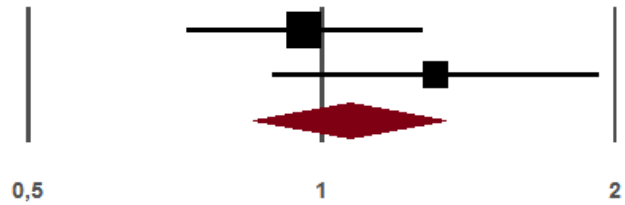
Statistics for each study



Overall survival

Study name	Comparison	Outcome	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
CAO/ARO/AIO 04	FP +/- Oxal	OS	0,960	0,726	1,270	-0,286	0,775	65,67
PETACC 6	FP +/- Oxal	OS	1,310	0,890	1,929	1,367	0,171	34,33
			1,068	0,851	1,340	0,569	0,569	

Statistics for each study



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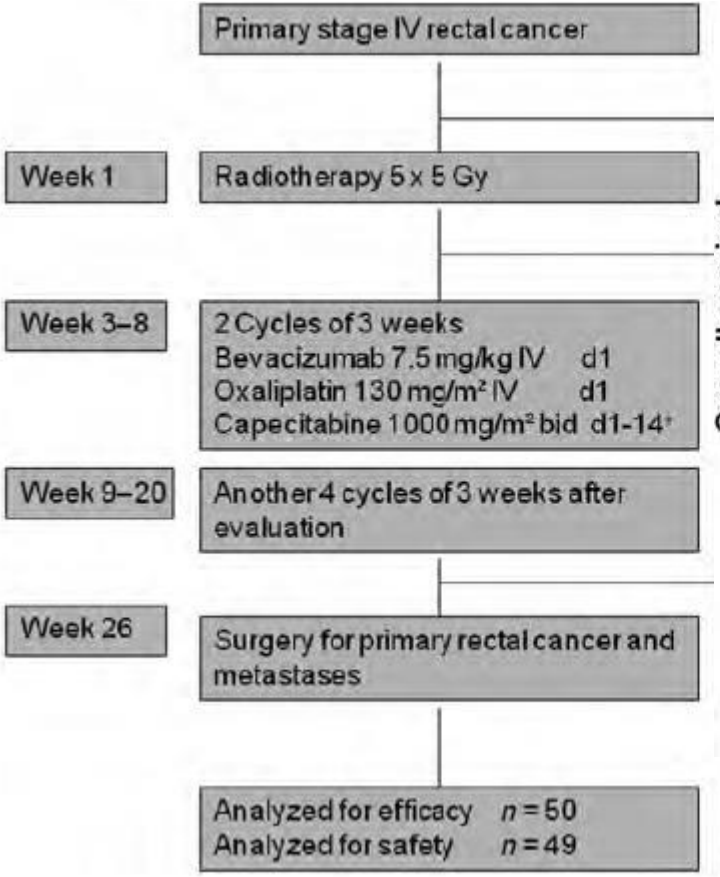
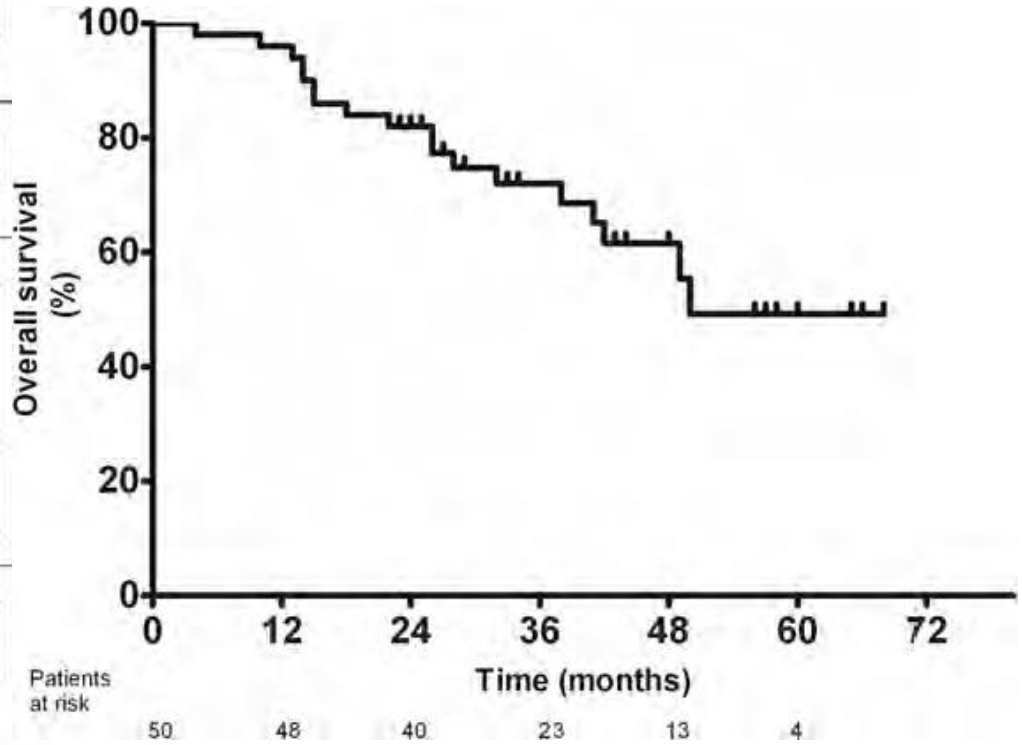
Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer†

T. H. van Dijk[1]*, K. Tamas[2], J. C. Beukema[3], G. L. Beets[4], A. J. Gelderblom[5], K. P. de Jong[6], I. D. Nagtegaal[7], H. J. Rutten[8], C. J. van de Velde[9], T. Wiggers[1], G. A. Hospers[2] & K. Havenga[1]





*Abbreviations: bid, two times daily; d, day; IV, intravenous.

Cancer of the rectum and synchronous metastases

No randomized trials

Only retrospective series

- A minority of patients with rectal cancer

- Patients undergoing simultaneous resections had limited metastatic disease

Treatment options depend on site and extent of primary tumor

Upper third or T2 rectal cancer

No need for radiation

Treatment strategy similar to colon cancer

Locally advanced or low rectal cancer

Objectives:

1. **Control of rectal primary: integration of RT or CRT in the treatment strategy.**
2. **Control of liver metastases and avoid progression during treatment of primary.**

Limitations:

Chemoradiation

- Provides suboptimal control of metastases during the 5 weeks of treatment.

- Determines the date of surgery, 6 to 8 weeks after the end of radiation.

- 5X5 Gy an alternative.

– **Chemotherapy alone: suboptimal control of rectal primary.**

Sequence of treatment in colorectal cancer with synchronous metastases

Gunnar Folprecht · Bernard Nordlinger