



Management of metastatic colorectal cancer

Adam Bartlett PhD, FRACS

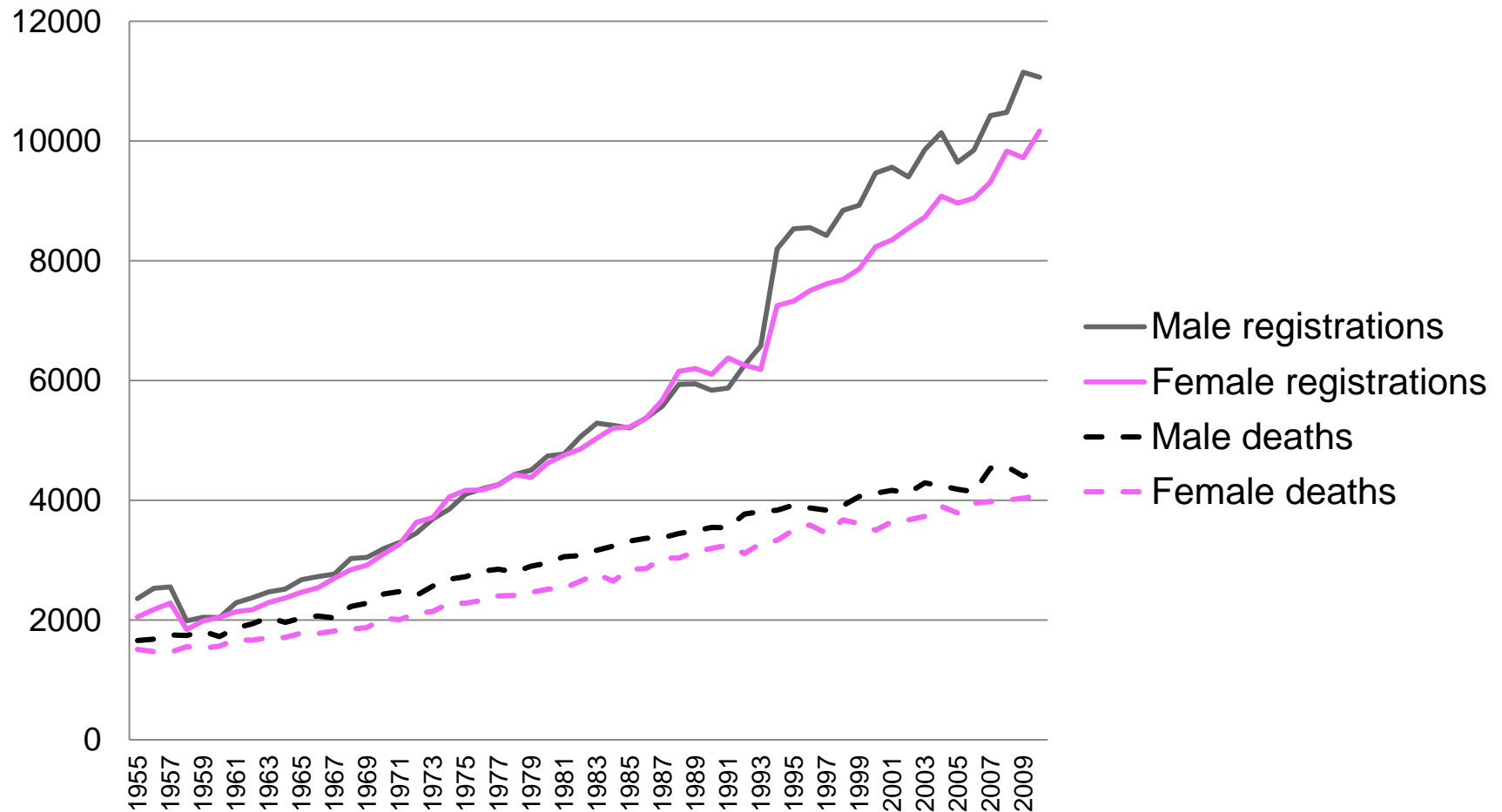
Hepato-pancreatico-biliary (HPB), General and Transplant Surgeon



