Colorectal Liver Metastases – Metachronous

Professor Rowan Parks

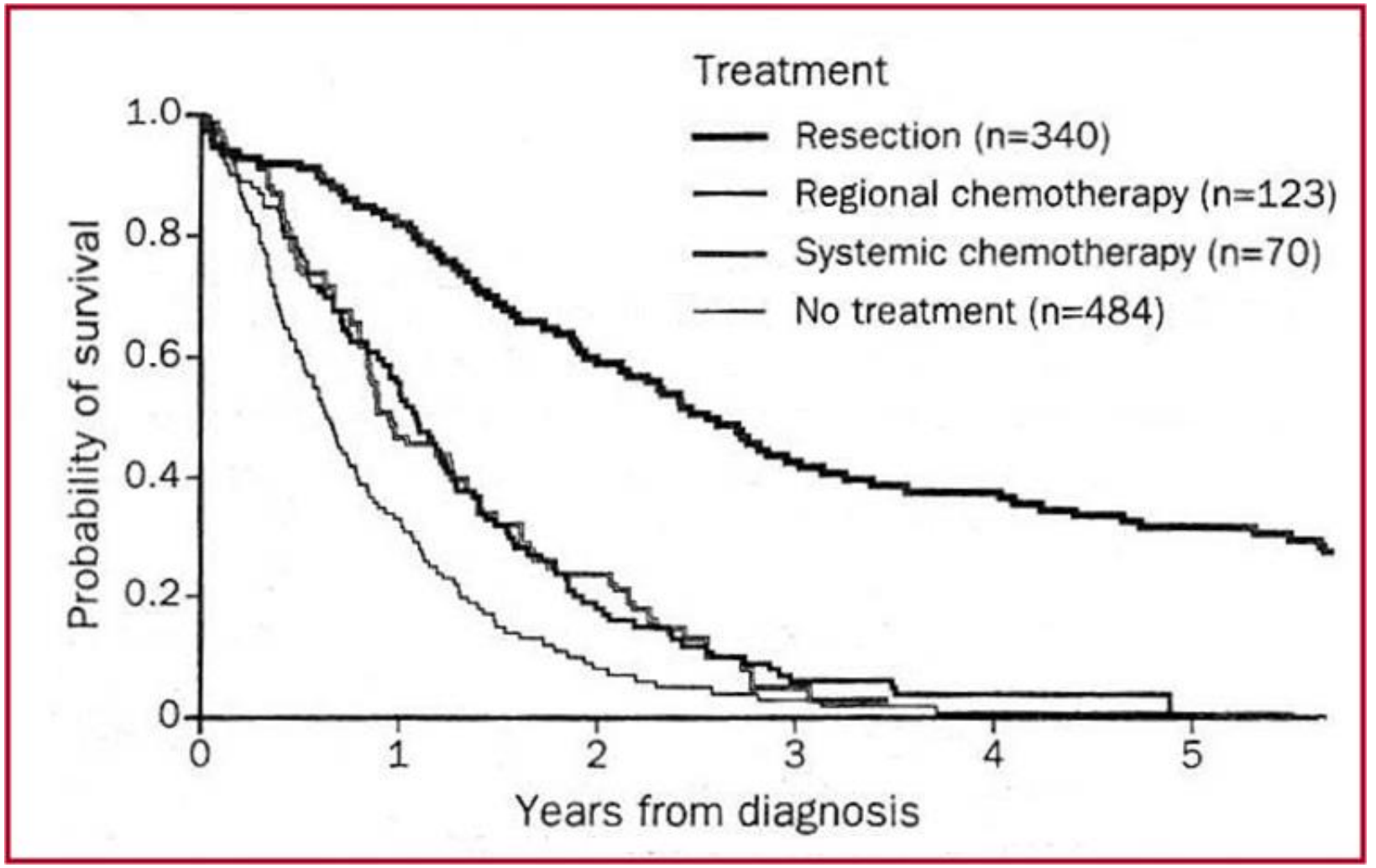
Professor of Surgical Sciences
University of Edinburgh

No disclosures

Natural History of Unresected Untreated Colorectal Metastases

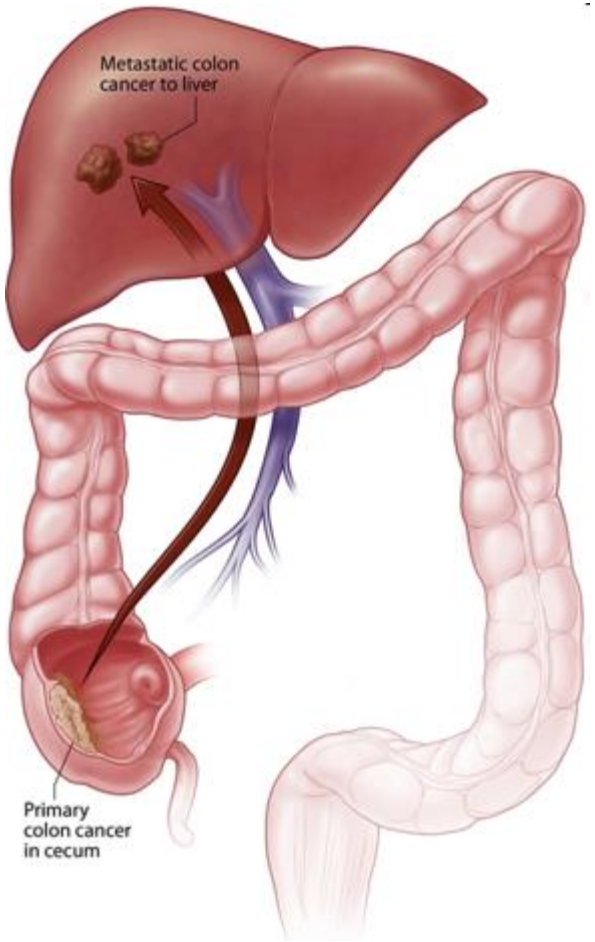
	Year	N	Median (months)	5-Year
Stearns & Brinkley	1954	50	18	1%
Pestaria	1964	353	9	3%
Cady	1970	269	13	1%
Laho	1983	175	6	1%
Wagner	1984	252	19	2%
Scheele	1990	921	6.9	0%
Stangle	1994	484	7.5	1%
Rougier	1995	318	5.7	0%

Hepatic resection of CLM represents the treatment of choice for selected patients after resection of the primary colorectal cancer.



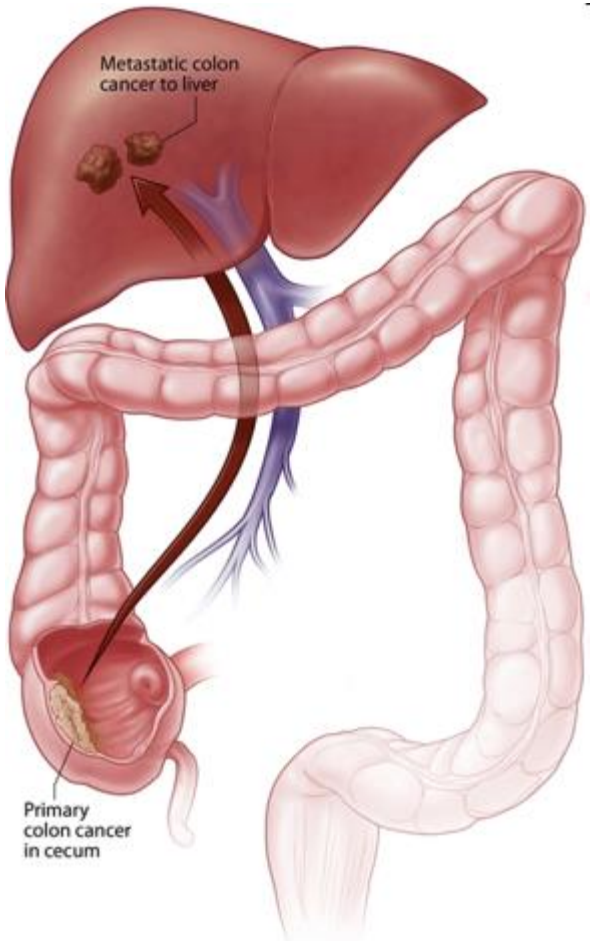
Strangl R, Altendorf-Hofmann A, et al. Lancet 1994; 343: 1405-10

Liver Resection for Metastases - traditional view



- Liver frequent site for tumour
- Spread from GI tract via portal vein
- Further spread from liver to lung
- Treating isolated liver metastases halts tumour spread
- Liver resection has limited application in systemic tumour spread

Liver Resection for Metastases - modern view



- Colorectal cancer cells shed into lymphatics and portal system and most cells are not trapped by liver
- Micro-metastases present in blood, bone marrow and lymph nodes of most advanced cancers
- Cells shed into portal and systemic circulation during ‘curative’ colorectal surgery
- Surgery is cytoreductive with ‘cure’ achieved by immune system and/or chemotherapy

Follow up after CRC Surgery

Effect of 3 to 5 Years of Scheduled CEA and CT Follow-up to Detect Recurrence of Colorectal Cancer

The FACS Randomized Clinical Trial FREE

John N. Primrose, MD, FRCS[1]; Rafael Perera, DPhil[2]; Alastair Gray, BA, PhD[2]; Peter Rose, MD, FRCGP[2]; Alice Fuller, BSc[2]; Andrea Corkhill, BN[1]; Steve George, MD, FRCP[1]; David Mant, FRCGP, FRCP, FMedSci[2] ; for the FACS Trial Investigators

- CEA only – 3/12 for 2 yrs, 6/12 for 3 yrs ➢ 6.7%
- CT only – 6/12 for 2 yrs, annually for 3 yrs ➢ 8%
- CEA + CT ➢ 6.6%
- Symptoms ➢ 2.3%

GUIDELINES

Guidelines for resection of colorectal cancer liver metastases

O J Garden, M Rees, G J Poston, D Mirza, M Saunders, J Ledermann, J N Primrose, R W Parks

Gut 2006;**55**(Suppl III):iii1–iii8. doi: 10.1136/gut.2006.098053

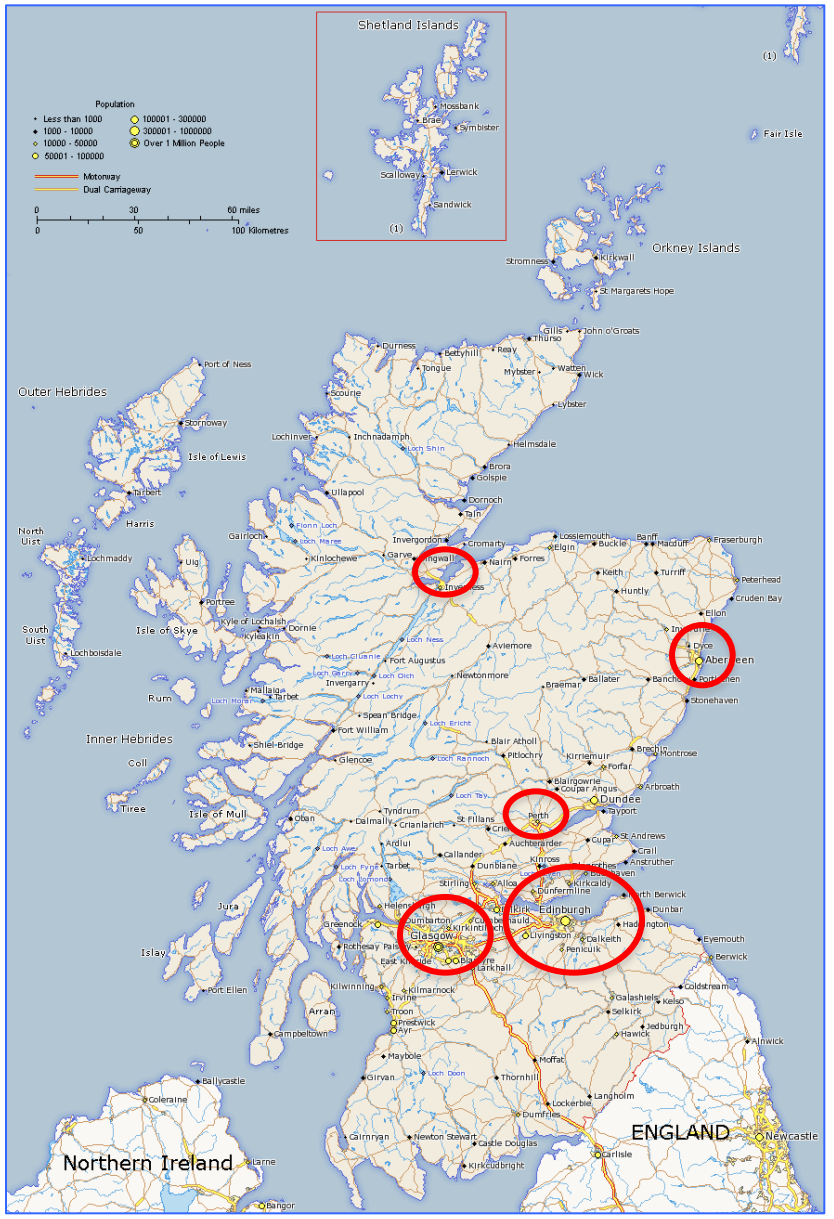
- Patients under consideration of treatment of hepatic metastases should be discussed at a multidisciplinary meeting which has experience in the management of liver metastases.

