

35.Schweizerische Koloproktologie-Tagung

# Treatment strategy of metastatic rectal cancer

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University hospital of Geneva



Bern, January 18th, 2014

## Colorectal cancer is the third most frequent cancer in the western world

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- 25% of patients have liver metastases at the time of diagnosis
- 25% will develop liver metastases during the course of the disease
- Two thirds of patients with liver metastases will die of their liver metastases

## Only 15 years ago...

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A patient suffering from a colorectal cancer with synchronous liver metastases

would have a resection of the primary tumour followed by chemotherapy with 5-Fu / leucovorine...

and in case of good response (16%) a resection of the liver metastases

# What is new?

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- New chemotherapeutic agents with a high response rate
- Effective pelvic radiochemotherapy
- Better MRI, CT scan and echoendoscopy
- Precise rectal surgery with mesorectal excision
- Safe R0 liver surgery
- Portal vein embolisation and radiofrequency ablation

However, with all these new tools .. How to use them and to choose the best strategy for a given patient?

# Three approaches may be applied

- The classical staged
- The simultaneous approach....but...
- The liver-first approach or reverse strategy

We want to increase the number of patients treated with a curative intent

→ the aim is the long-term survival!

## Primary first when...

- Threat of large bowel occlusion
- The patient is unable to withstand a strong chemotherapy (side effects++)
- A large rectal tumour with little metastatic disease in the liver
- A probably perforated primary (e.g. fistula into the small bowel) with fever

54 year-old man

T4 symptomatic rectal cancer with small amount of liver cancer

→ Best treated by pelvic radiotherapy followed by rectal surgery



# New thinking

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- For the 25% of the patients who have synchronous liver metastases → systemic disease at diagnosis
- Complete synchronous resection (primary and liver metastases rarely possible)
- **Goat-cabbage-wolf situation:**
  - While taking care of the **colon** the liver disease will progress
  - neo-adjuvant **rectal** radiochemotherapy is ineffective on the liver
  - Optimal **liver** chemotherapy too radio-sensitizing



Our approach:

liver first ...

Our approach:

Liver-oriented chemotherapy- first

Team work!

# Liver (oriented chemo-) first For whom?

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1. No occlusion
2. Fit enough to support side effects of chemotherapy
3. R0 resection(s) at all sites whatever the number of surgical procedures used to reach the goal

# How did this approach become ethically possible ?

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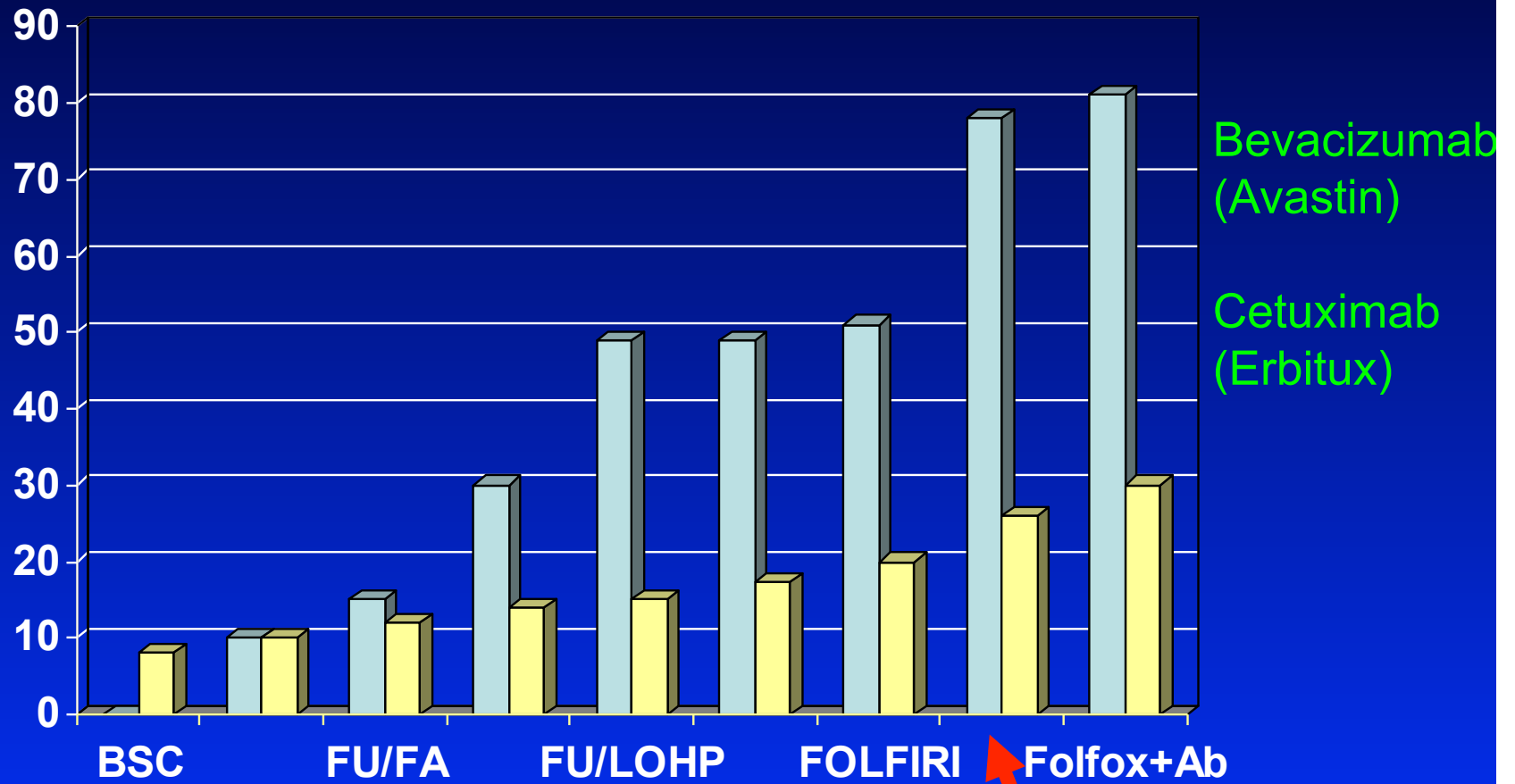
New agents used in new chemotherapy combinations

→ response rate from 16% to 80%

→ liver surgery has become a low risk procedure

Only possible with new chemotherapeutic agents!