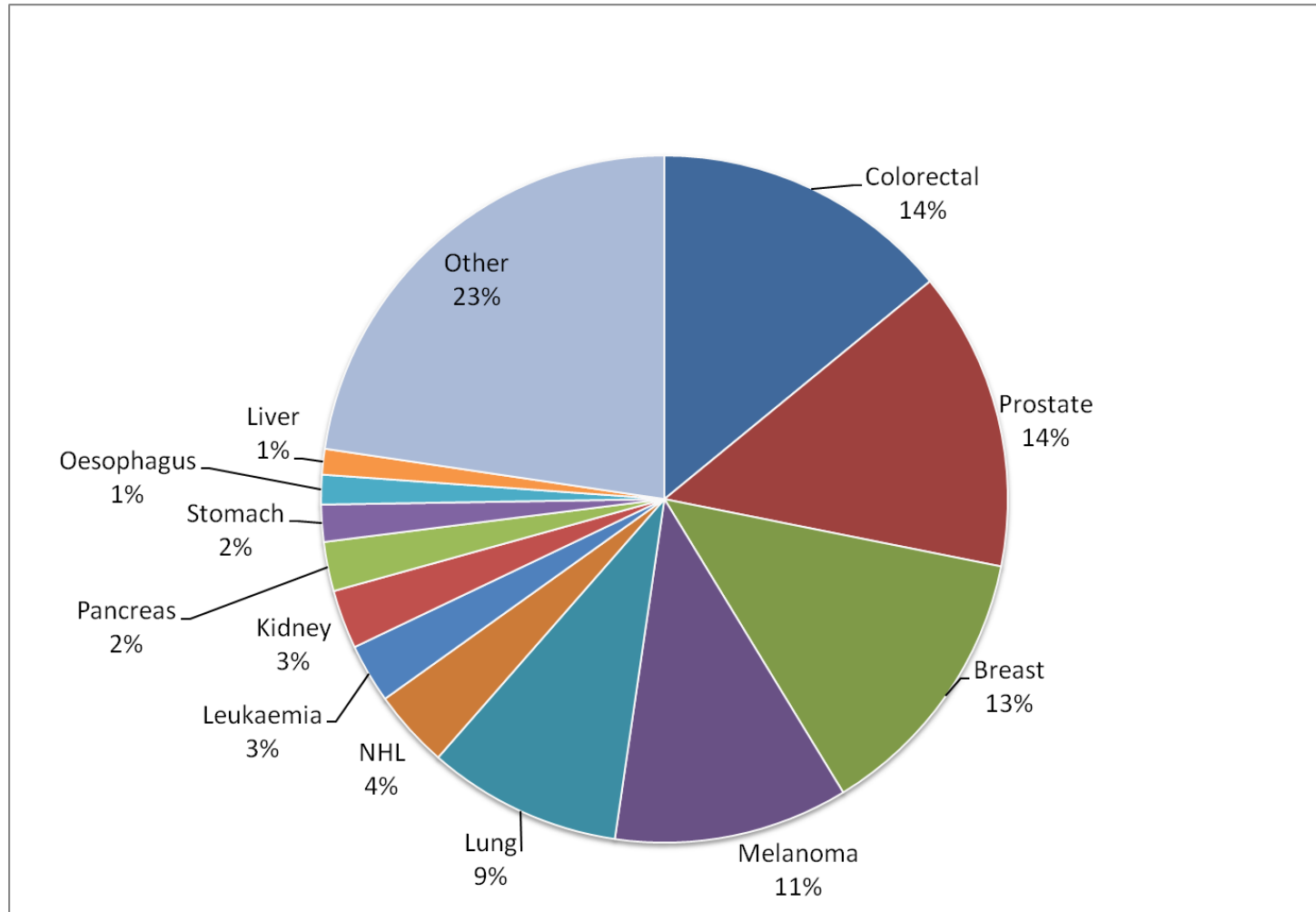
“It is impossible to be a competent surgeon without using higher-order cognitive skills”

Spencer et al Bulletin of the American College of Surgery, 64, 9-12 1978.