Scotland

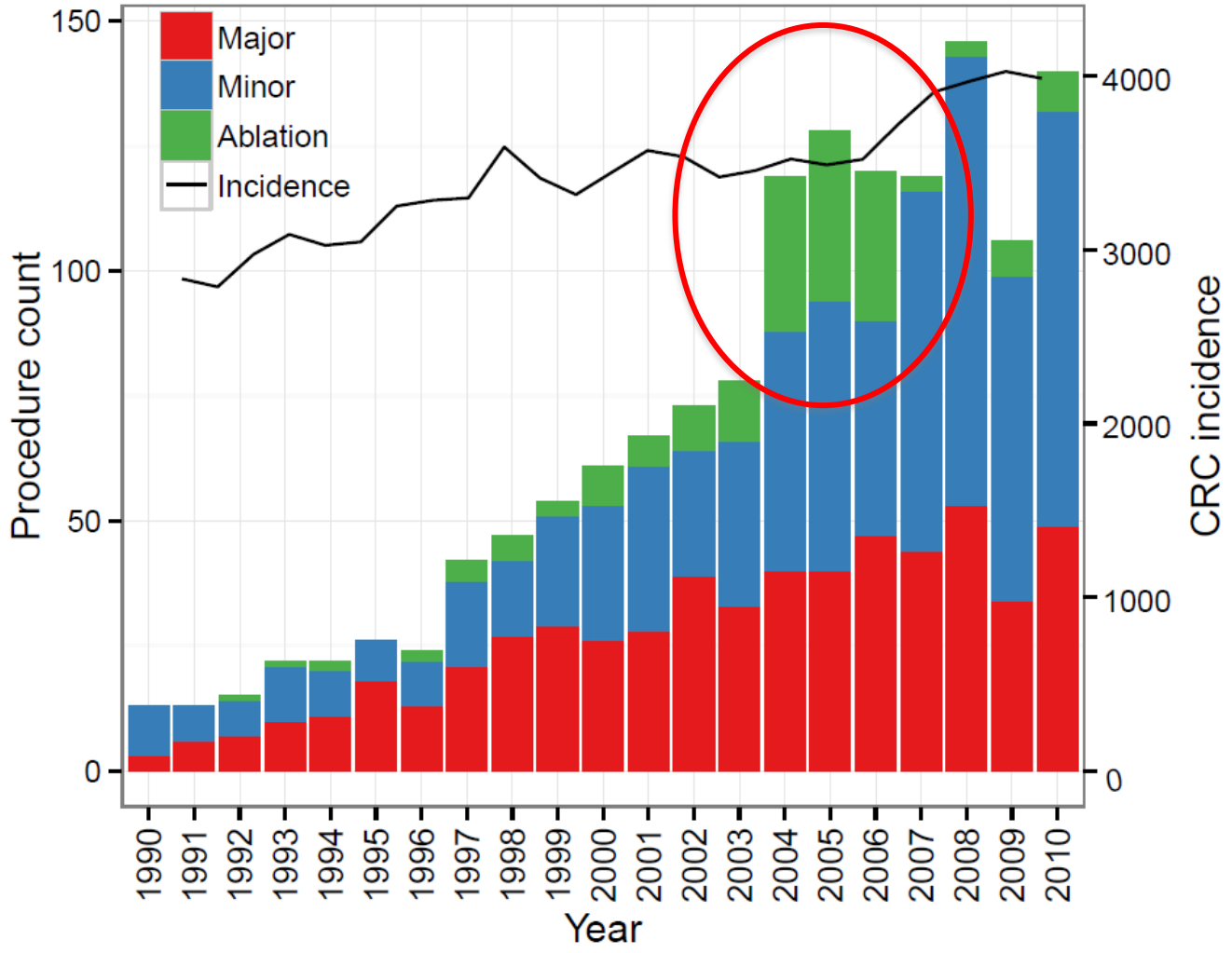
~ 5,000,000 population

5 centres undertaking liver resection

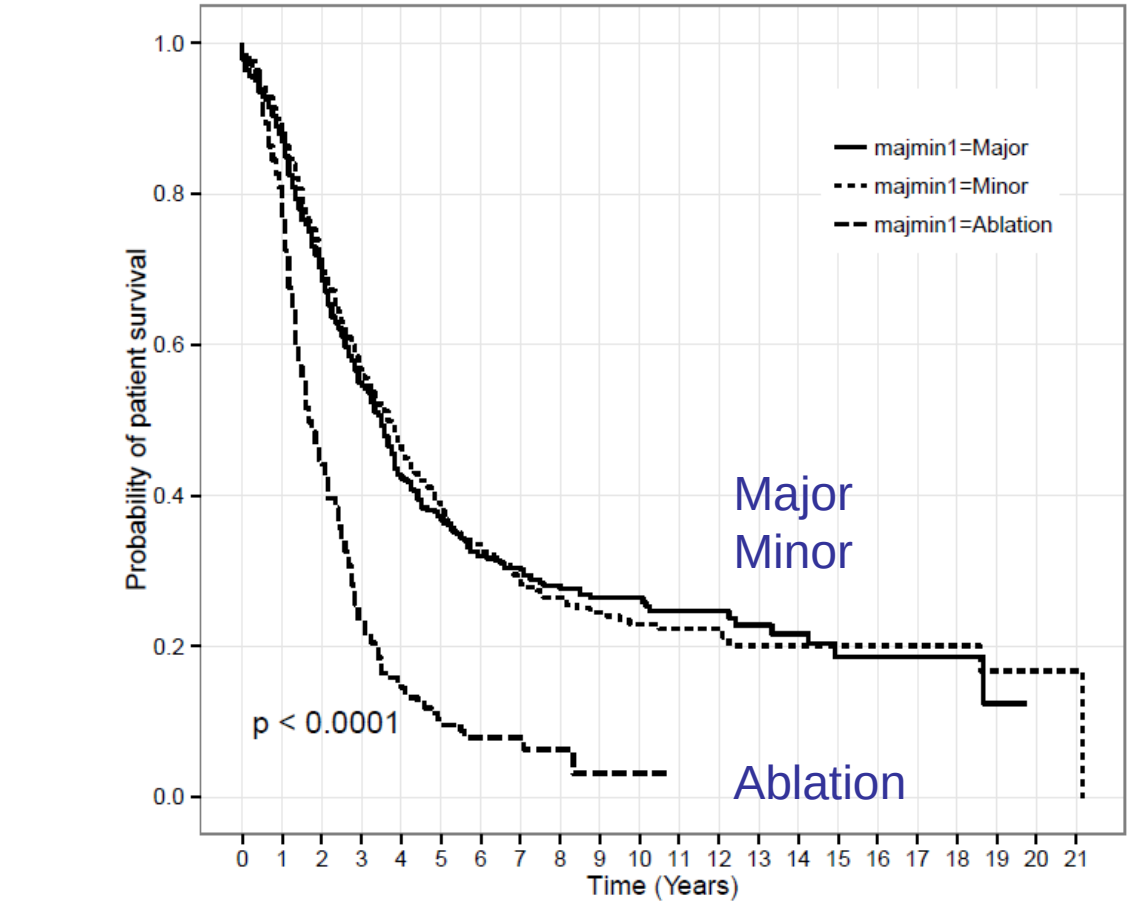
Managed Clinical Network



Scottish CRLM 1990 – 2010



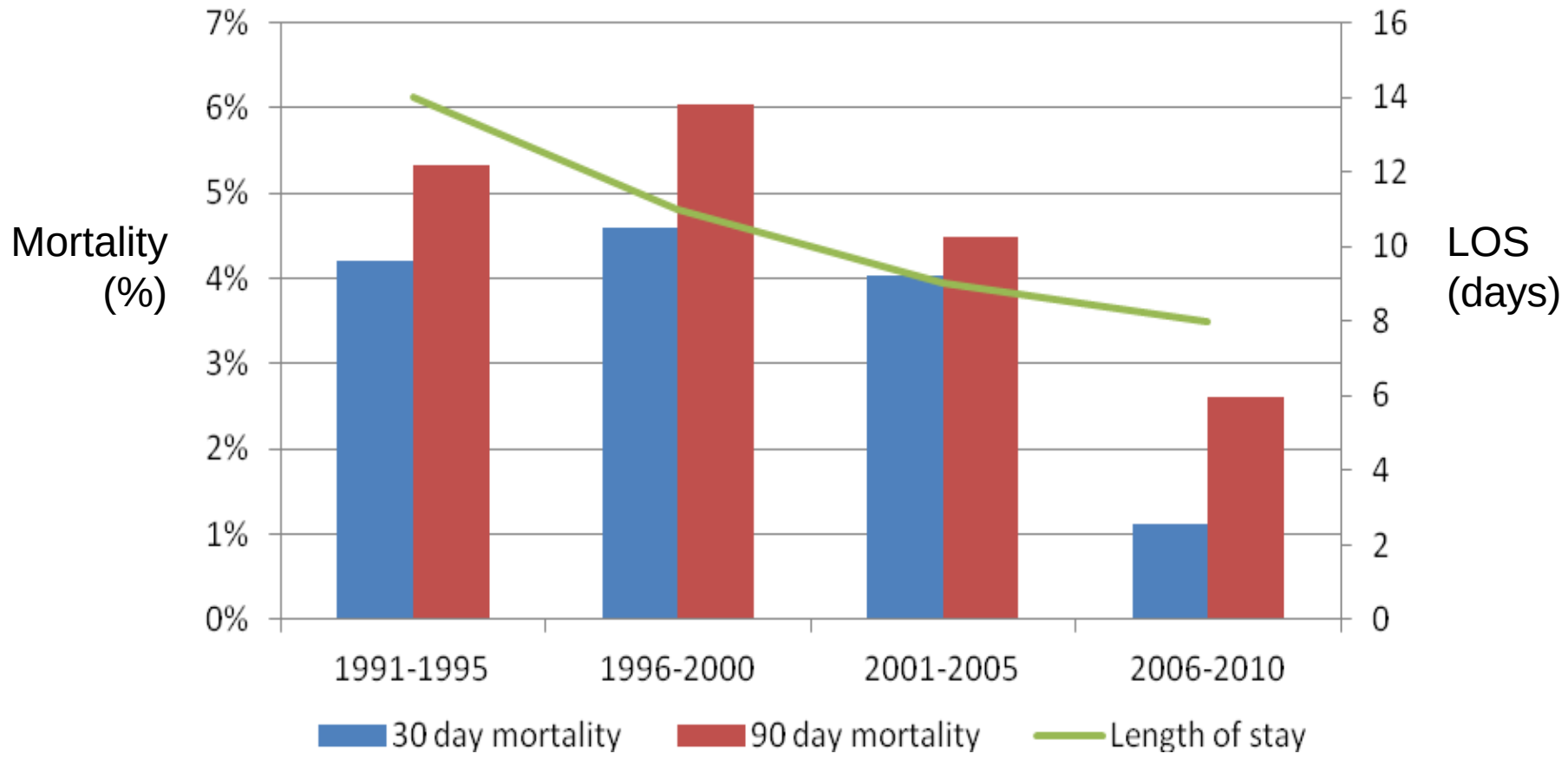
Procedure type overall survival



Major/minor resection

1 year – 89%
3 year – 56%
5 year – 40%

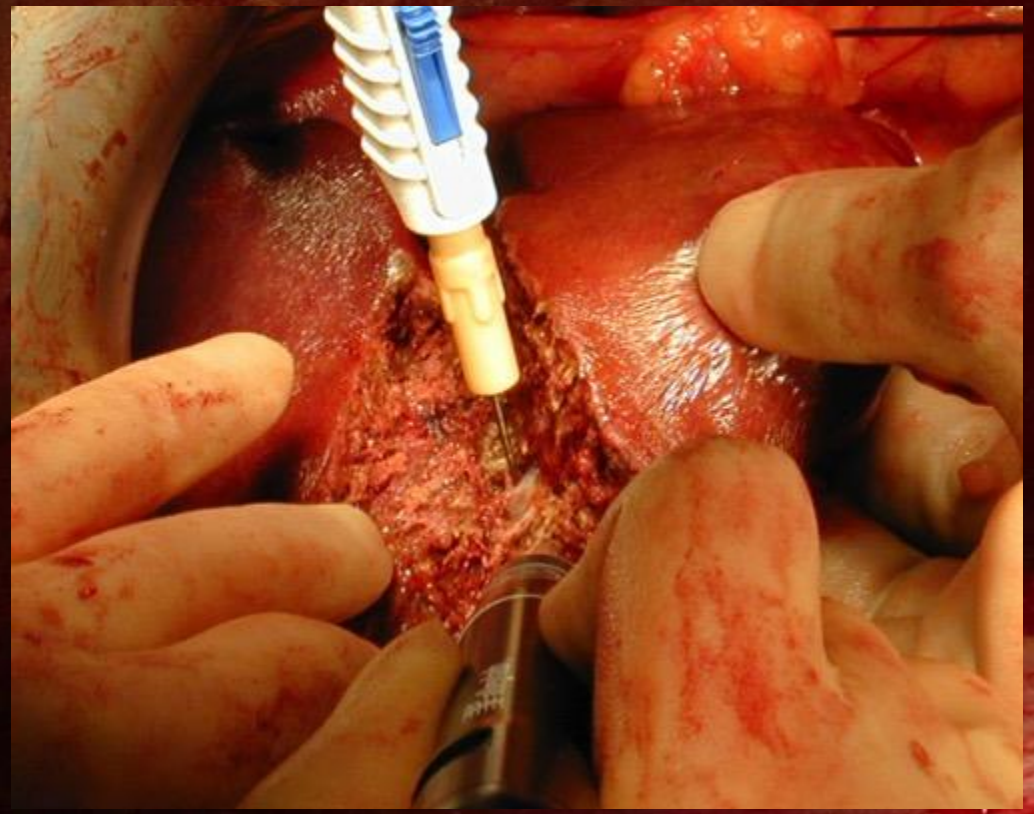
Early outcomes

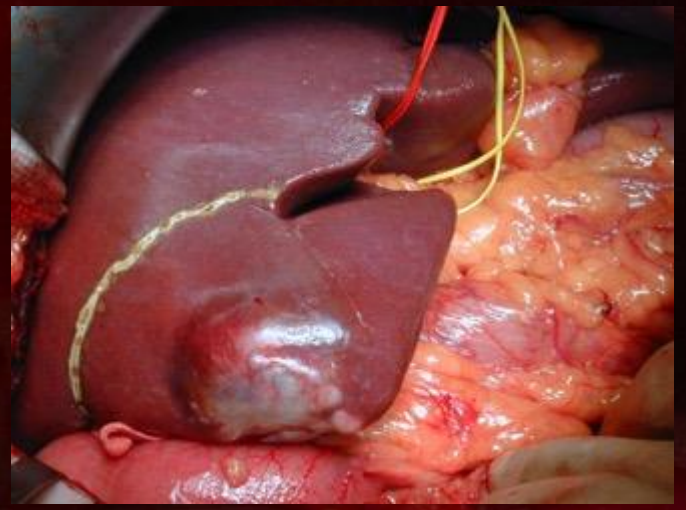


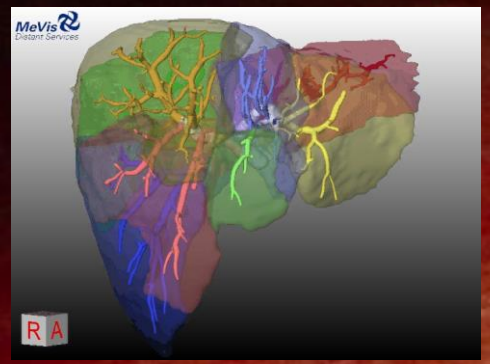
What has changed?