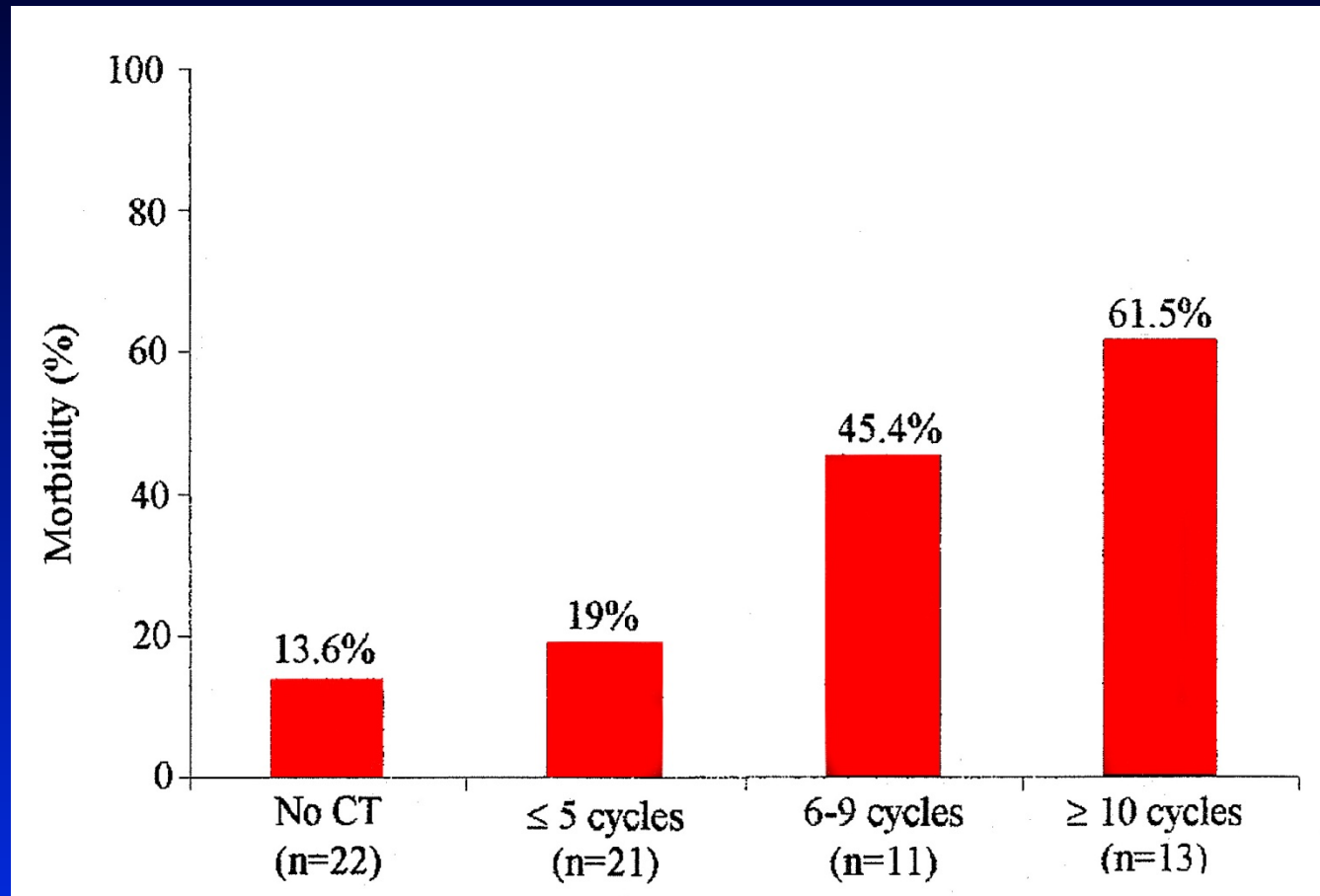
## First Line Chemotherapy in Metastatic CRC: evolution of response rate and median survival



Seium Y et al. Ann  
Oncology 2005; 16: 762-766

Oxaliplatin and  
Irinotecan

# Influence of preoperative chemotherapy on the risk associated to major hepatectomy for CRLM



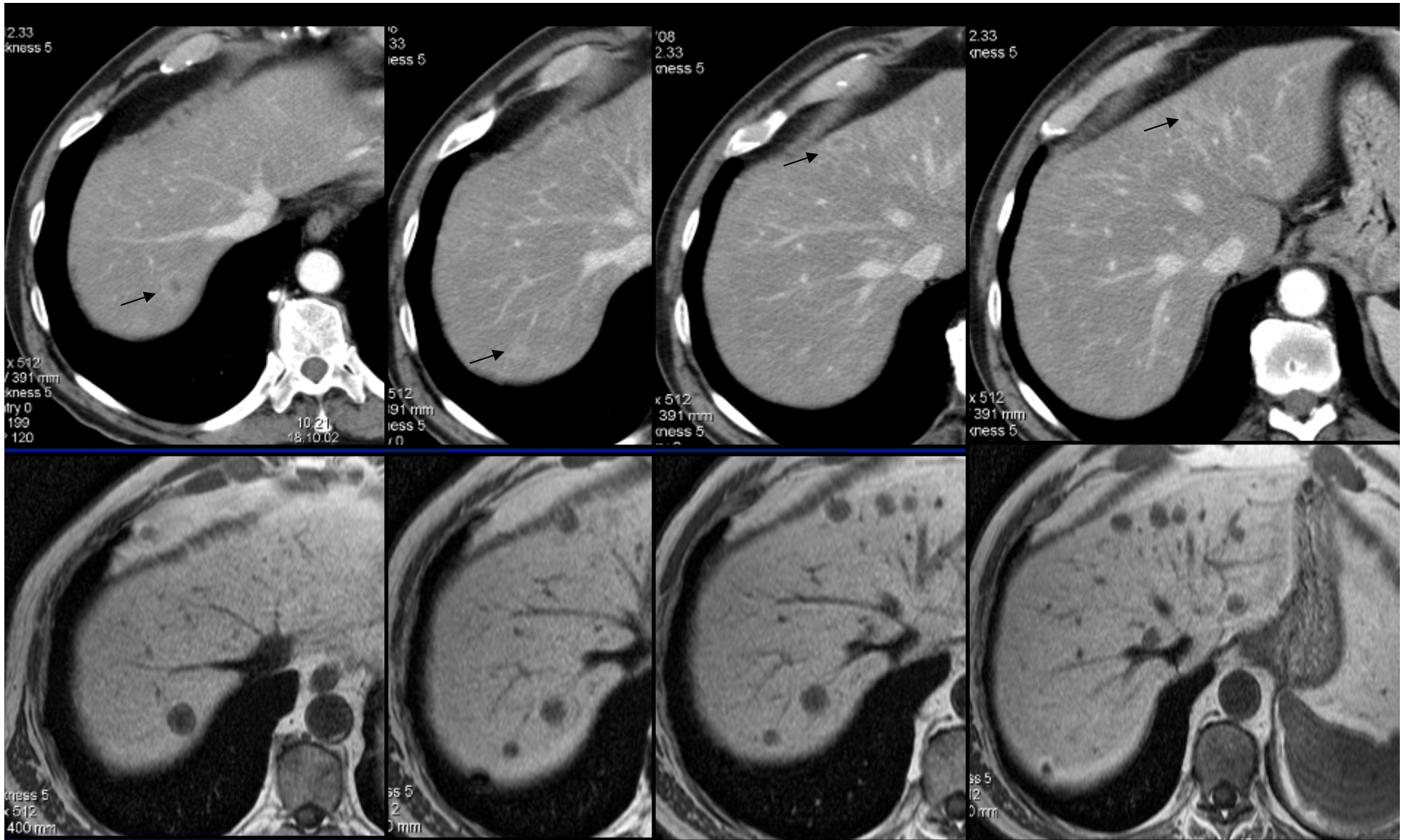
Influence of the number of cycles of chemotherapy on the percentage of postoperative morbidity

Karoui M. et al. Ann Surg 2006; 243: 1-7

# Implications for clinical practice I

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- Patients should be evaluated by experienced colorectal and liver surgeons and oncologists before starting therapy to avoid unduly prolonged treatment.
- Radiological imaging of the highest quality should be obtained at the beginning and at the latest after 3 cycles of chemo, as well as the CEA levels.



With this level of sophistication, traditional CT imaging is insufficient!

After chemotherapy rely on MRI with hepato-specific contrast



# Implications for clinical practice II

- Go to surgery as soon as the CRLM are resectable with a decrease of the CEA (usually 3 cycles of chemo are enough!).
- Do not give Avastin in the last 6 weeks before surgery (cave: perforation or poor cicatrization)

Mrs Y.R. 38 year-old, low rectal cancer T3 N1, CEA 525, one pulmonary nodule: CT 30.09.2003



OCX chemo: CT after OCX



01/2004 liver first → pelvic Rxth → LAR → Lung surgery

Last CT scan: she died of recurrence after 7 years  
....after 7 surgical procedures....