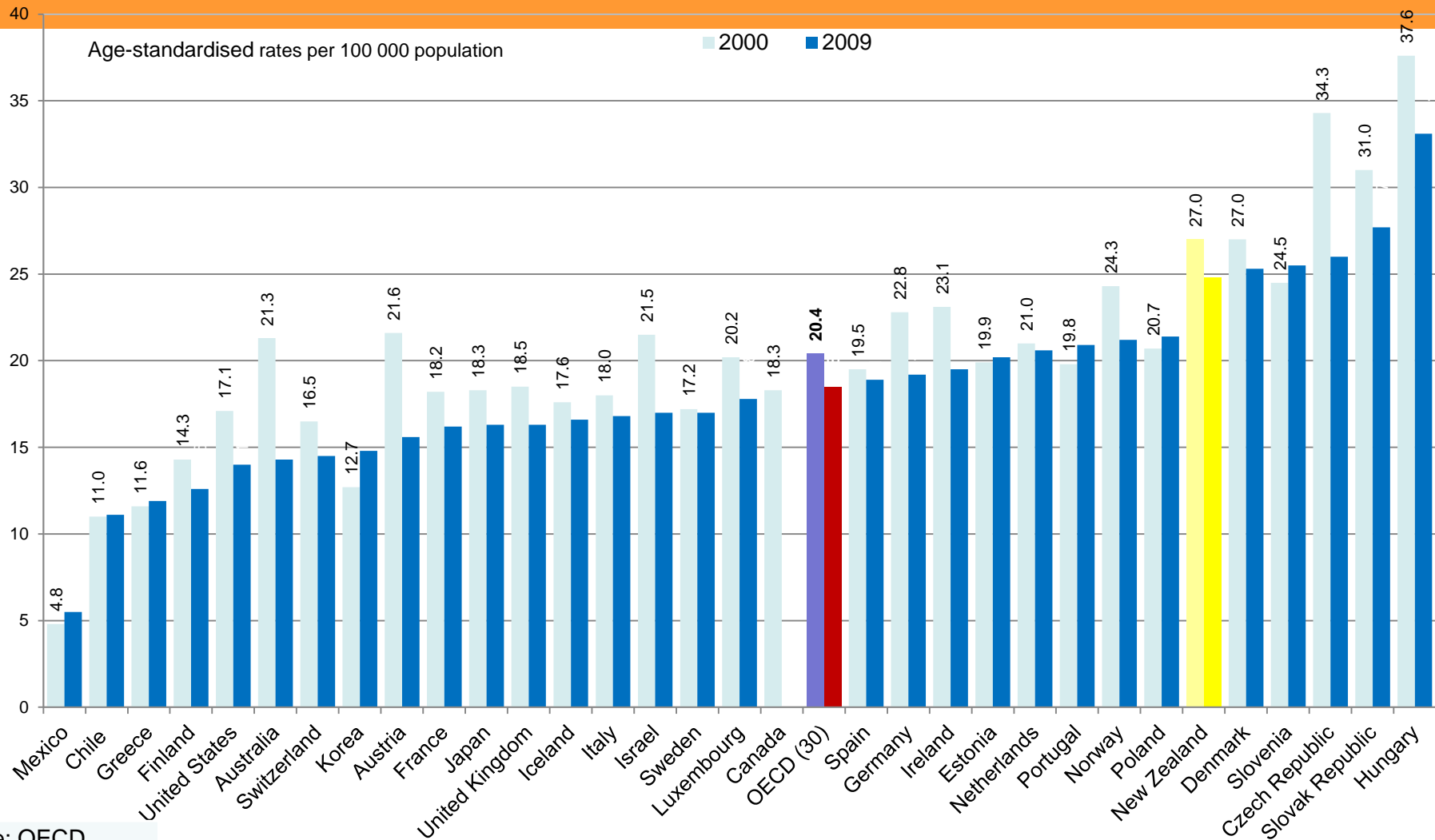
NZ Cancer Registrations and Deaths



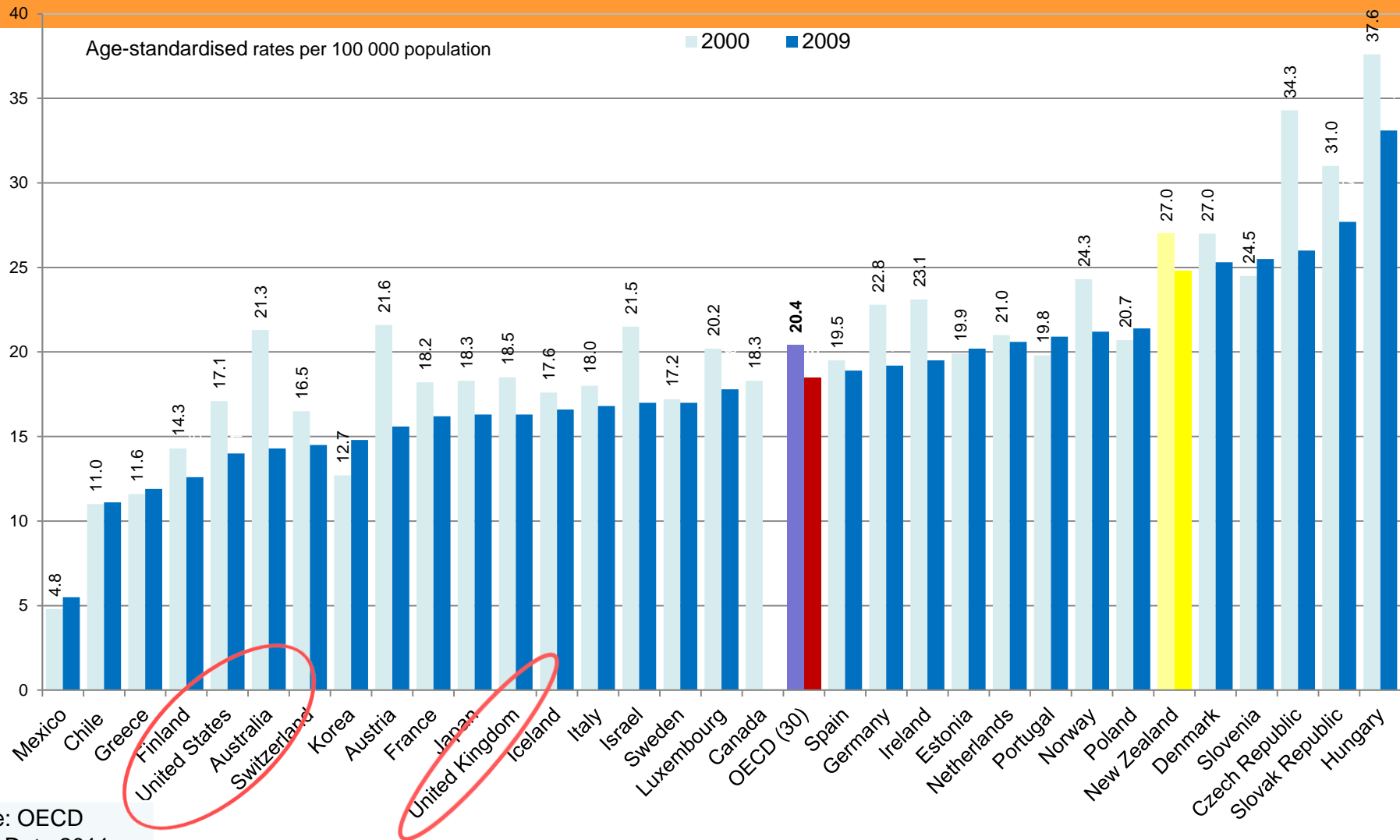