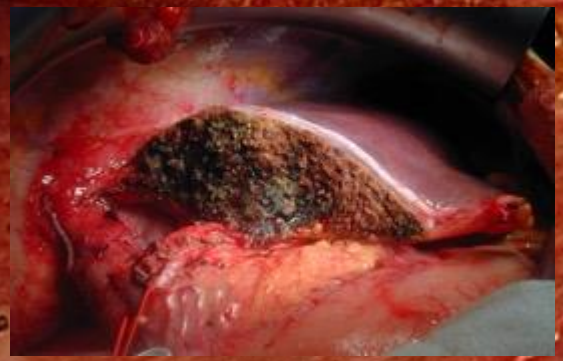
- Advances in Surgical Management

- Advances in Chemotherapy

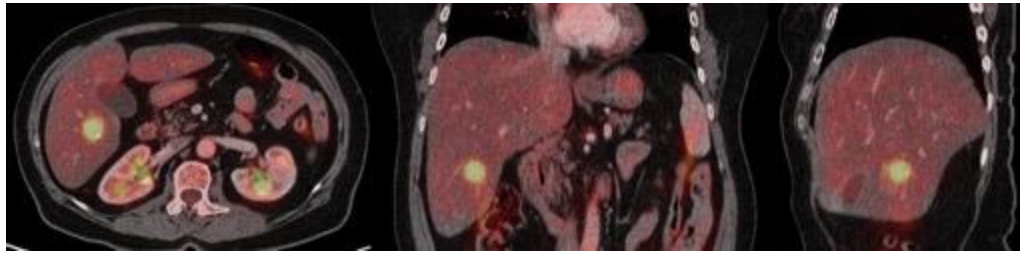


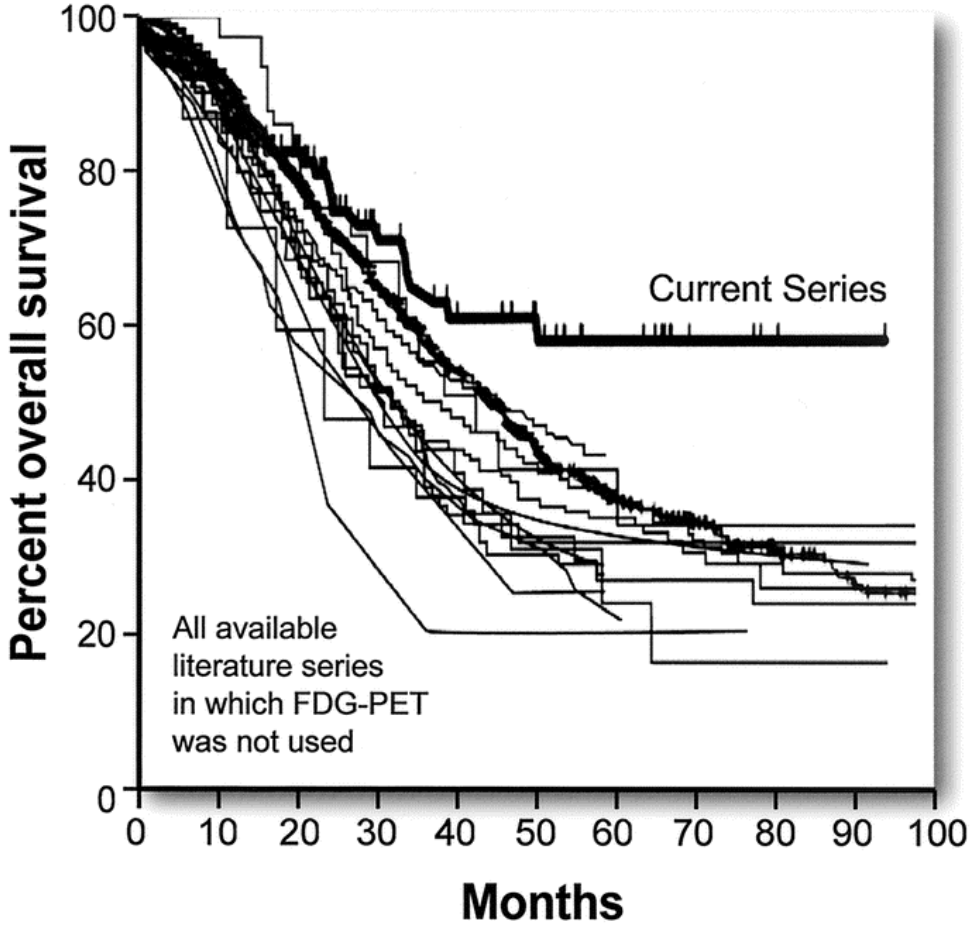



MeVis
Distant Services
R A



PET Scan and Liver resection





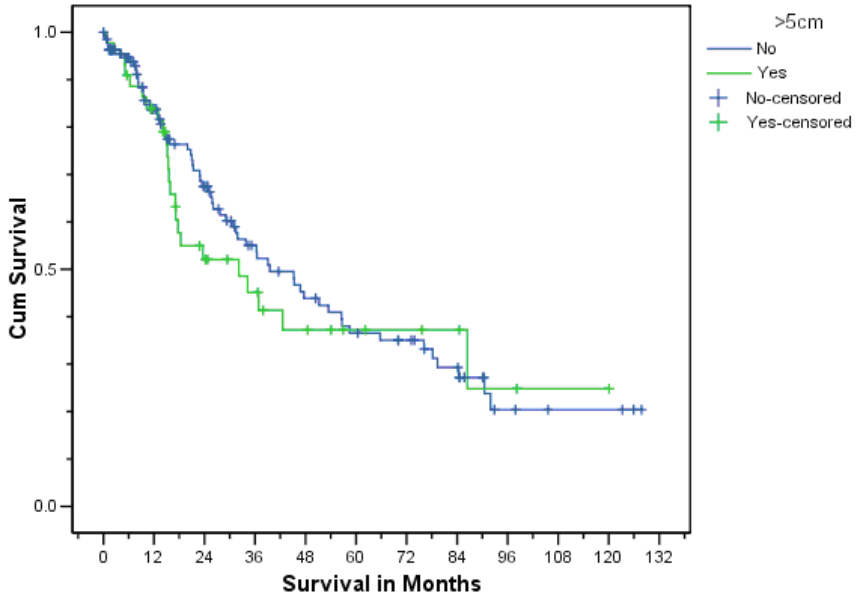
Fernandez et al,
Ann Surg 2004;240:438-50

“Conventional rules” of surgical management of colorectal liver metastases have all been challenged

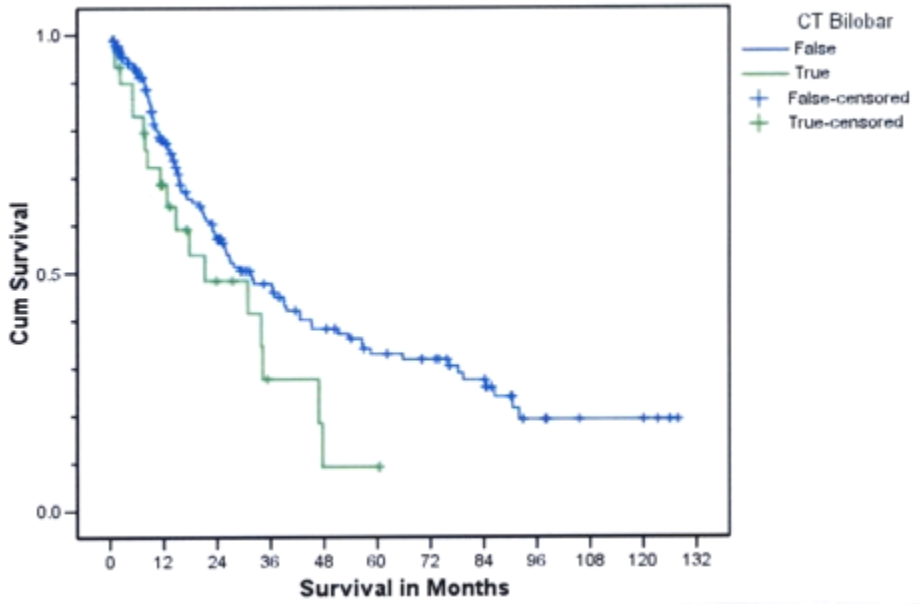
- Bilobar disease = inoperable/futile
- Must have 1cm margins
- Don’t operate on more than 4 metastases
- Repeat resection is futile
- Don’t resect if require more than one procedure
- Liver regeneration drives metastatic growth
- Extrahepatic disease absolute barrier to liver resection
- Non curative resection must never be done

Size and distribution not important

Size: <5cm v >5cm

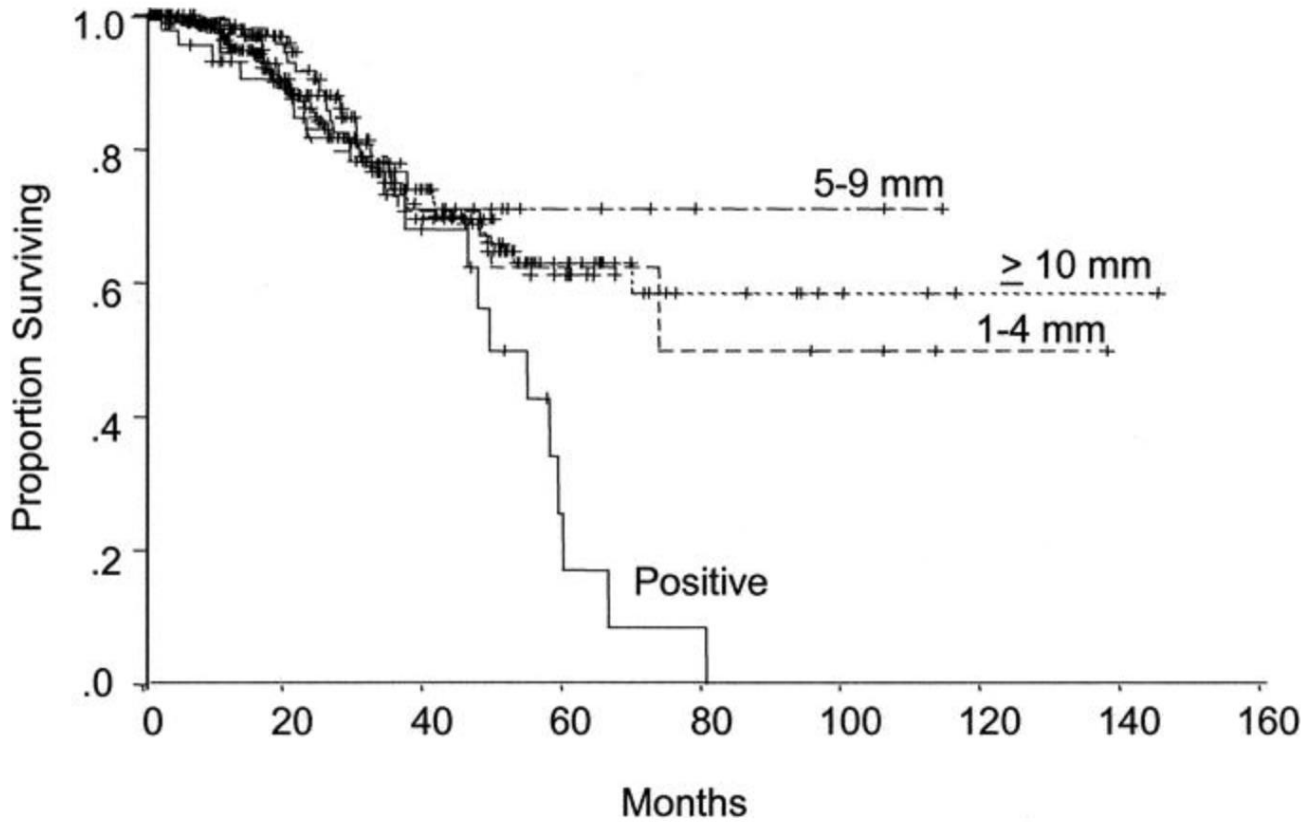


Unilobar v Bilobar



Fong et al, Ann Surg, 1999

Resection margin not important as long as it is negative



Pawlik TM et al, Ann Surg. 2005

Number of metastases not important as long as disease is addressed adequately

- 159 patients with >4 mets (5, 4-14)

Neoadjuvant chemo 89%

Surgery alone 46

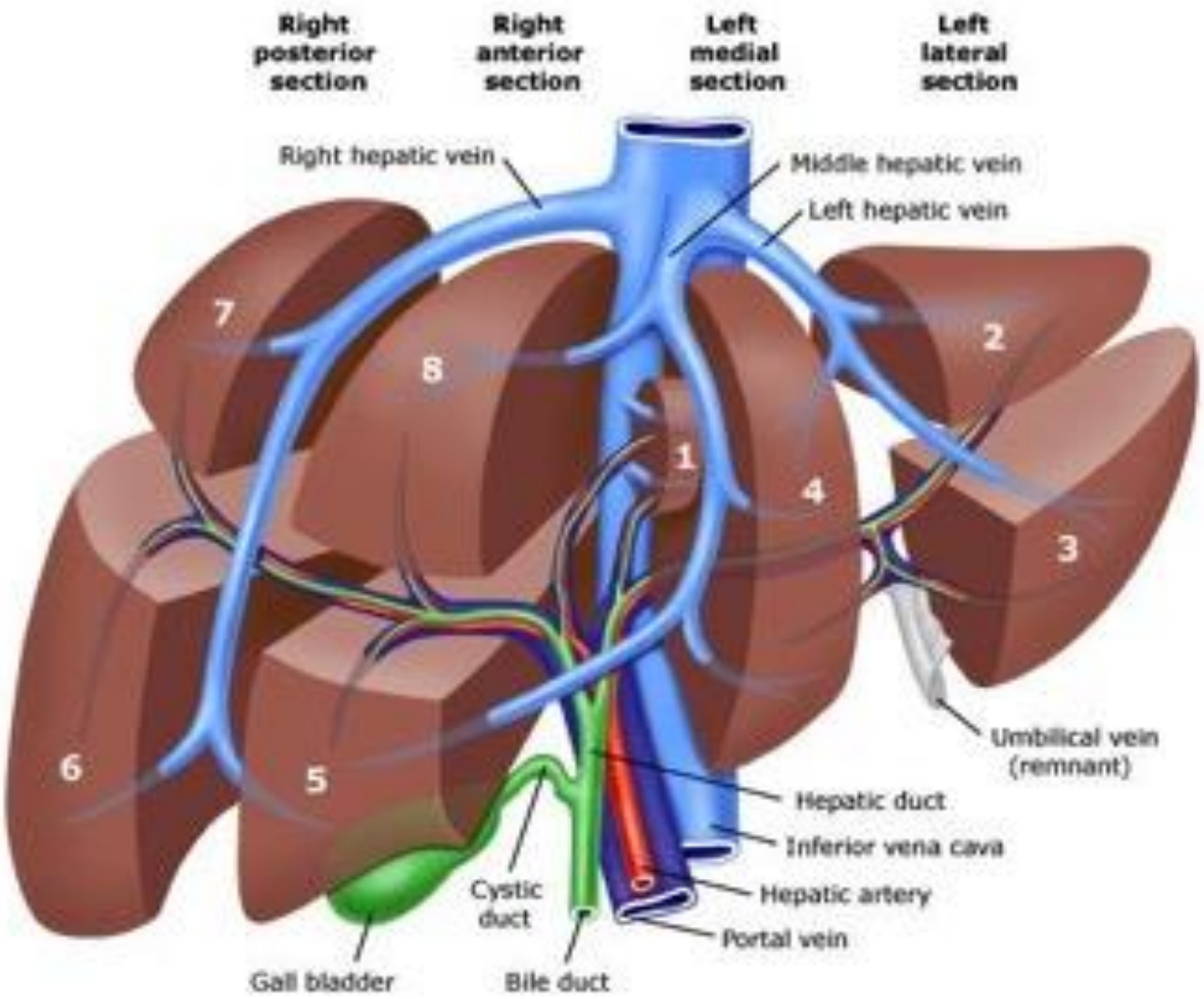
RFA alone 12

Surgery + RFA 101

- 5yr DFS 22%
- Overall survival 51%

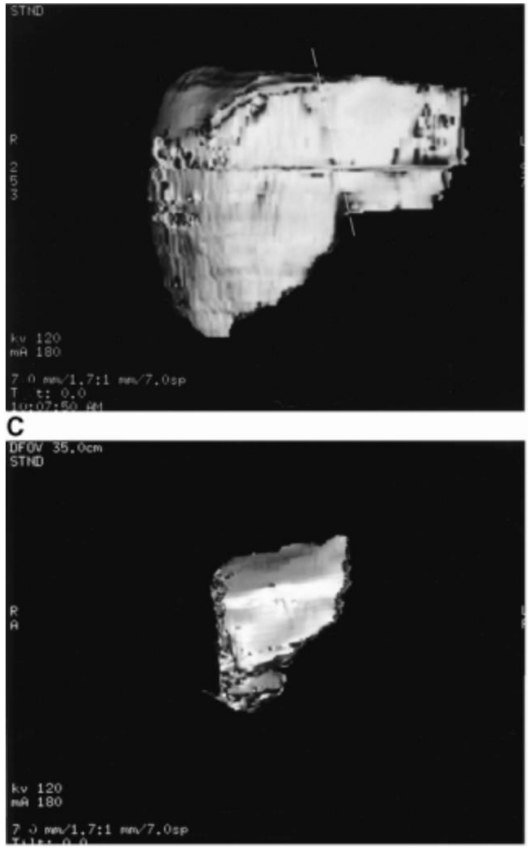
Pawlik T, et al, J Gastrointest Surg. 2006