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# The « ideal concept » of the reverse strategy

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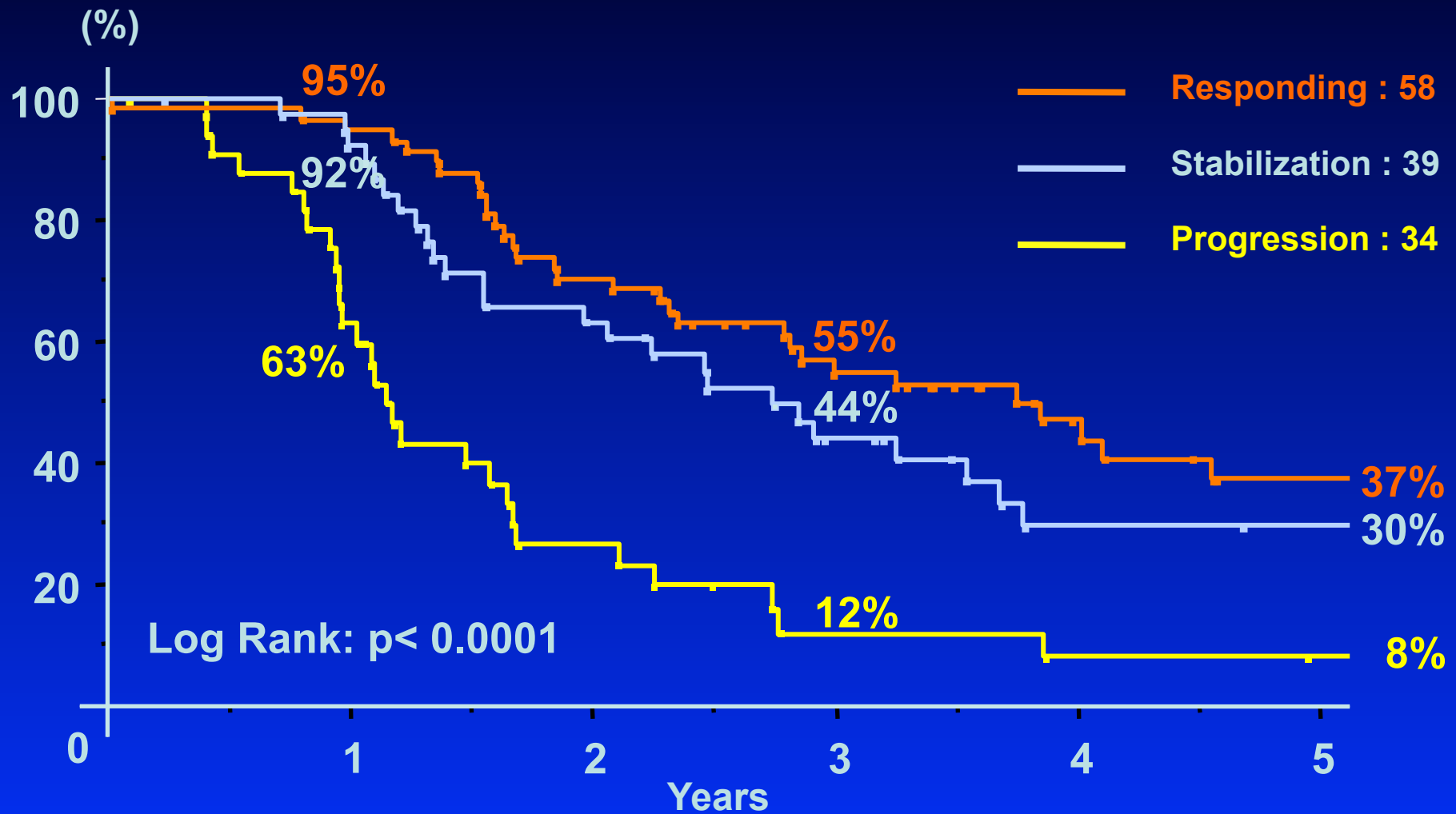
- Very efficient neoadjuvant chemotherapy  
→ **short and strong!**
- Followed 3 weeks later by a R0 resection of the liver metastases
- And 4 weeks later by colorectal surgery or first pelvic radiochemotherapy when needed
- Adjuvant chemotherapy

# Chemotherapy first in resectable disease...

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- Is it just a waste of time ?
- Are we decreasing the chance for a patient with resectable disease to be cured?

# Overall survival after resection of multiple liver metastases ( $\geq 4$ ) according to chemotherapy response



Update: Adam R et al. Ann Surg 2004; 240:644-658

Pathological response to preoperative chemotherapy: **a new outcome end point** after resection of hepatic colorectal metastases.

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- 305 patients
- 25 with complete histological response (8.1%)
- **5-year overall survival 75%**

Blazer DG et al., JCO 2008

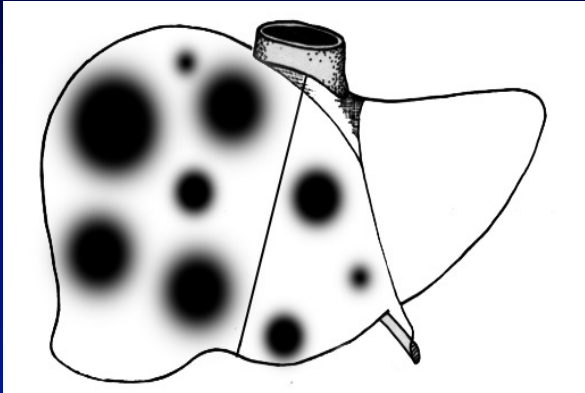


Liver surgery has become a low  
risk procedure...

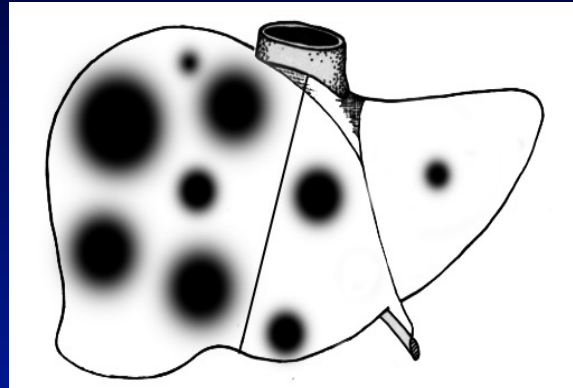
at some conditions!