New Zealand Cancer registrations 2010



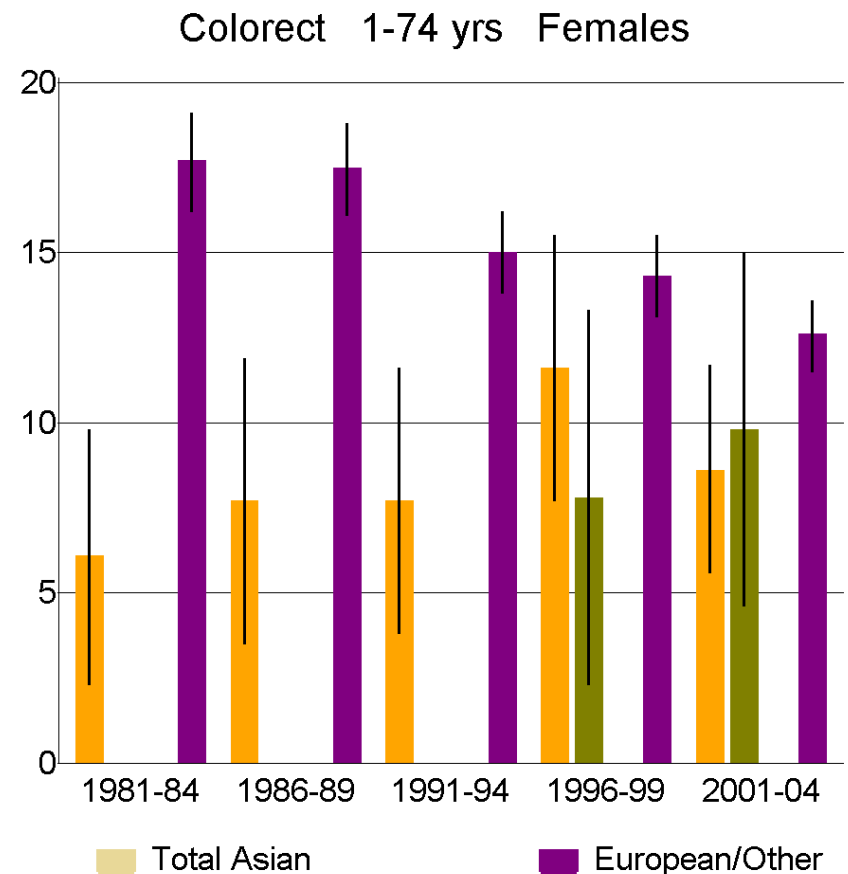
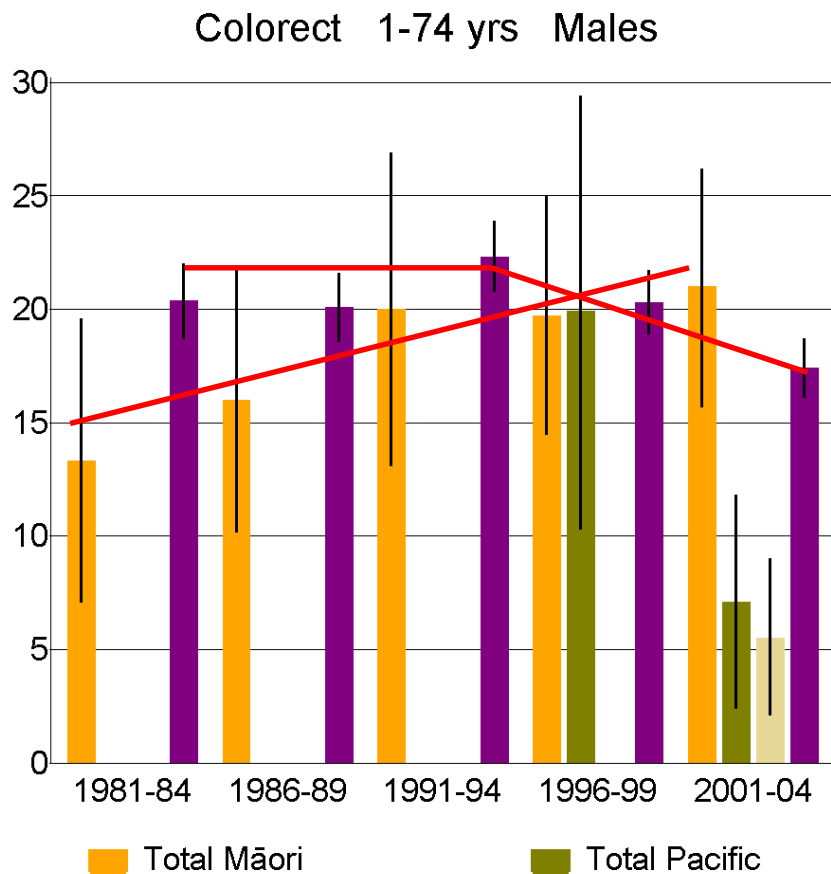
NZ has high death rates from colorectal cancer



NZ has high death rates from colorectal cancer



Bowel cancer mortality: What's happening over time?