Surgical Strategy

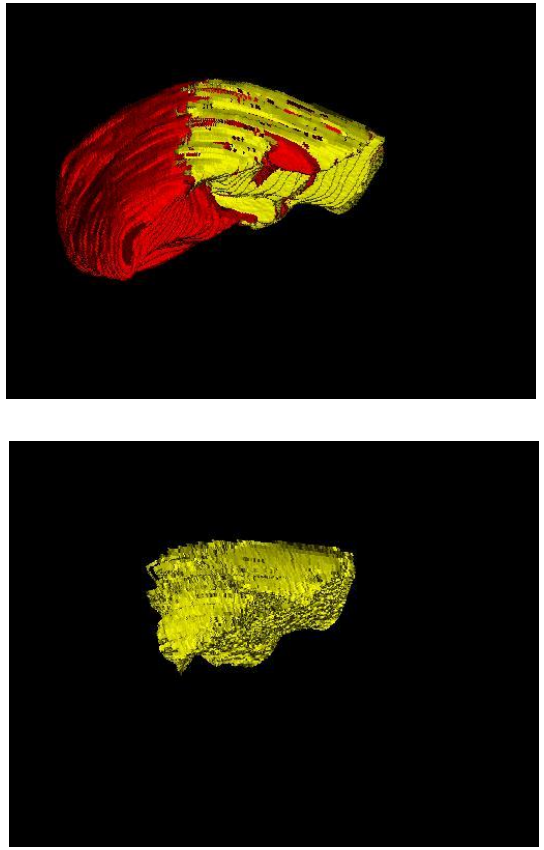


Understanding the liver volume - function relationship

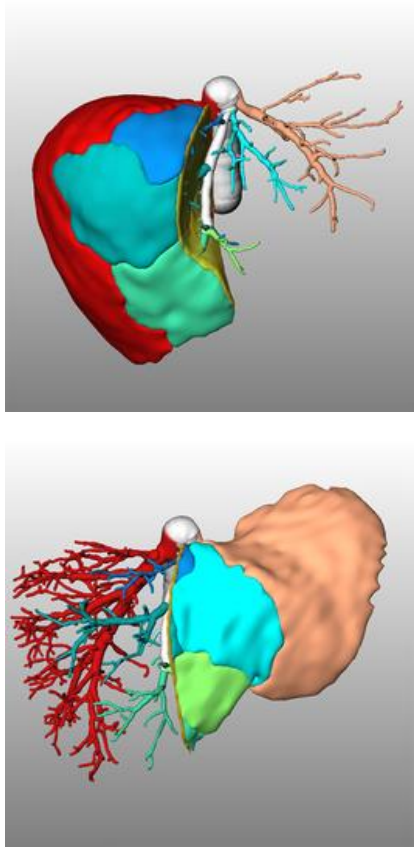
2001



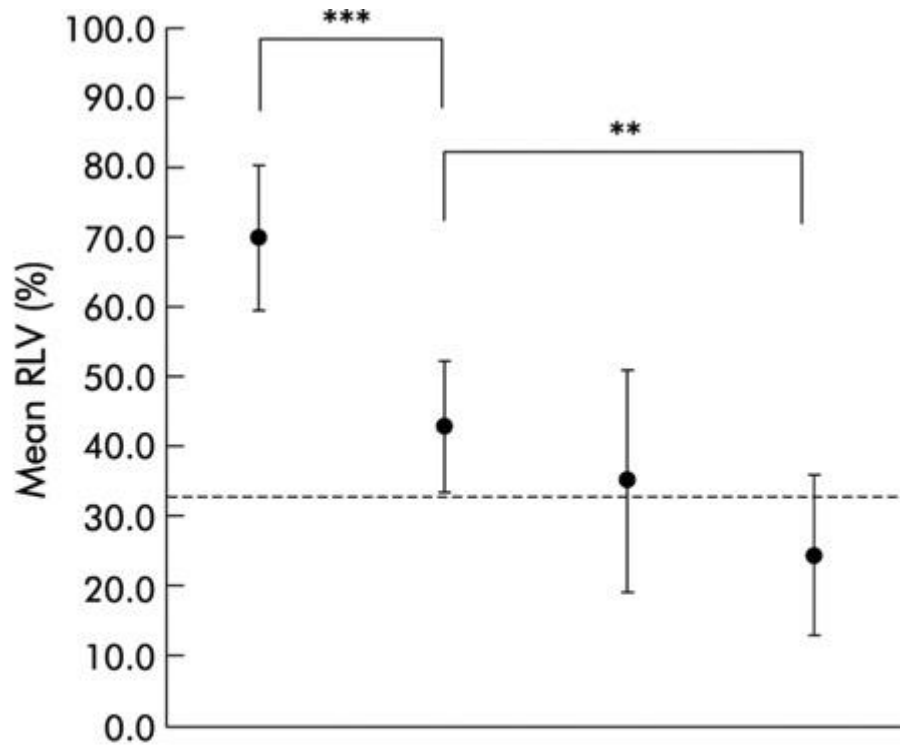
2005



Present



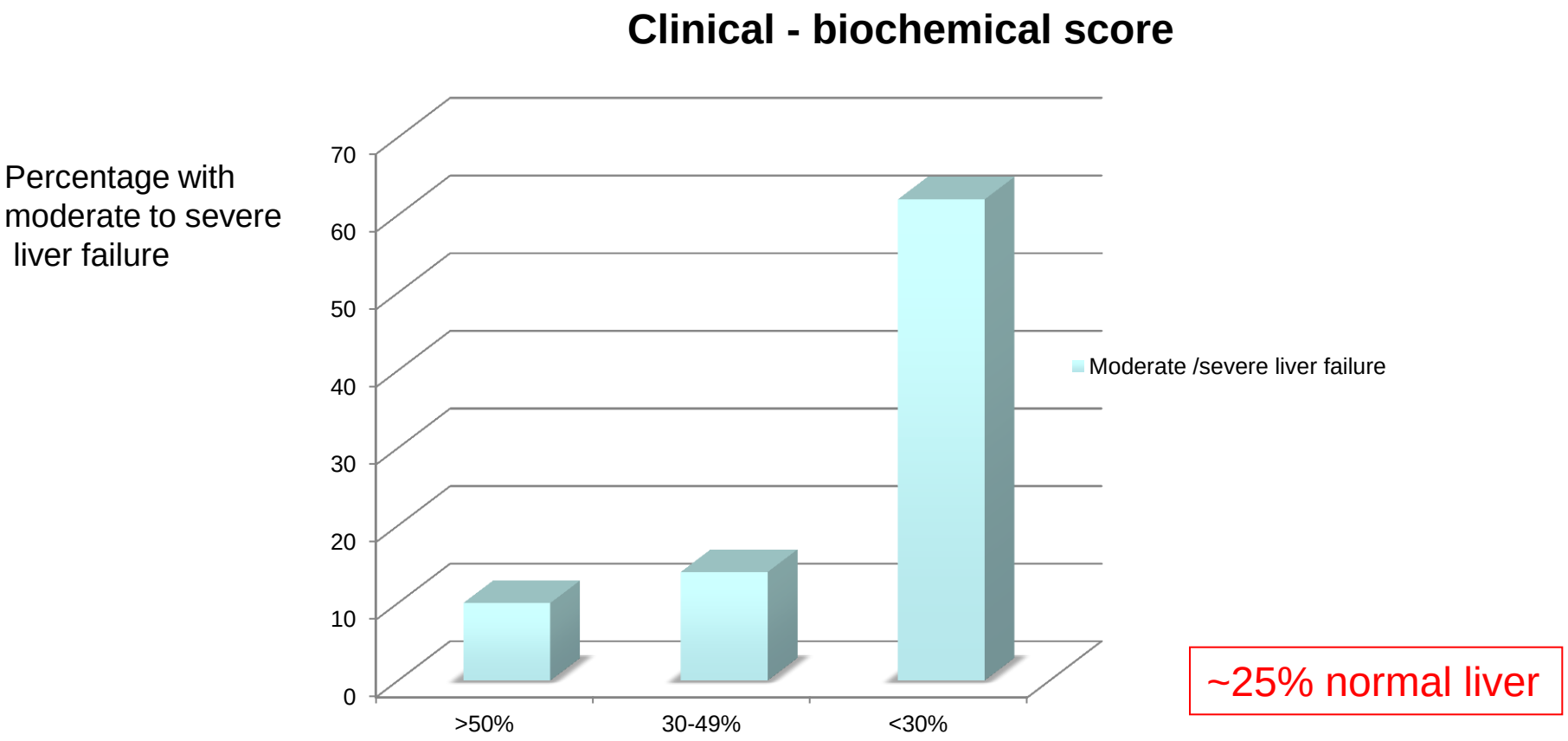
Relative residual liver volume (%RLV) in patients with no, mild, moderate, and severe hepatic dysfunction following liver resection



Hepatic dysfunction	No	Mild	Moderate	Severe
n	27	42	22	13
Mean %RLV	69.9	42.9	35.3	24.5
SD	22.6	15.4	15.3	6.0

Schindl MJ et al. Gut 2005

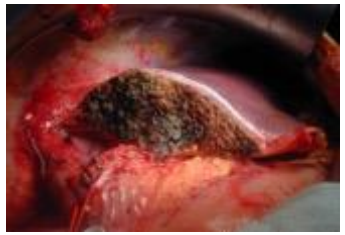
How much liver tissue do you need?

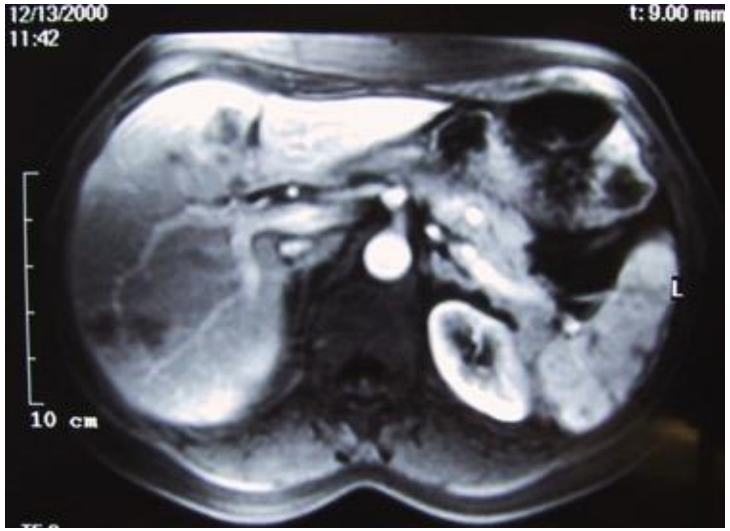


~25% normal liver

Schindl et al Gut 2005

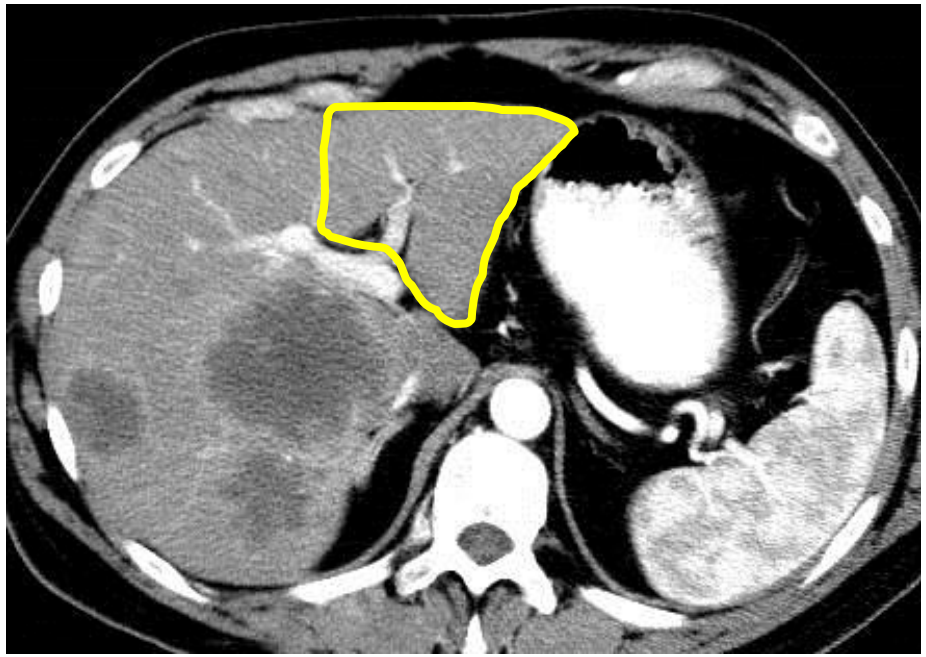
Tumours borderline for resection





- Portal Vein Embolisation
- Two stage hepatectomy
- Combine surgery with ablative therapy
- Downstaging chemotherapy