# Contribution of « pro-generative » strategies

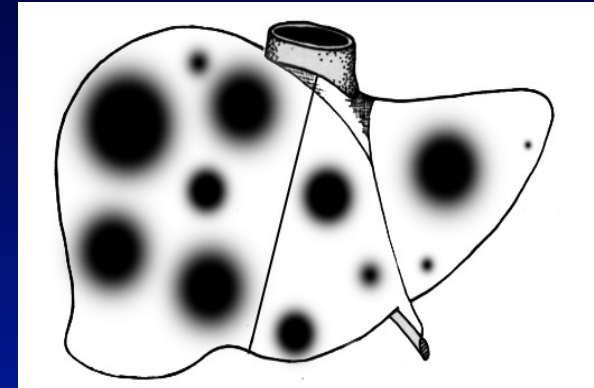
Multi Unilobar



Multi Bilobar



Multi Bilobar



Remnant Liver < 30% ≤ 3 nod. ≤ 30 mm

> 3 nod > 30 mm

chemo ↓ +++ < 40%

Portal Embolization

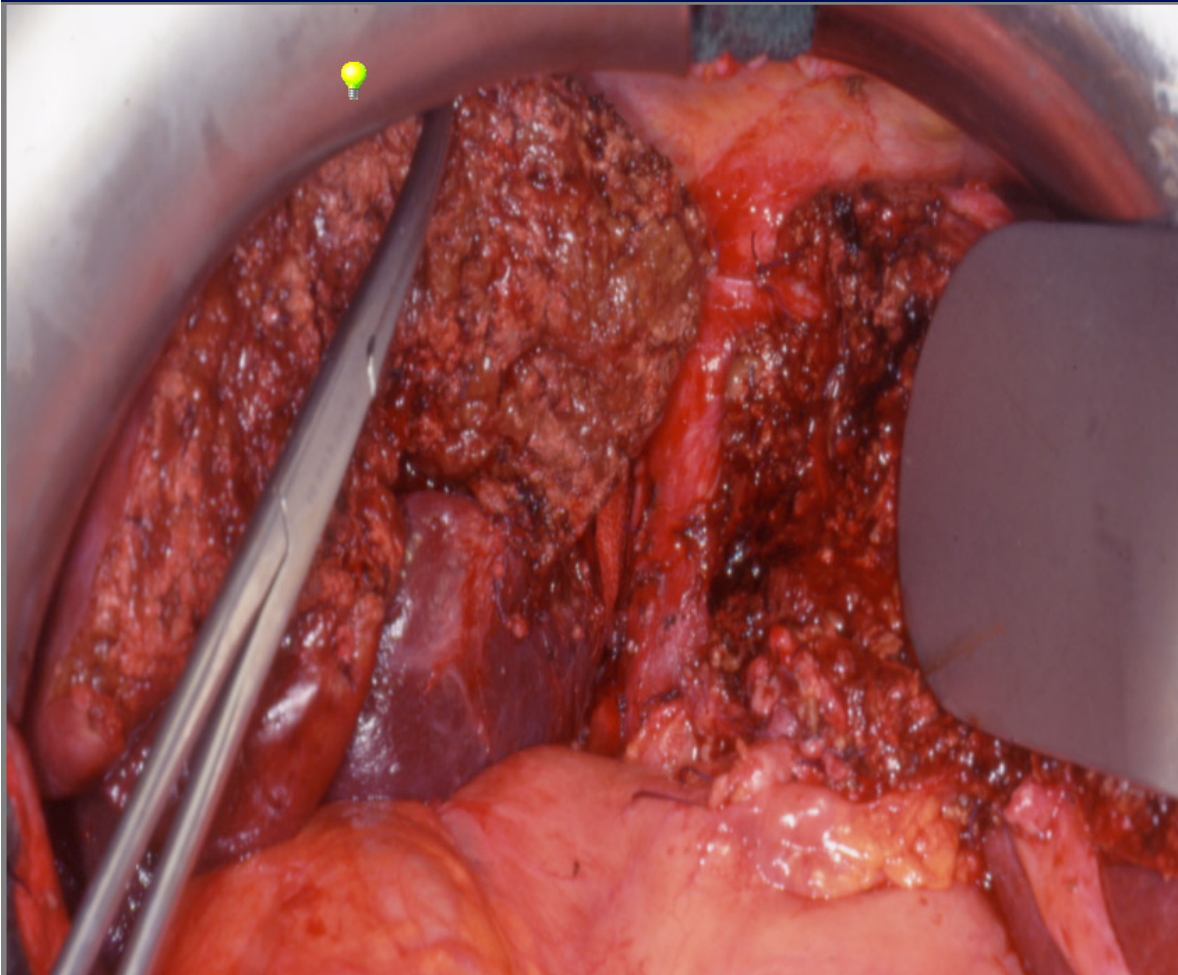
Portal embolization +  
Percutaneous RxF

2-Stage Hepatectomy

By courtesy of René Adam

# Use of transplantation techniques in liver resections for cancer

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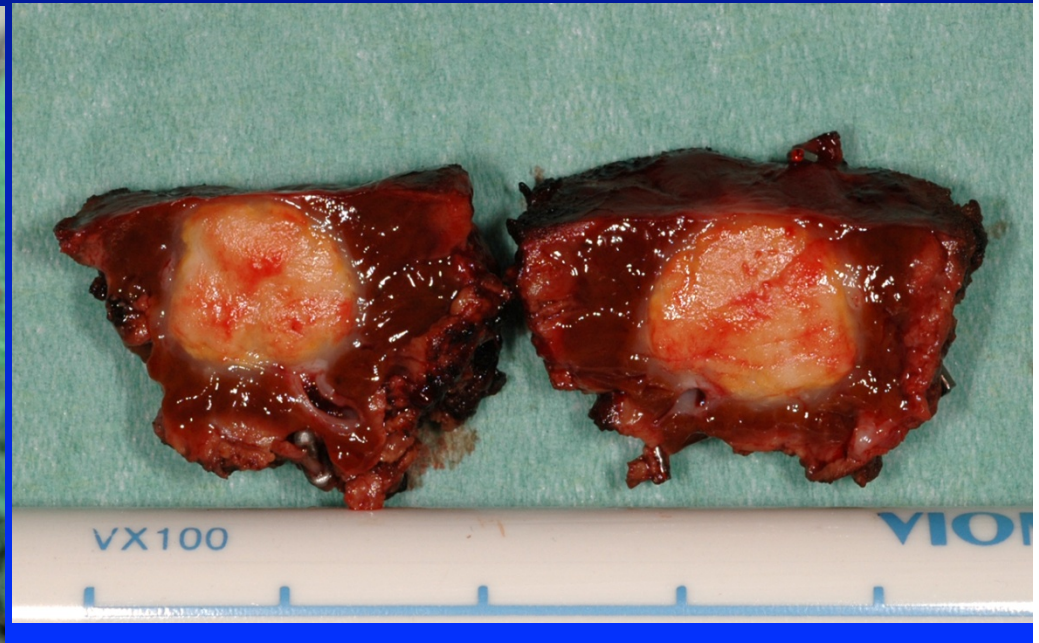
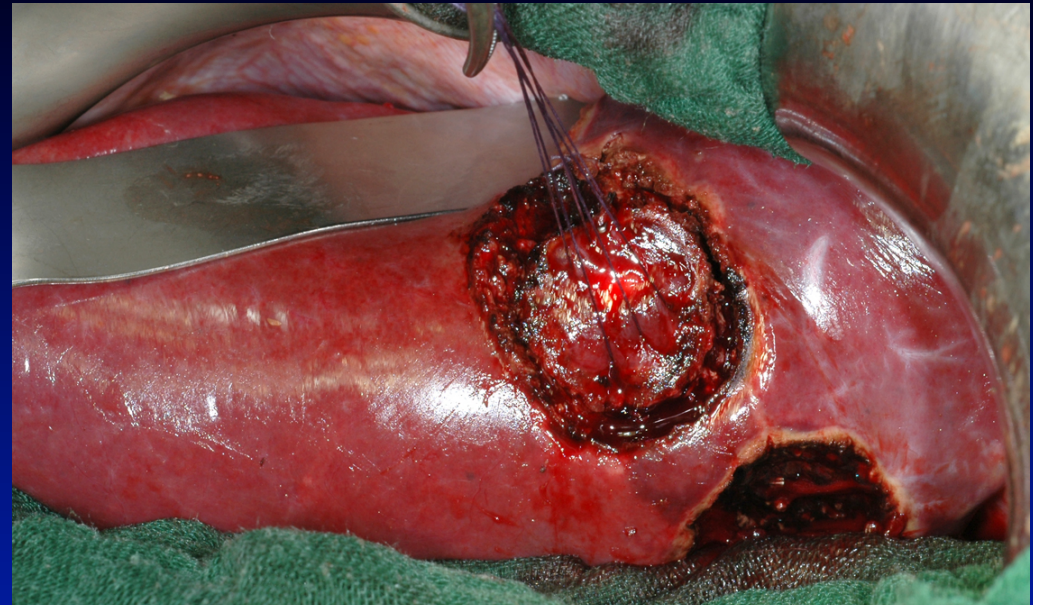
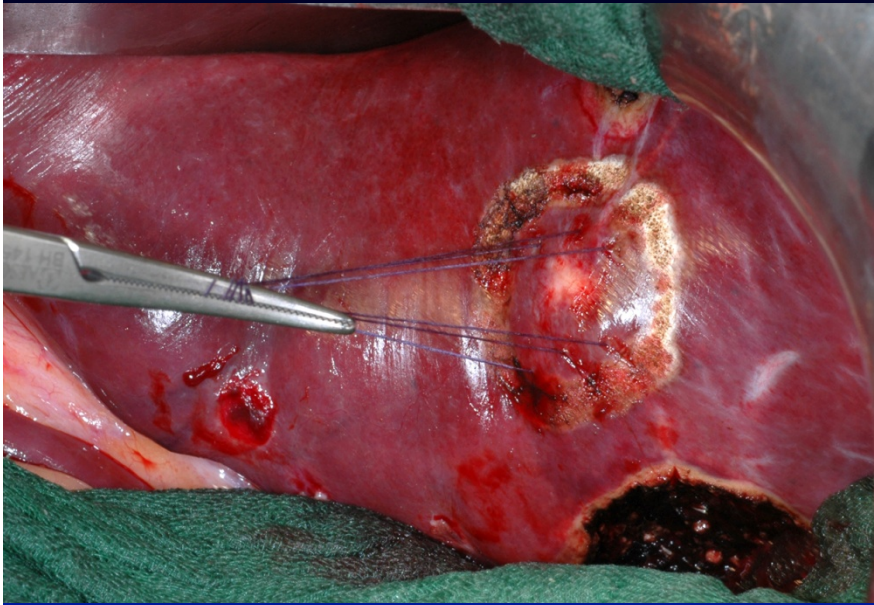
- In situ split