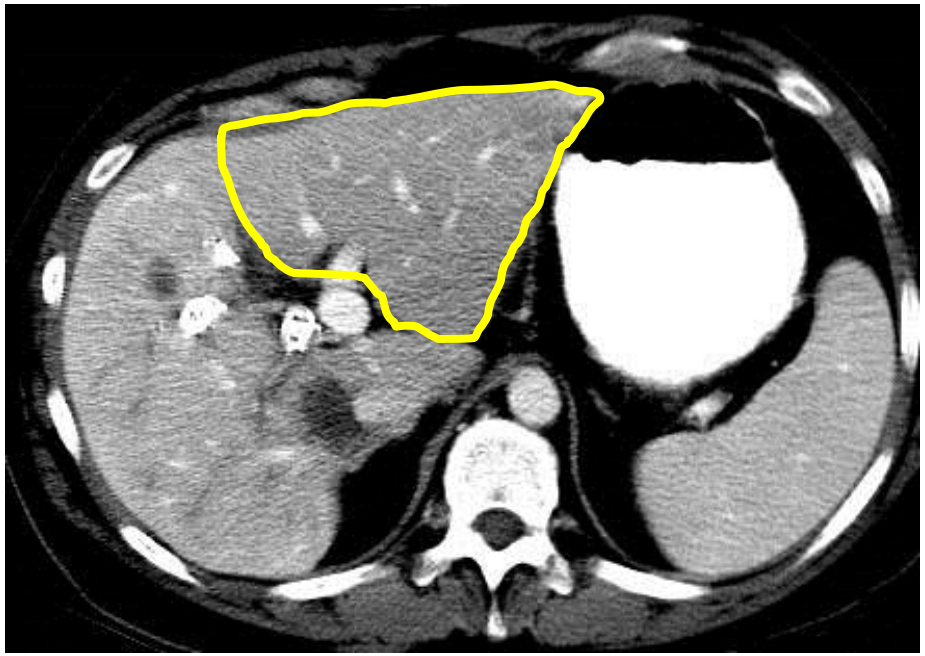
Pre-embolization
Pre-chemotherapy



Vol II + III= 291 cc

FLR pre= 17%

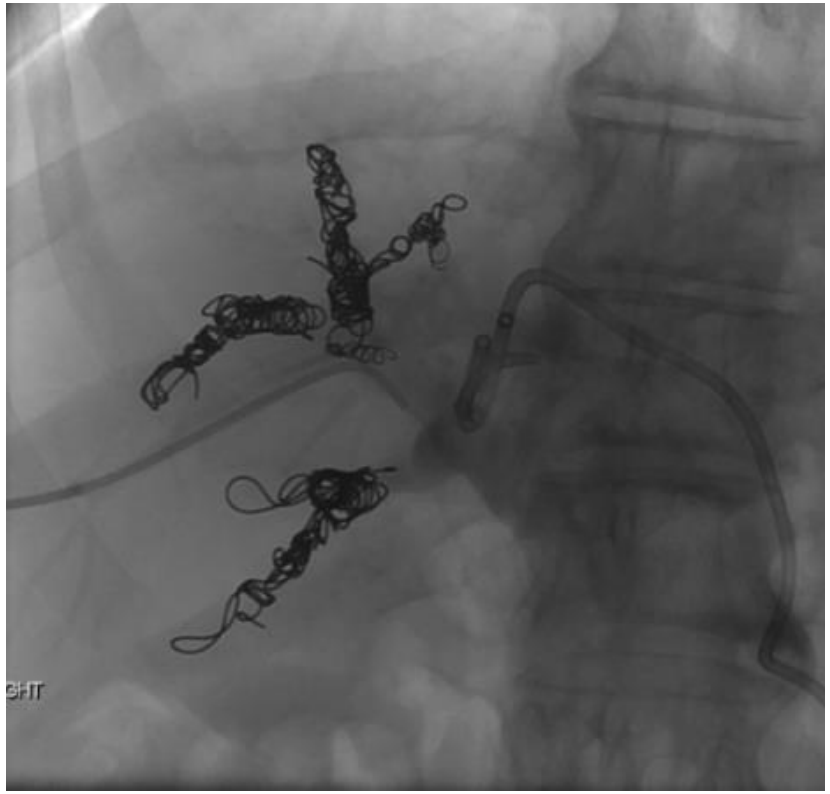
Post-embolization
Post-chemotherapy



Vol II + III= 510 cc

FLR post= 30%

PVE



PVE enabled resection in 2/3 of patients with an inadequate future liver remnant volume who needed an extended right hepatectomy

Similar PFS and OS to patients with adequate volume not requiring PVE

Portal vein embolization improves rate of resection of extensive **colorectal liver metastases** without worsening survival.

Shindoh J, et al. Br J Surg. 2013

PVE or PVL

- Depends on anticipated second stage and need to preserve segment 4
- PVE- segment 4 and right PV planning to do extended right hepatetomy
- PVL – Right hepatectomy

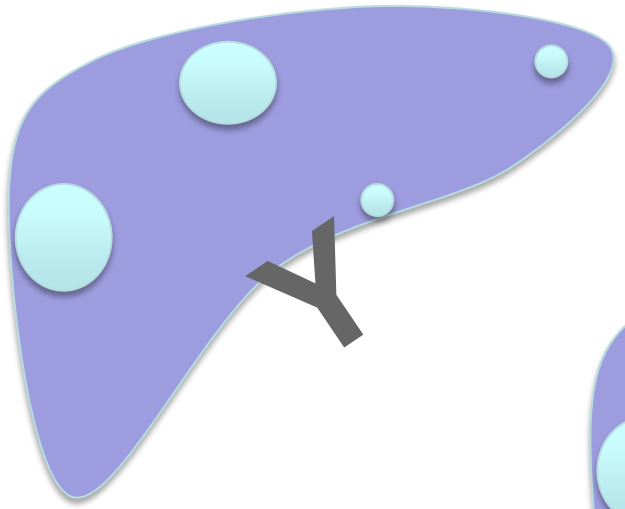
Portal vein embolization induces more liver **regeneration** than **portal vein ligation** in a standardized rabbit model.
van den Esschert JW et al, Surgery. 2011

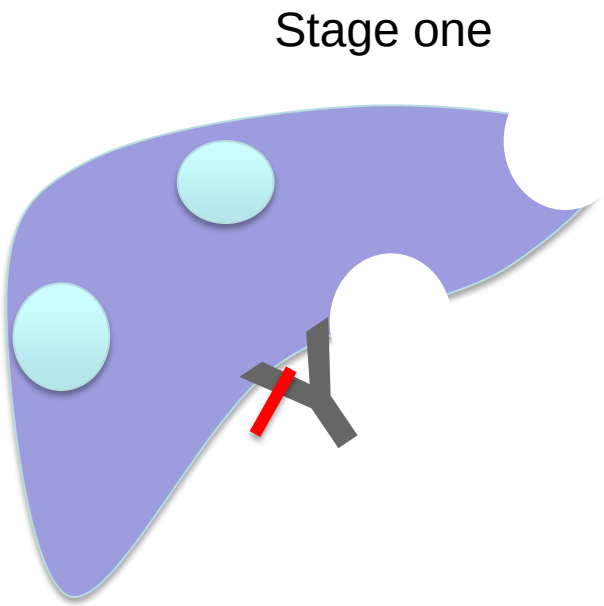
HVE

Sequential preoperative ipsilateral hepatic vein embolization after portal vein embolization to induce further liver regeneration in patients with hepatobiliary malignancy.