- Reverse in situ split for extended right resections, without liver clamping nor blood transfusions

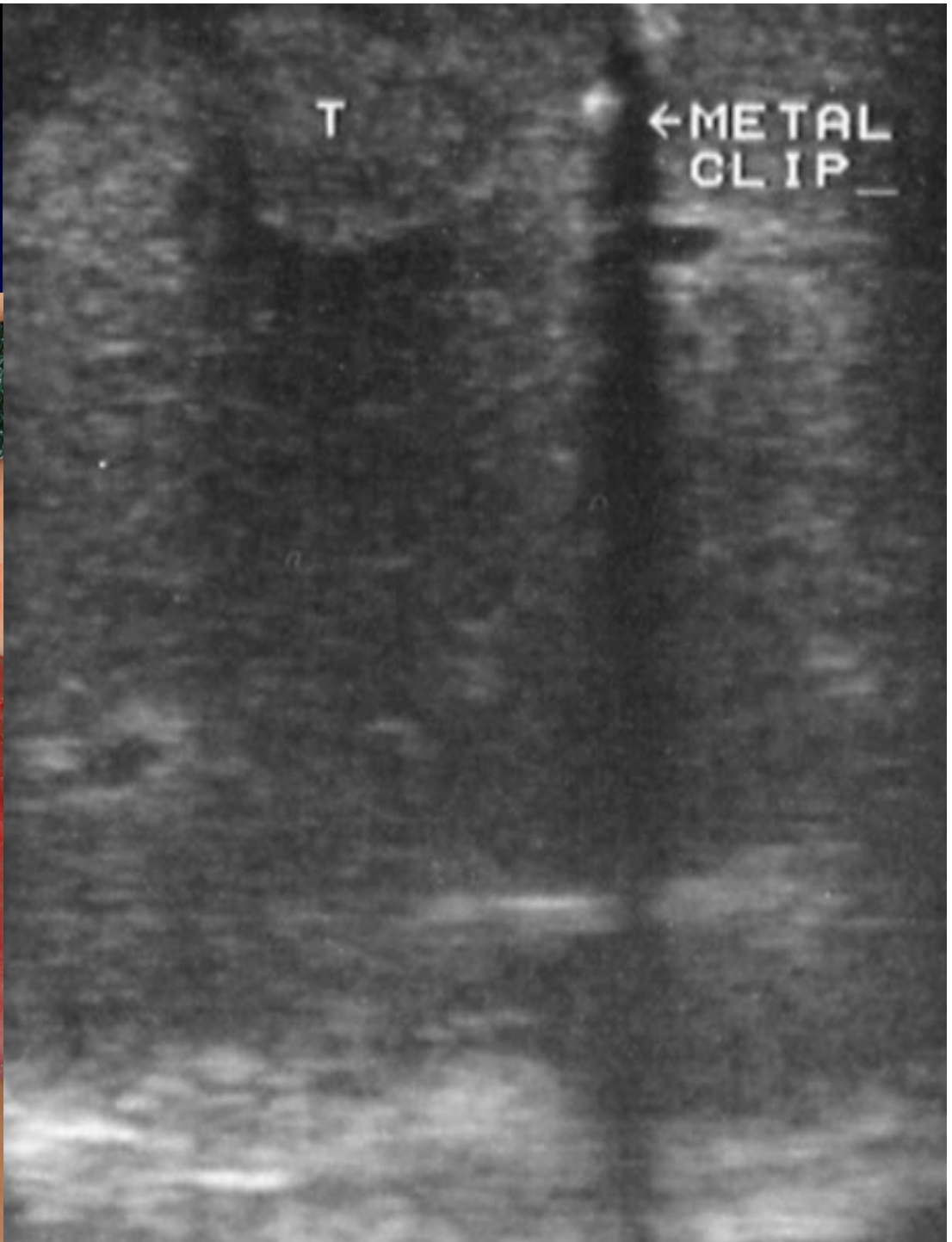
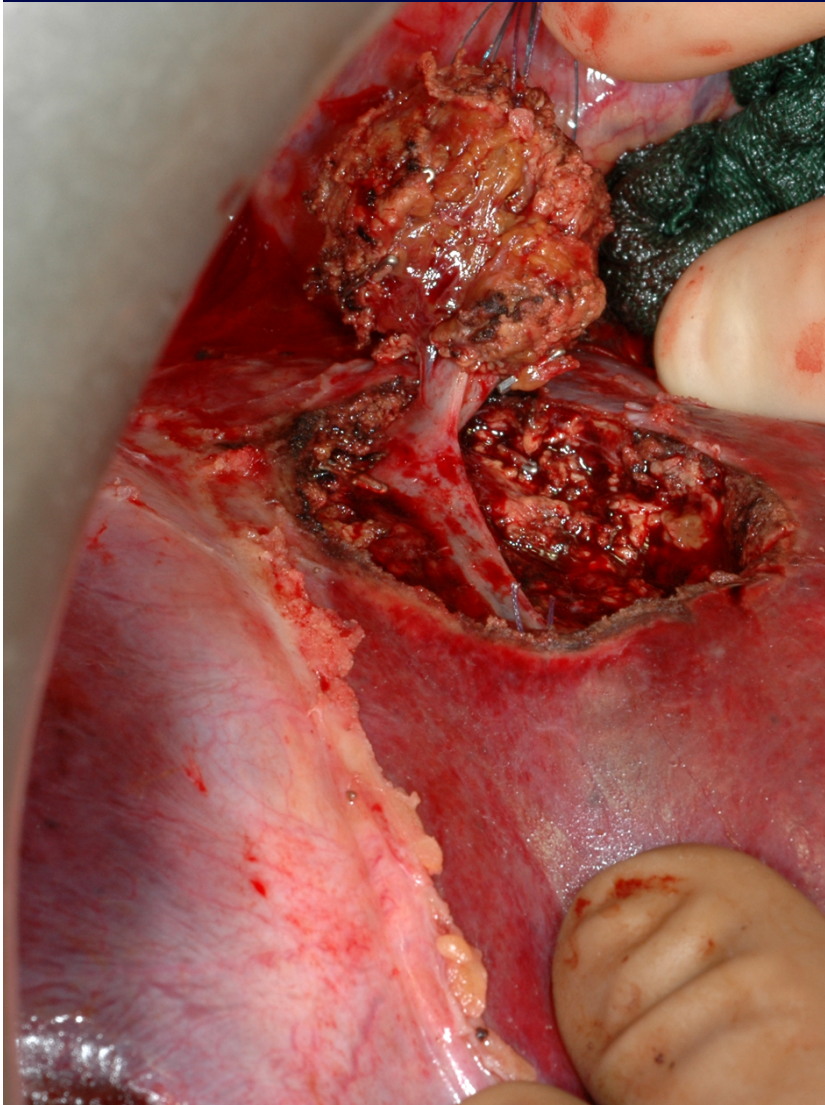


# Conservative radical metastasectomy: the sling technique





# Depth control by US



# Liver surgery: a low risk procedure

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Since 1991, liver surgery at the University Hospitals of Geneva (prospective database).

8 deaths out of 1012 hepatectomies

→ mortality of 0,8%

450 hepatectomies were major (45%)

65% of hepatectomies without blood transfusion

Kooby DA et al. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. *Ann Surg* 2003; 237: 860-69

# Rationale of the reverse approach

Colorectal surgery in real life

# Morbidity and anastomotic leakage of colorectal surgery

Authors	Journal and year of p.	Patients	Mortality	Morbidity	Anastomotic leak
G.Mantion Y. Panis	Survey AFC 2003	997 Low rectum = 238	3.7% 2.5%	38.3% 43%	5% colon 11% rectum
Matthiessen P.	Colorectal disease 2004	432 rectum	2.1%	?	12%
Lipska MG	ANZ J Surg 2006	541 colon and rectum	3.7%	?	6.5%
Chiappa A	J Surg Oncol 2006	264 rectum	0%	39.4%	12%
Tran CL	Am J Surg 2006	48 patients rectum	0%	52%	17% abcess and fistula



## Mortality After Colorectal Cancer Surgery

### *A French Survey of More Than 84,000 Patients*

*Yves Panis, MD, PhD,\* Léon Maggiori, MD,\* Gilbert Caranhac,† Frederic Bretagnol, MD, PhD,\* and Eric Vicaut, MD, PhD‡*

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**Objectives:** This study aimed to identify risk factors of postoperative 30-day mortality (POM) after colorectal cancer resection.

**Summary:** Meta-analyses have failed to demonstrate any significant benefit of laparoscopy in terms of postoperative mortality. This could be explained by the lack of a large sample size.

**Methods:** All patients who underwent colorectal resection for cancer between 2006 and 2008 in France were included. Data were extracted from the French National Health Service Database. A multivariate analysis evaluating risk factors for POM was performed including the following factors: age, gender, tumor location, associated comorbidities, emergency surgery, synchronous liver metastasis, malnutrition, and surgical approach.

results for rectal cancer.<sup>6,7</sup> Concerning rectal cancer, data remain scarce, but at least 2 American and European randomized studies are currently in progress (COST II and COLOR II).

Although meta-analyses have confirmed the benefit observed in postoperative outcome, they have failed to demonstrate any significant benefit of laparoscopy in terms of postoperative mortality.<sup>8,9</sup> This could be explained by the lack of a large sample size. However, the largest randomized studies all showed similar results: a trend toward a lower mortality rate was more apparent after laparoscopy than after laparotomy.<sup>1,2,10,11</sup>

A low percentage of patients with colorectal cancer are currently operated on through laparoscopy. In a recent study that included

**TABLE 2.** Uni- and Multivariate Analysis of Predictive Factors for Postoperative Mortality for Patients Undergoing Colorectal Resection for Cancer in France Between 2006 and 2008

	Postoperative Death* (n = 4051)	No Postoperative Death* (n = 80,473)	Univariate P Value	Multivariate†	
				P Value	OR (95% CI)
Gender					
Male	2274 (5)	44,005 (95)	0.070	NS	–
Female	1777 (5)	36,468 (95)			
Age					
≥70 yrs	3420 (7)	45,250 (93)	<0.001	<0.001	3.28 (3.00–3.59)
<70 yrs	631 (2)	35,223 (98)			
Medical history					
Vascular comorbidity	1747 (12)	12,505 (88)	<0.001	<0.001	2.66 (2.48–2.85)
Respiratory comorbidity	1428 (14)	8713 (86)	<0.001	<0.001	3.13 (2.91–3.37)
Neurologic comorbidity	196 (10)	1725 (90)	<0.001	<0.001	1.78 (1.51–2.09)
Diabetes melitus	606 (6)	8906 (94)	<0.001	NS	–
Preoperative malnutrition					
Yes	391 (9)	4059 (91)	<0.001	<0.001	1.33 (1.19–1.50)
No	3660 (5)	76,414 (95)			
Tumor localization					
Colon	3228 (5)	59,581 (95)	<0.001	NS	–
Rectum	823 (4)	20,892 (96)			
Synchronous liver metastasis					
Yes	848 (10)	7791 (90)	<0.001	<0.001	2.63 (2.41–2.86)
No	3203 (4)	72,682 (96)			
Emergency surgery					
Yes	1092 (13)	7542 (87)	<0.001	<0.001	2.68 (2.48–2.90)
No	2959 (4)	72,931 (96)			
Surgical approach					
Laparoscopy	527 (2)	21,832 (98)	<0.001	<0.001	0.59 (0.54–0.65)
Laparotomy	3524 (6)	58,641 (94)			

\*Number of cases (percent of cases).

†Nonsignificative variables after logistic regression are marked as NS.

# Preoperative versus postoperative chemoradiotherapy for rectal cancer

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843 patients randomly assigned to receive:

preoperative RxChemotherapy

n = 421 patients

Postoperative complications 36%

Received full dose of radiotherapy

N = 380 patients (92%)

Received full dose of chemotherapy

N = 369 patients (**89%**)

Local relapse 6%

postoperative RxChemotherapy

n = 402 patients

Postoperative complications 34%

Received full dose of radiotherapy

N = 206 patients (54%)

Received full dose of chemotherapy

N = 193 patients (**50%**)

Local relapse 13%

# Neoadjuvant chemotherapy

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- Increases the resectability rate
- Allows to spare liver parenchyma
- May select responders versus non responders
- Probably (?) increases the long-term survival after CRLM resection

Provided that the patient can have it!

Illustration of the reverse approach  
by our first case

# Reverse management of CRLM

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Case 1 Mrs R. 54 year-old

Consultation for diarrhea

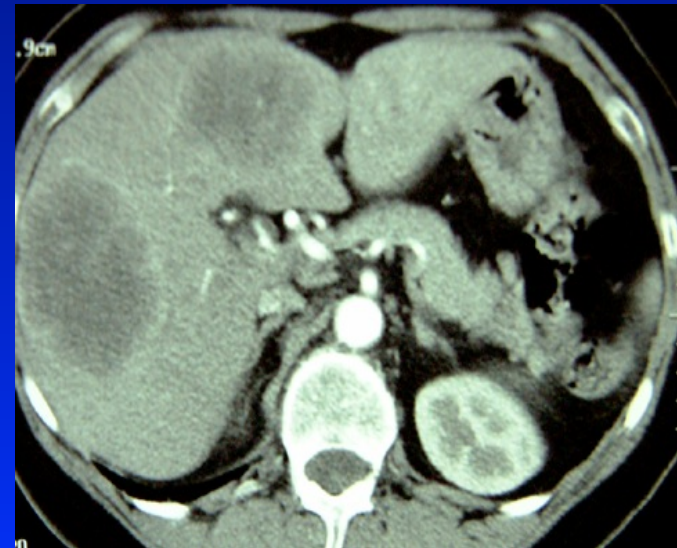
- Colonoscopy: adenocarcinoma at 8 cm from the anal margin, (T3 echoendoscopy)
- CEA 247
- CTscan 07.12.1999: 3 liver metastases
- CRS: 4