Hwang S et al. Ann Surg. 2009

Staged hepatic resection

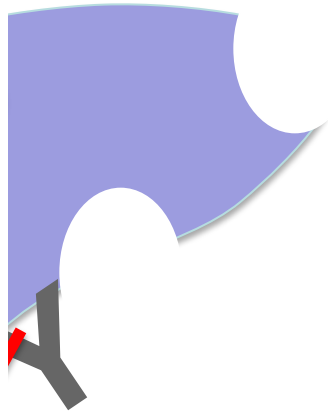




Stage one

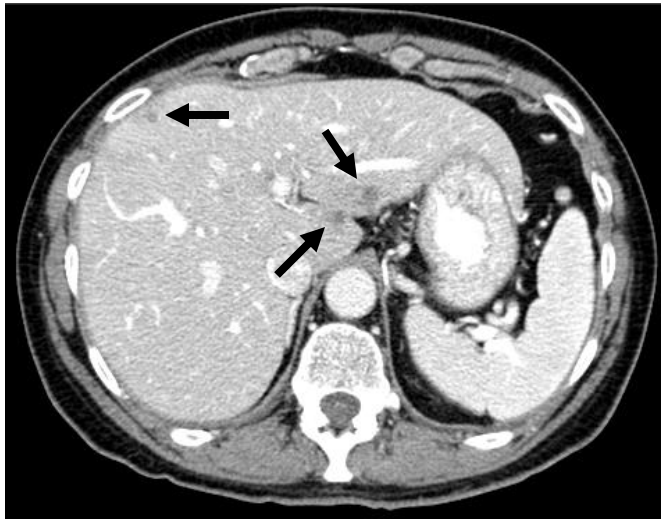
PVL or PVE

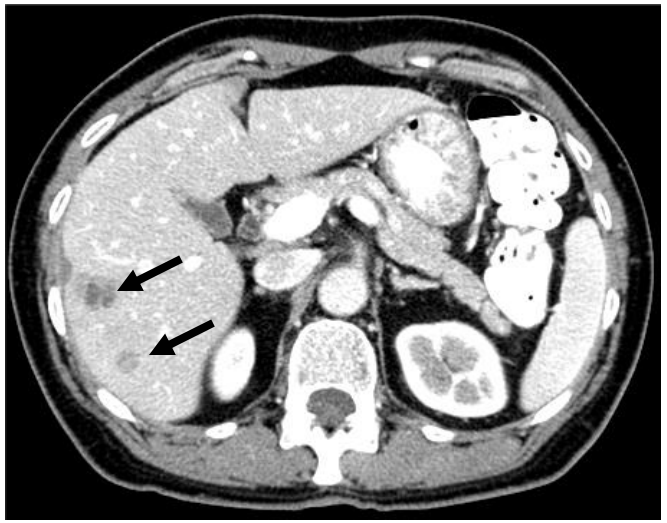
Stage two

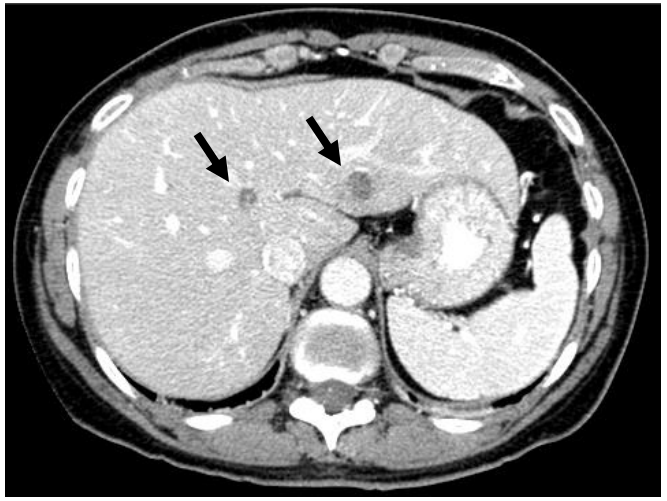


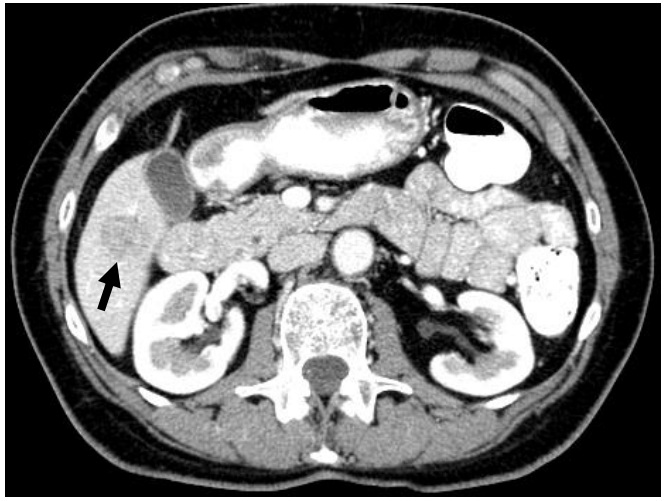
Multiple Bilateral Metastases

8 tumors in 6 of 8 anatomic segments



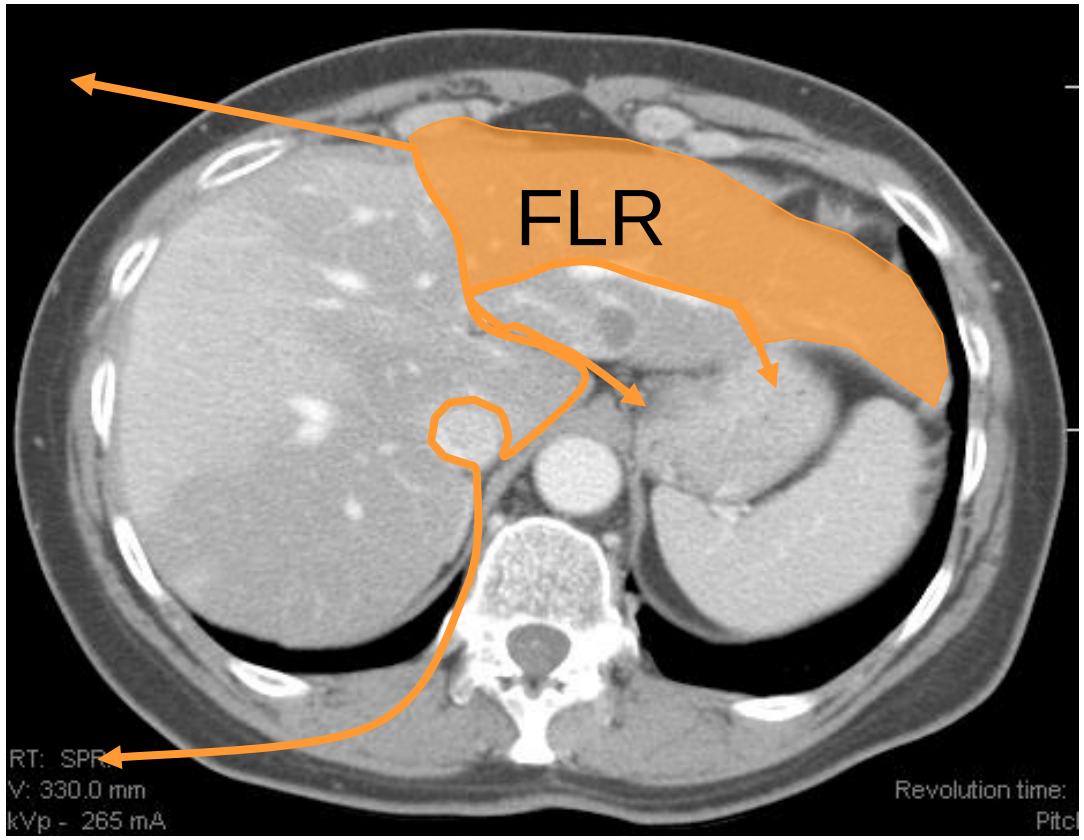






Multiple Bilateral Metastases

Extended R hepatectomy



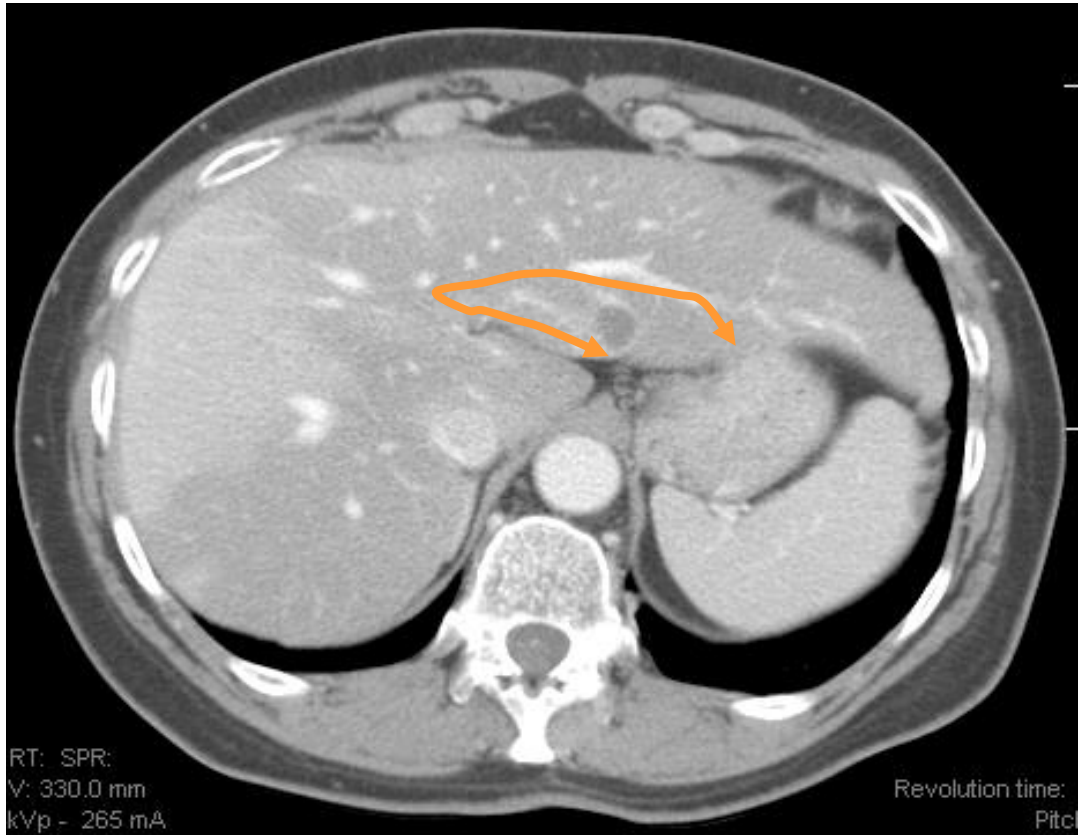
Segment II resection

Stable Disease
Segment III
Spared

Plan: Resect

Measure RFLV

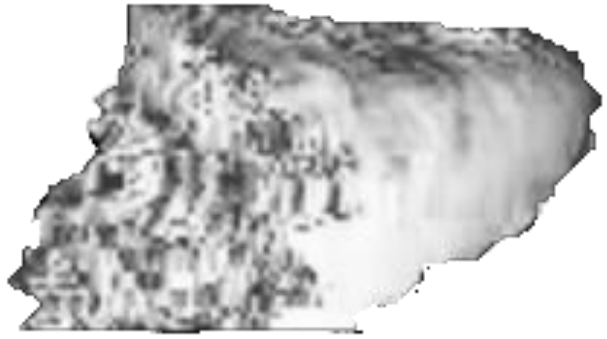
Multiple Bilateral Metastases
1st Stage Hepatectomy



- Clear FLR (segment II resection)
- 1.3 cm tumor, negative margins

Multiple Bilateral Metastases
Portal Vein Embolization

Pre-embolization
Segment III

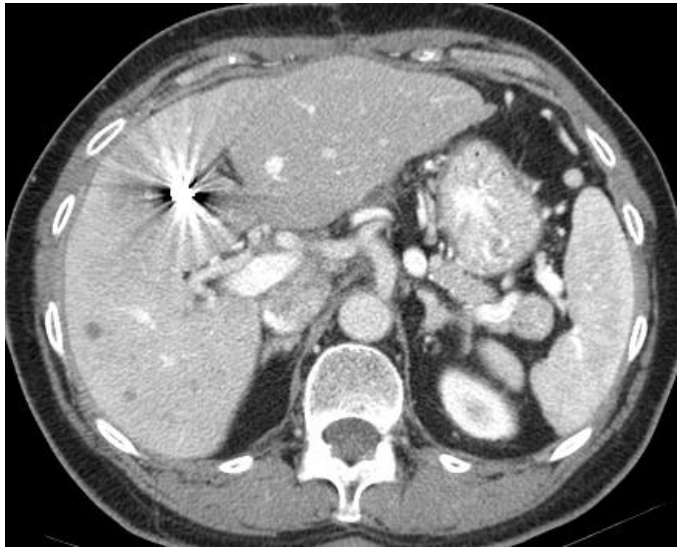


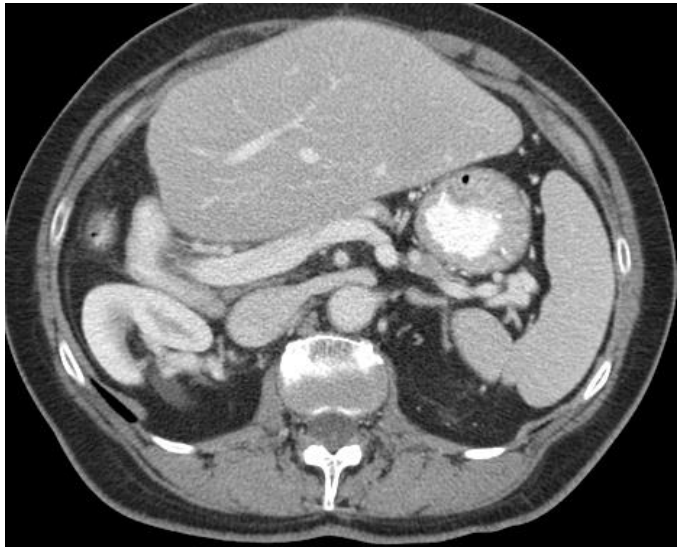
Post-embolization
Segment III

FLR Volume	301 cm^3	→	401 cm^3
% TLV	**20%**	→	**27%**

Degree of Hypertrophy = 7%

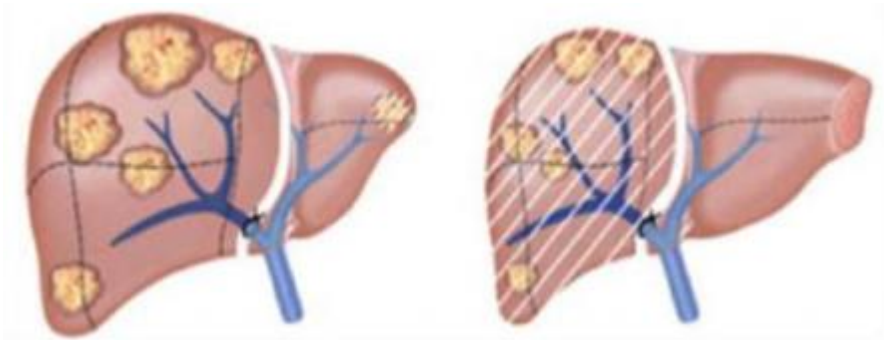
Multiple Bilateral Metastases
2nd Stage Hepatectomy





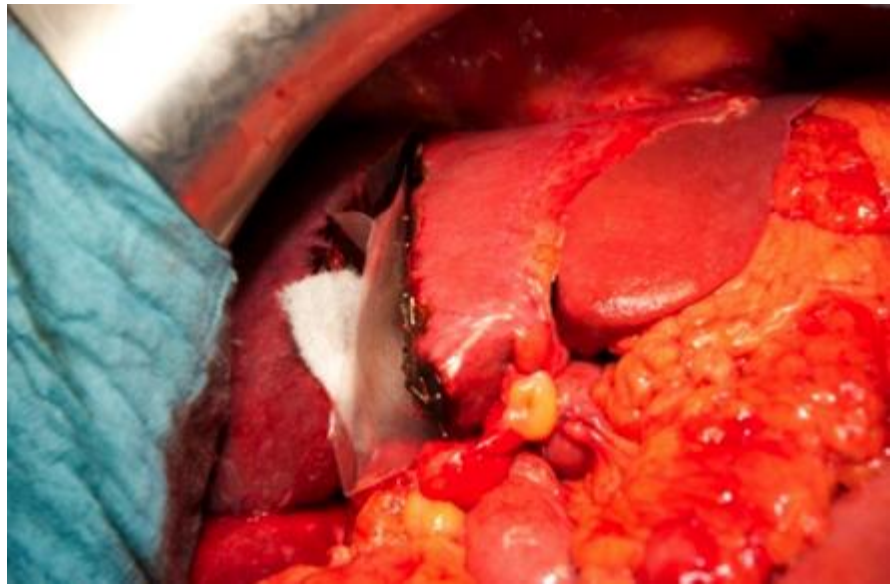
- 4 weeks later uncomplicated ext right hepatectomy (IV-VIII)
- Pathology: major response (3 tumors) and complete response (4 tumors)
- No evidence of disease 2.5 years later
- No evidence of disease 2 ½ years later

Associating Liver Partition and Portal vein ligation for staged hepatectomy procedure (ALPPS)



2 stages separated by around 7 days

Concerns –
- higher postoperative morbidity/mortality



Downstaging Chemotherapy

Unresectable tumours may be converted to resectable lesions by high dose chemotherapy

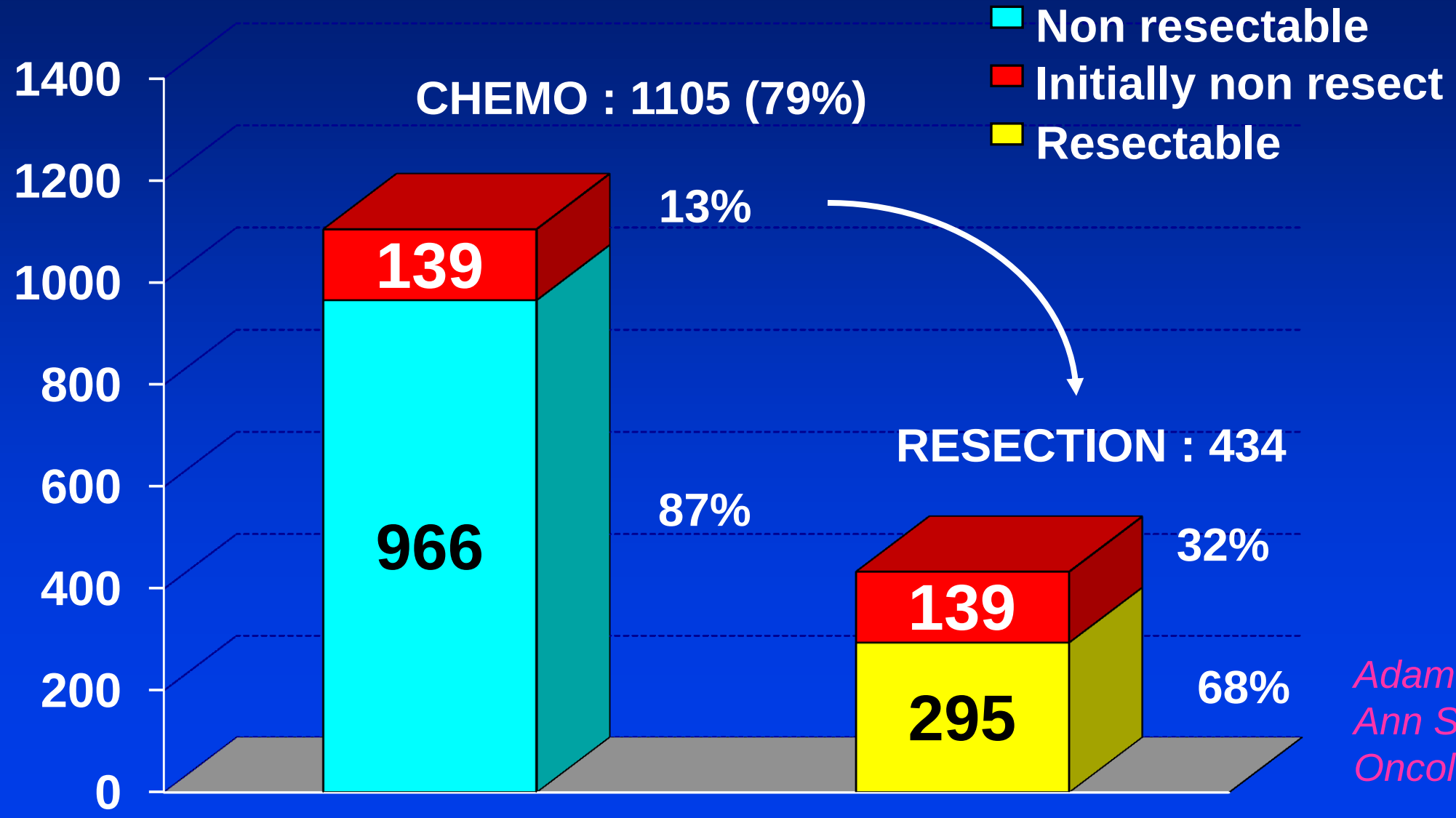
- 53 patients – initially unresectable
- 5-FU + Folinic acid + oxaliplatin