# Reverse management of CRLM

Case 1 Mrs R.  
54 year-old  
before  
chemotherapy

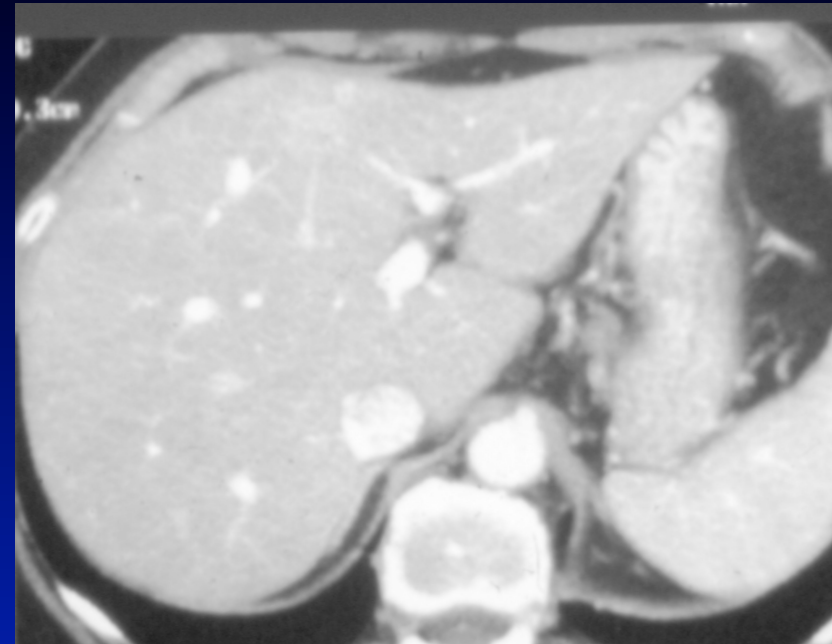
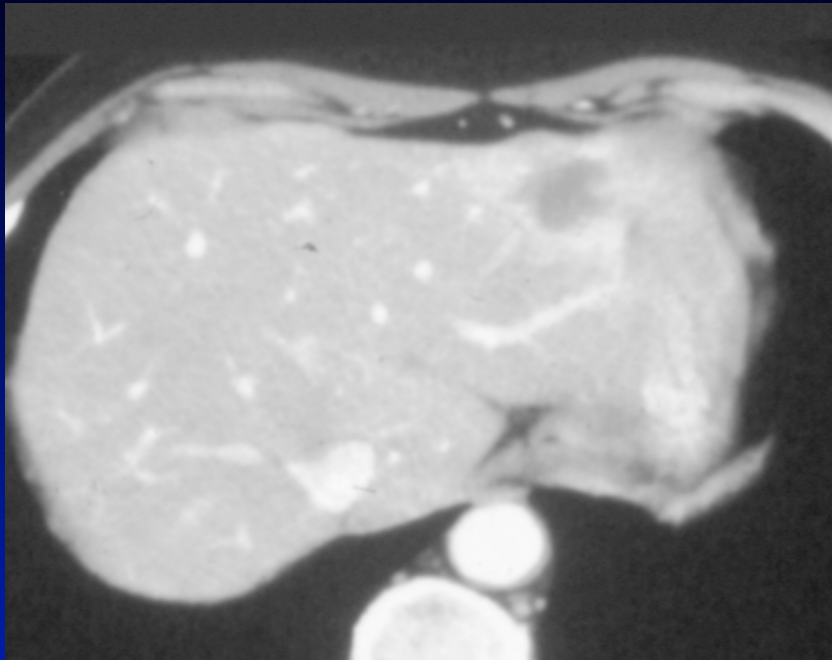


CT scan  
07.12.1999

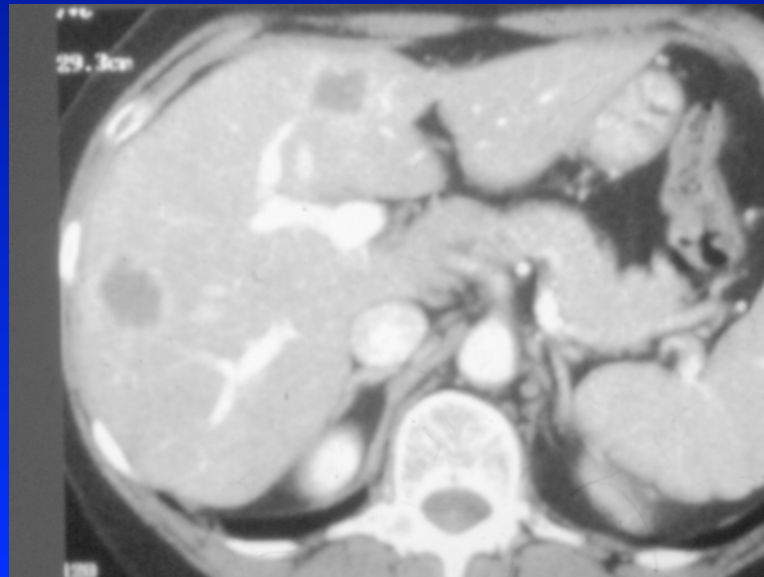




# Reverse management of CRLM



Case 1 Mrs R.  
54 year-old



After OCFL  
chemotherapy

- Almost no tumour,
- No rectal symptoms



# Reverse management of CRLM

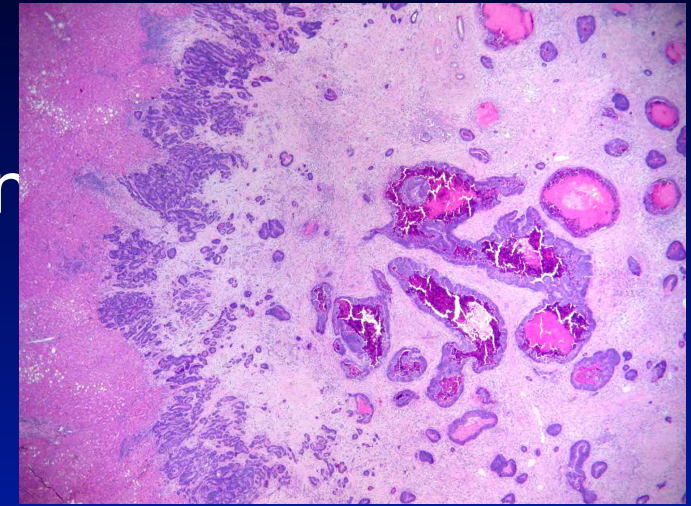
Case 1 Mrs R. 54 year-old

- → OCFL 4 months
- 16.05.2000 left lobectomy, resection of segment IVa, atypical resection segments VI-VII
- Pelvic radiotherapy from 17.07 to 4.08 (39Gy)
- Low anterior abdominal resection 28.09.2000

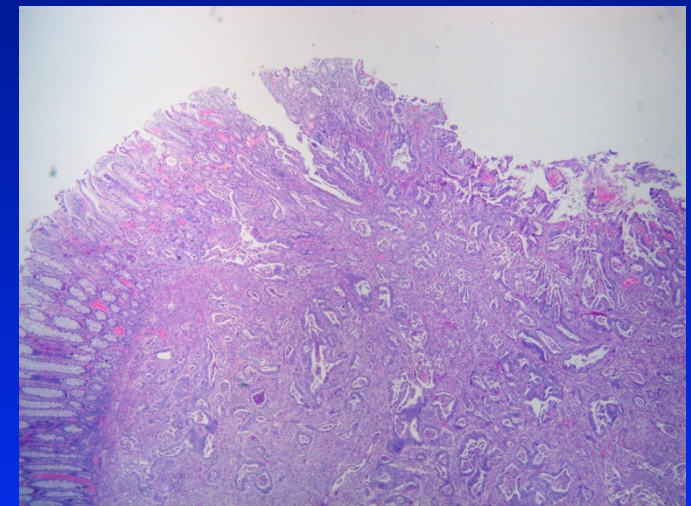
# Histology

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**Liver metastases**— mostly scar tissue with viable tumor cells in the periphery (1/3)



**Rectum** –Ulcerated scar lesion with microscopic island of residual adenocarcinoma and one focus of perineural invasion