  → resection
- 40% 5 year survival

Bismuth et al, Ann Surg, 1996

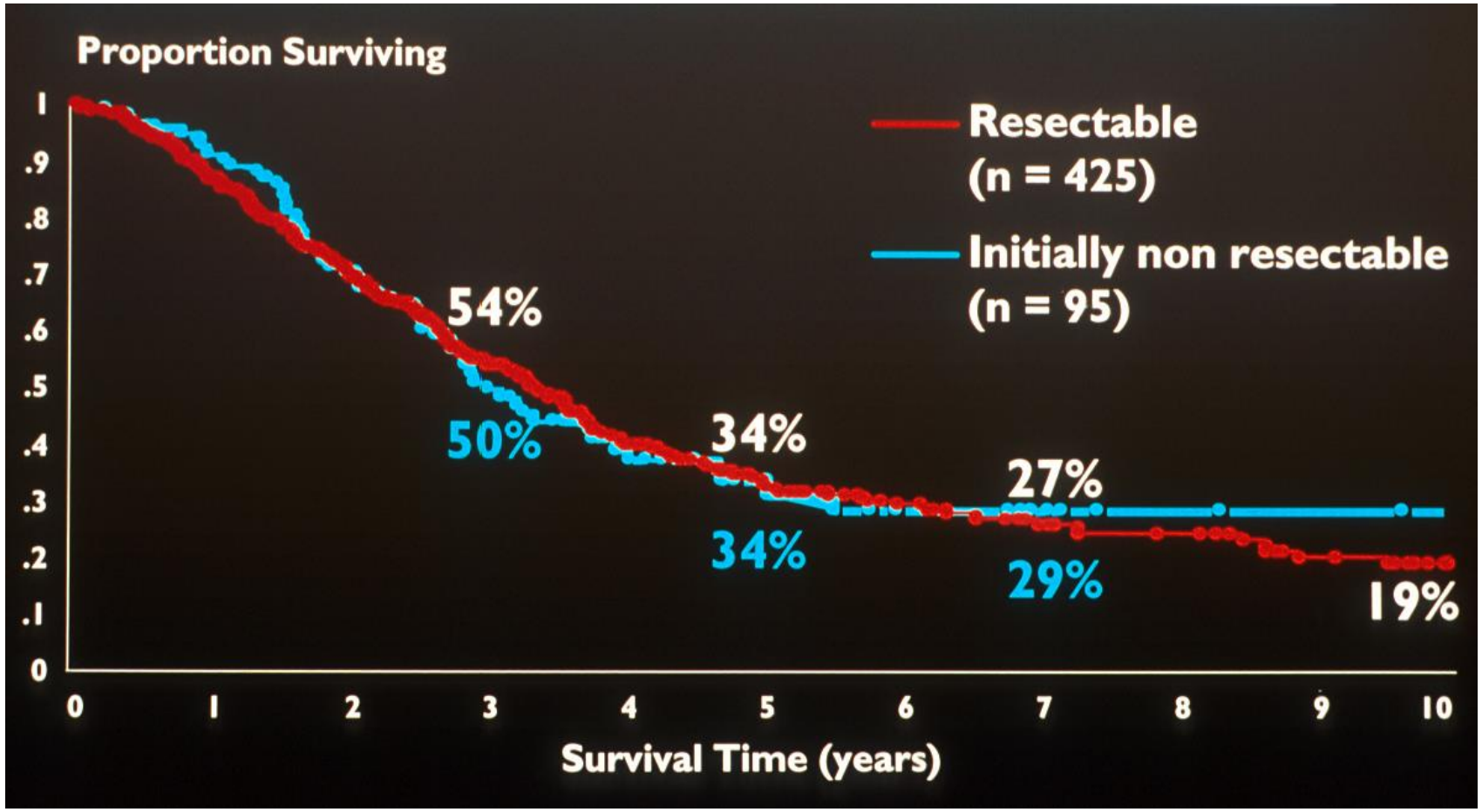
Colorectal liver metastases

Paul Brousse Hospital - 1400 patients (1988 - 2000)



Adam R et al. Ann Surg Oncol 2001

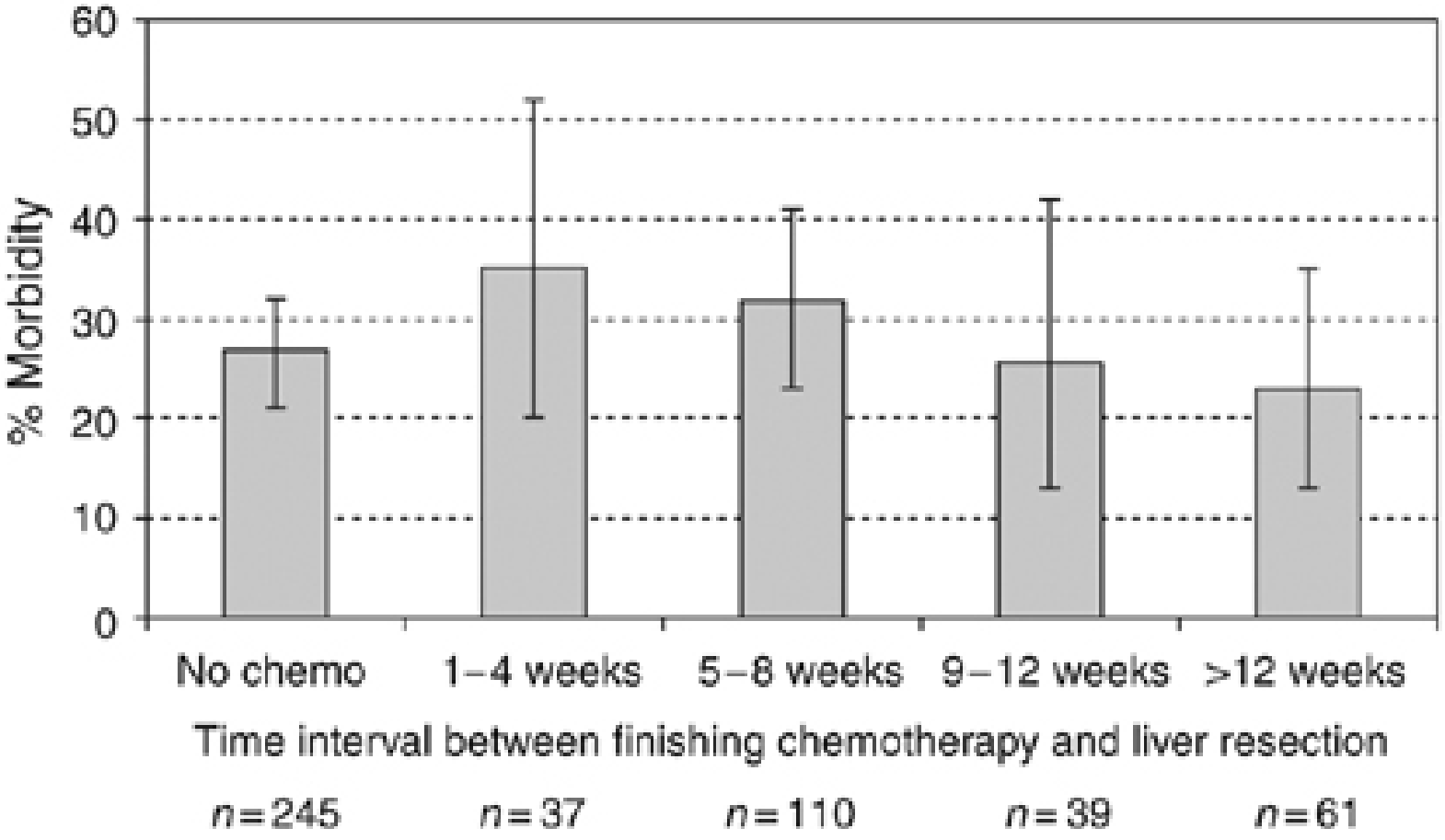
Survival after downstaging chemotherapy



Downstaging Chemotherapy

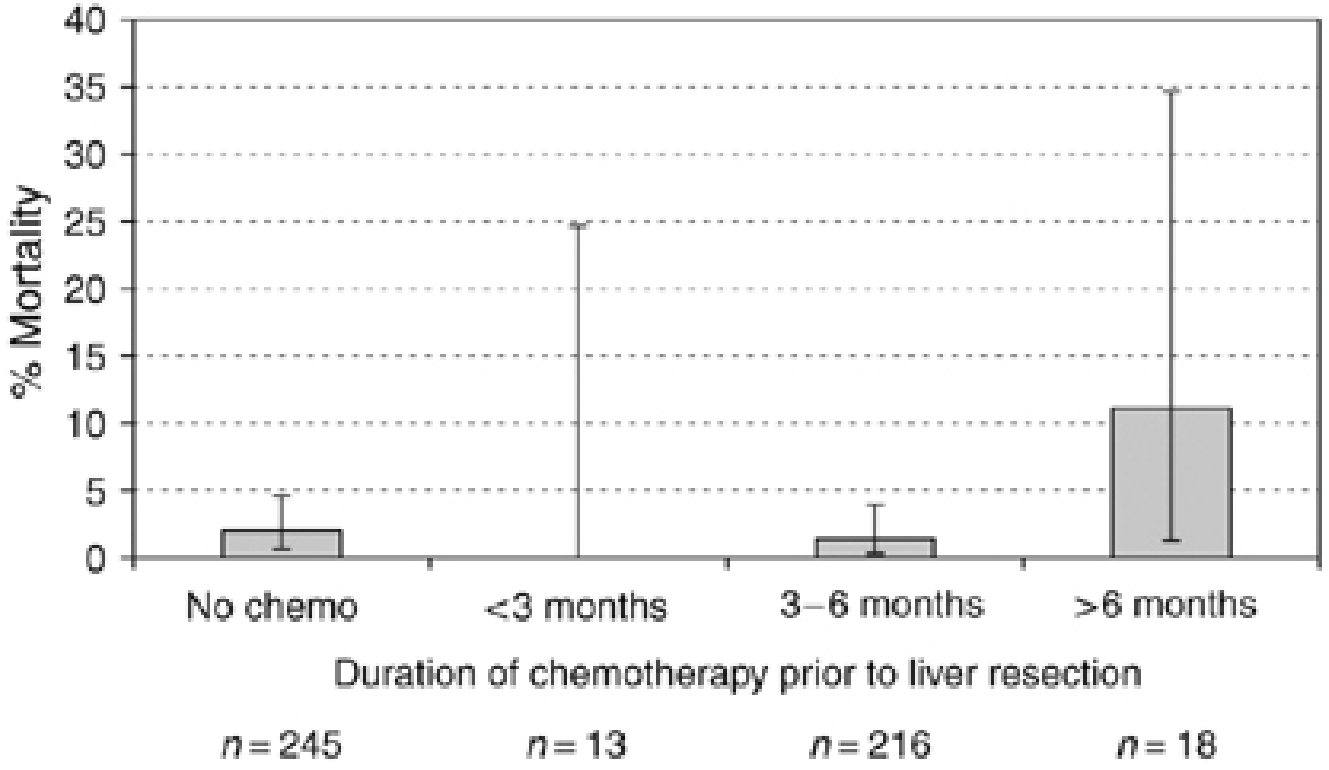
- Large lesion
- Ill-located lesions
- Multiple, bilateral lesions
- Extra-hepatic tumour

Timing of cessation of chemotherapy on postop morbidity and complications



F Welsh et al, Br J Cancer, 2007

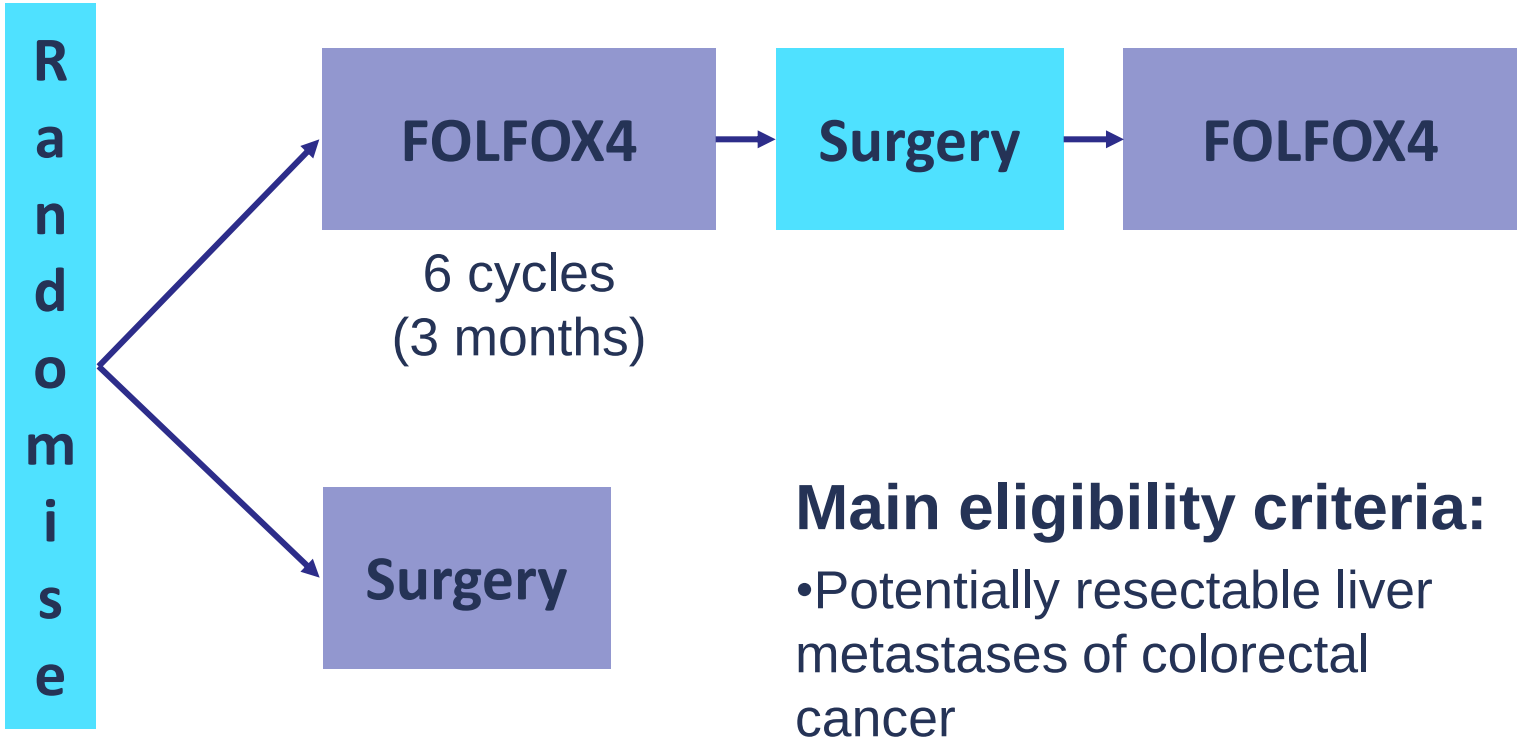
Effect of the duration of chemotherapy on postoperative mortality



F Welsh et al, Br J Cancer, 2007

Neoadjuvant chemotherapy for Resectable CRLM ?

EPOC trial (EORTC 40983)

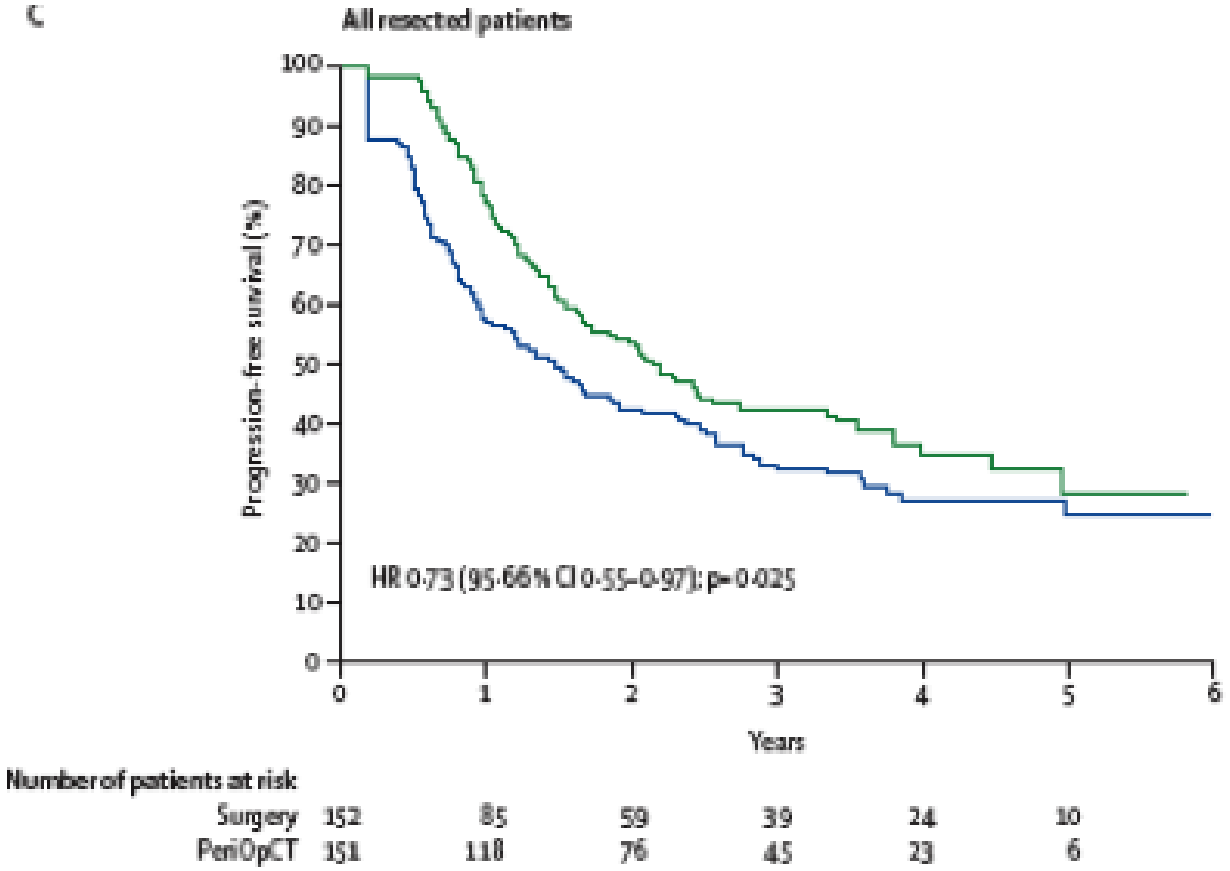


n=364 patients

Main eligibility criteria:

- Potentially resectable liver metastases of colorectal cancer
- Up to 4 deposits (on CT-scan, at randomisation)

33% improvement in 3-year disease free survival



EORTC multicentre trial of preop chemotherapy (5-FUFA+oxaliplatin) and surgery for resectable CR *vs* surgery alone

- Slight increase in postoperative complications
- No difference in 30-day mortality
- Improved disease free survival
- No difference in overall survival

Nordlinger, J Clin Onc 2005

Repeat resection

- Recurrent liver metastases can have excellent outcome following re-resection

- 1036 hepatectomies, 29% went on to repeat resection
- Up to max 4 resections
- 3yr survival 76%
- 5 yr survival 54%

Wicherts DA et al, Br J Surg. 2013

Original article

Initial experience with a multimodal enhanced recovery programme in patients undergoing liver resection

R. M. van Dam[1], P. O. Hendry[3], M. M. E. Coolsen[1], M. H. A. Bemelmans[1], K. Lassen[4,5], A. Revhaug[4,5], K. C. H. Fearon[3], O. J. Garden[3] and C. H. C. Dejong[1,2], on behalf of the Enhanced Recovery After Surgery (ERAS) Group

[1]Department of Surgery, Maastricht University Medical Centre and [2]Nutrition and Toxicology Research Institute, Maastricht University, Maastricht, The Netherlands, [3]Department of Surgery, Royal Infirmary, Edinburgh, UK, and [4]Department of Gastrointestinal Surgery, University Hospital Northern Norway, and [5]Faculty of Medicine, University of Tromsø, Tromsø, Norway

Correspondence to: Dr R. M. van Dam, Department of Surgery, Maastricht University Medical Centre, PO Box 5800, 6202 AZ Maastricht, The Netherlands (e-mail: rvdm@surgery.azm.nl)

Hypothesis :- goal directed (fast track) programme which optimised peri-operative care reduces accelerates recovery, reduces hospital stay and shortens hospital stay

British Journal of Surgery 2008; **95**: 969–975

Enhanced Recovery After Surgery

- same day admission
- oral carbohydrate loading 2 hours prior to anaesthesia
- thoracic epidural and short-acting anaesthetic agent
- no nasogastric tube or intra-abdominal drain
- recovery area or surgical HDU before transfer to ward
- commence fluids/diet and mobilisation on same day

Enhanced recovery after liver surgery

- Patients informed regarding protocol at preadmission counselling session
  - importance of early mobilization and oral intake explained
- Patients were discharged only if they met the discharge criteria and follow-up within 3 days was possible
- Patients were given the mobile telephone number of the operating consultant surgeon*
  - direct communication and safe deployment of protocol.

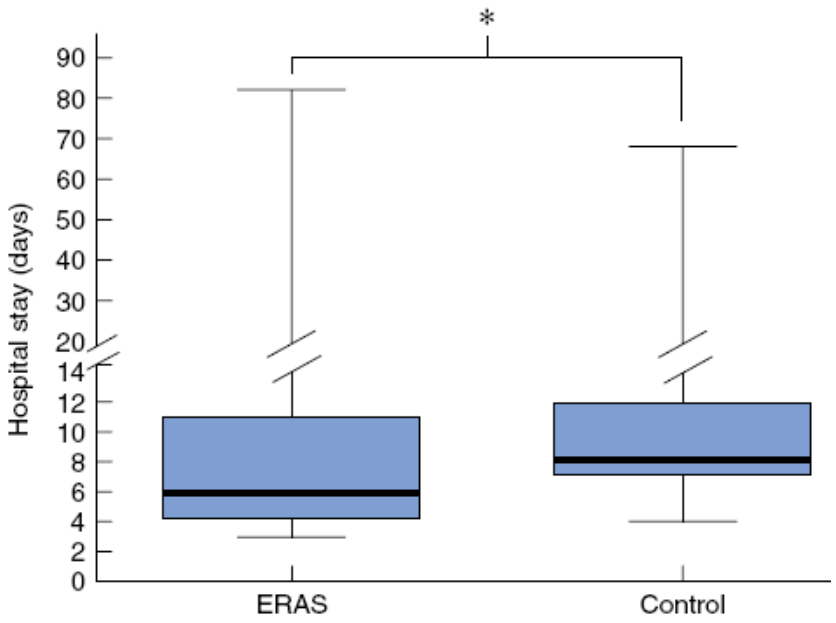
* Maastricht only

Outcomes

	ERAS	Control	P-value
	n=61	n=100	
Epidural analgesia	58(95)	89(89)	0.184
Abdominal Drain	1(2)	66(66)	<0.001
Complications	25(41)	31(31)	0.197
Mortality	0(0)	2(2)	0.526
Readmissions	8(13)	10(10)	0.543
Total length of hospital stay*	6(3-82)	8(4-65)	<0.001

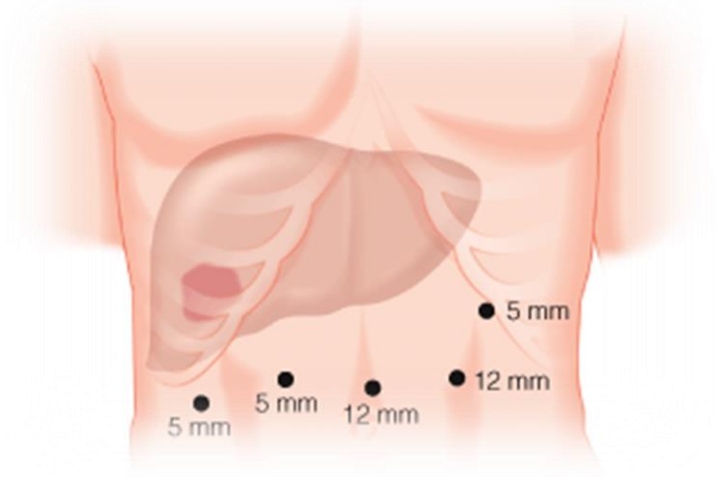
*Median (range) number of days all others incidence (percentage)

ERALS - markers of recovery



- 92% of patients resumed oral intake within 4 hours
- Normal diet resumed by day 1 (0-3) median (range)
- 2 patients required NG tube reinsertion
- 85% of patients fully mobile by day 3
- 48% discharged within 5 days

Advantages of Laparoscopic Liver Surgery



Short-term

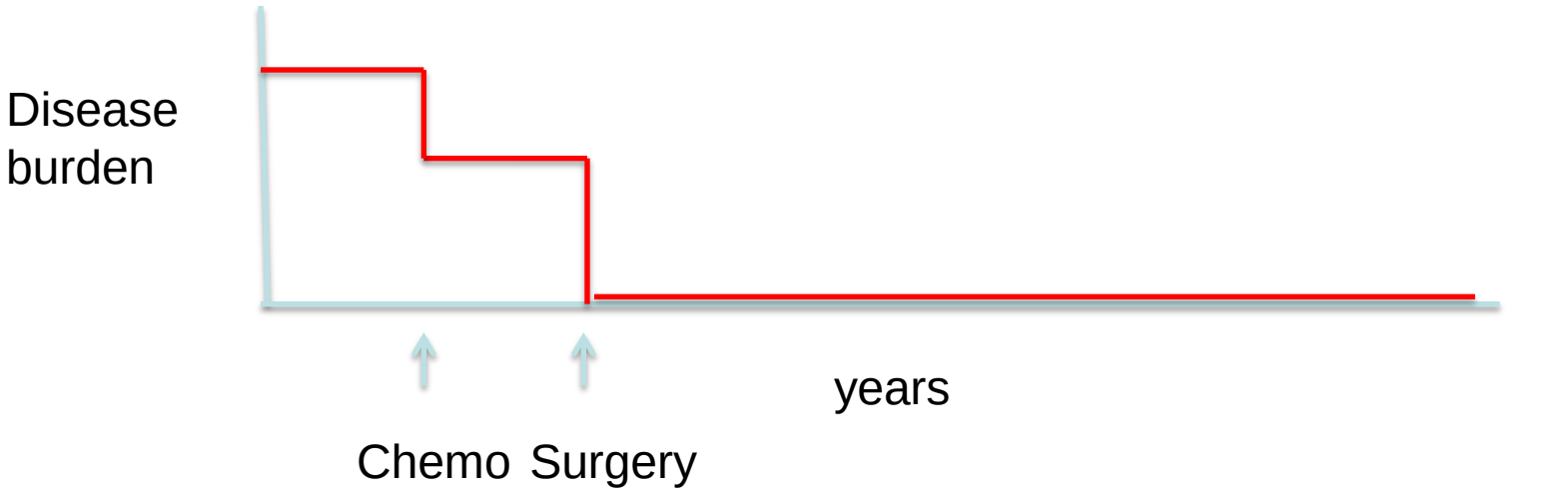
- Lower complication rates
- Less pain
- Shorter LOS
- Return to normal activity
- Decreased overall cost

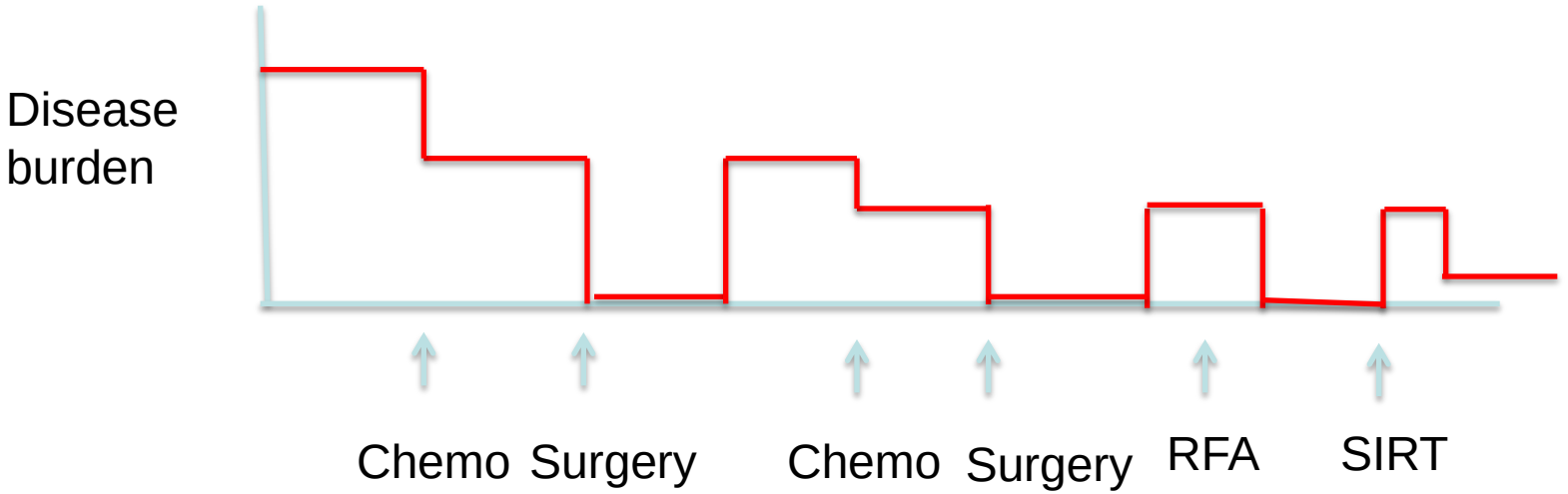
Long-term

- Incisional-related complications
- No oncological disadvantage

For colorectal liver metastases – The ability to control disease and the range of treatment options has been a game changer

Colorectal liver metastases





Colorectal metastases - the future ?

- Improved selection and staging of patients for resection
- Better understanding of residual liver volume and post resection liver failure
- Improvements in systemic (neoadjuvant) chemotherapy
- Extending conventional boundaries of resectability
    - radiological, surgical and ablative
- Multi-modal long-term treatment