**Follow up**

**No evidence of recurrence after > 13 years**

## Results of reverse strategy using chemotherapy first, liver resection second primary tumor resection third

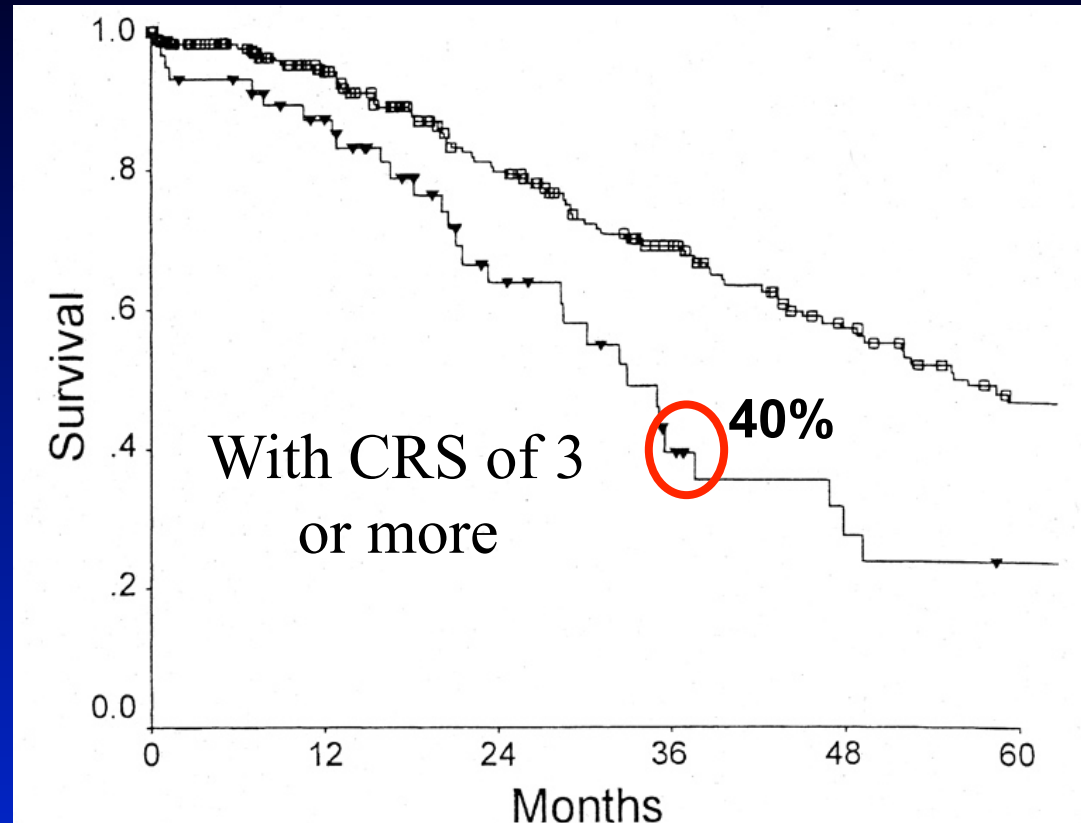
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- 58 patients with non obstructive CRC, 50% rectal tumor, 50% initially non resectable
- Median number of CRM was 6 (mean 7.2) (2-21)
- Median size 6 cm (1-14)
- Bilobar in 70%, 11% had lung metastases
- Fong clinical risk score 3 to 5 (mean 3.7)

# Clinical risk score = a scale with 5 criteria

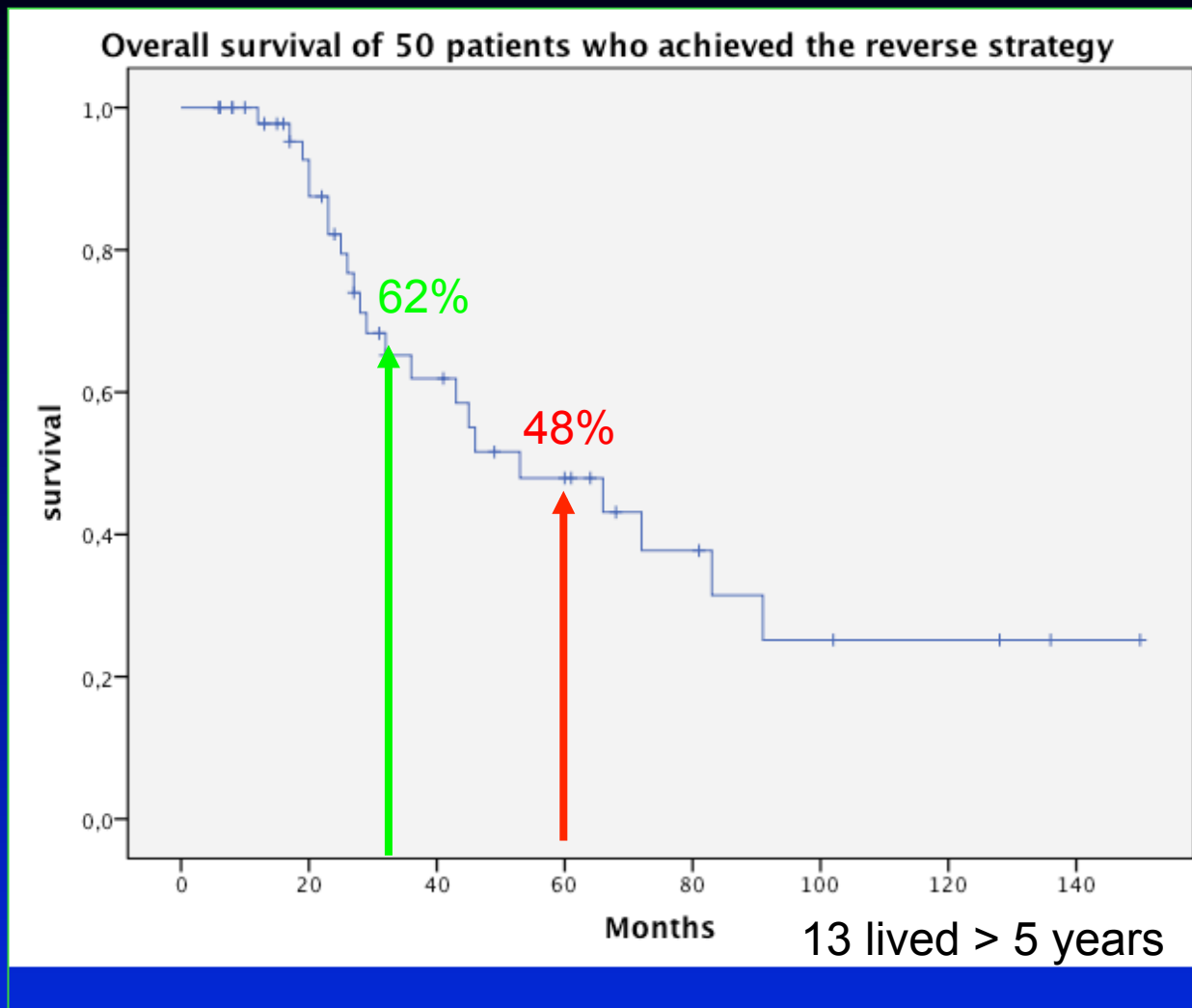
- Positive lymph node of the primary
- Disease-free interval < 12 months (primary to CRM)
- Number of CRM > 1
- Preoperative CEA level > 200 ng/ml
- Size of the largest CRM > 5 cm

Fong Y. Ann Surg  
1999; 230: 309  
(1001 resected patients)



**Figure .** Prediction of long-term outcome for small (<3 cm) metastatic deposits (n = 293). Correlation of long-term outcome with clinical risk score. For a score of 0 to 2 (n = 236) (open box), the median survival was 56 months and the 5-year survival rate was 47%. For a score of 3 or 4 (n = 57) (filled triangles), the median survival was 32 months and the 5-year survival rate was 24%.

# 50 patients (86%) who completed the programme



8 out of 50 patients (14%) had no resection  
→ 6 deaths < 12 months

# The « liver first approach »

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High-impact chemotherapy followed by resection of liver metastases

before removal of the primary tumour seems to be associated with an increased rate of curative resection and improved long-term survival

without detrimental effect on the evolution of the primary when a precise schedule is respected.

Mentha G. et al Br J Surg 2006; 93: 872-8

Mentha G. et al Dig Surg 2008; 25: 430-435

# Lessons we have learned

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- Some patients are more suitable than others ... and this you will see on the colorectal disease
- These patients are very sick and disease is likely to recur. Think about it from the beginning (conservative radical hepatectomies)
- If you have a chance to cure, it depends on « perfection » for all the steps (chemotherapy, liver surgery, colorectal surgery).



# Conclusions

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This new strategy for patients with advanced synchronous liver metastases allowed:

to downstage the CRM in 80% of the cases,

to select patients with responding disease  
avoiding unnecessary surgery

to deliver state of the art preoperative rectal  
radiotherapy without the fear that liver metastases  
will meanwhile progress beyond the possibility of  
cure

Mentha G. et al. Brit J. Surg 2006; 93: 872-878