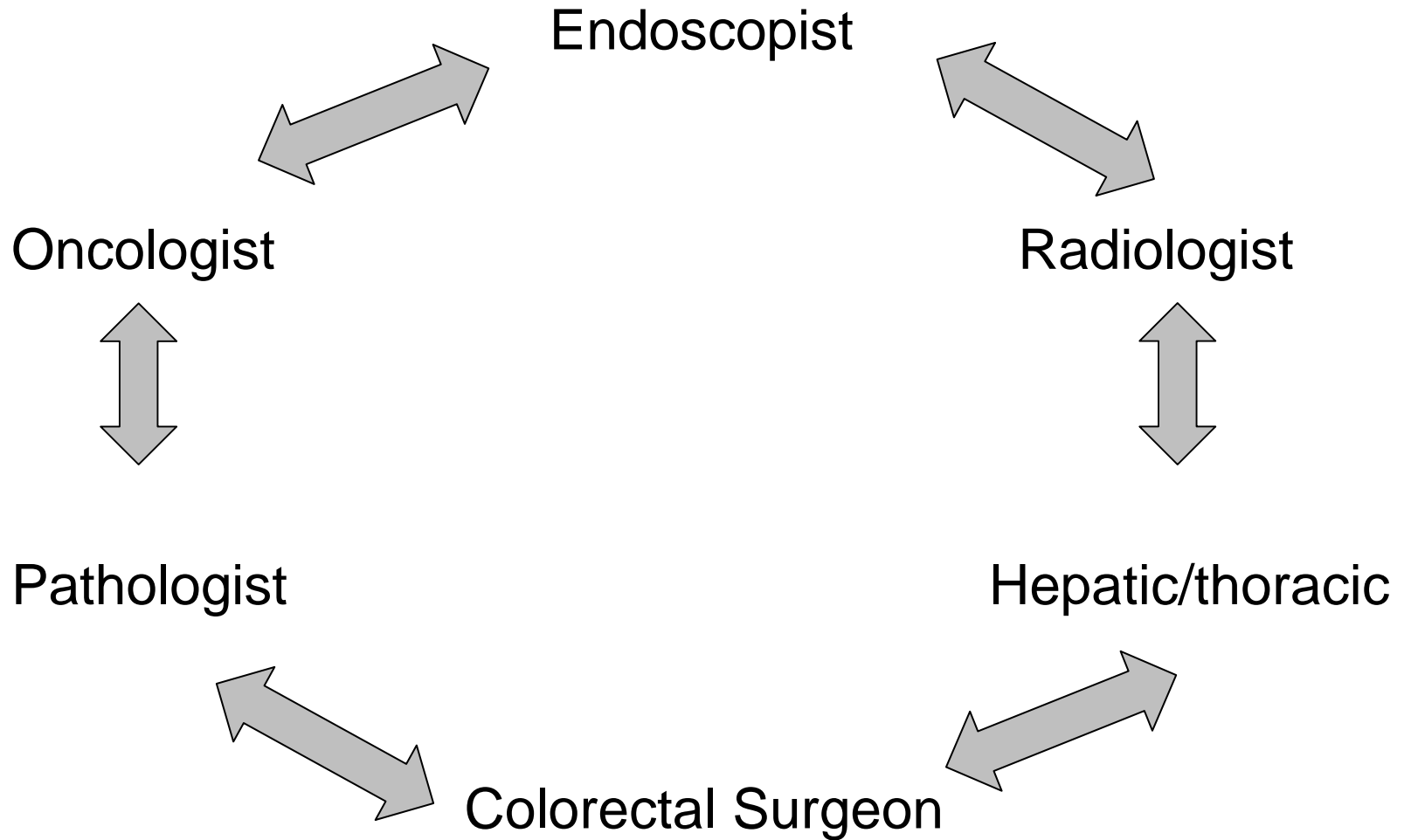


Shaw C, Blakely T, Sarfati D, et al. Trends in colorectal cancer mortality by ethnicity and socioeconomic position in New Zealand 1981-1999: One country, many stories. *Aust NZ J Public Health*. 2006; 30 (1): 64-70.

Metastatic colorectal cancer common

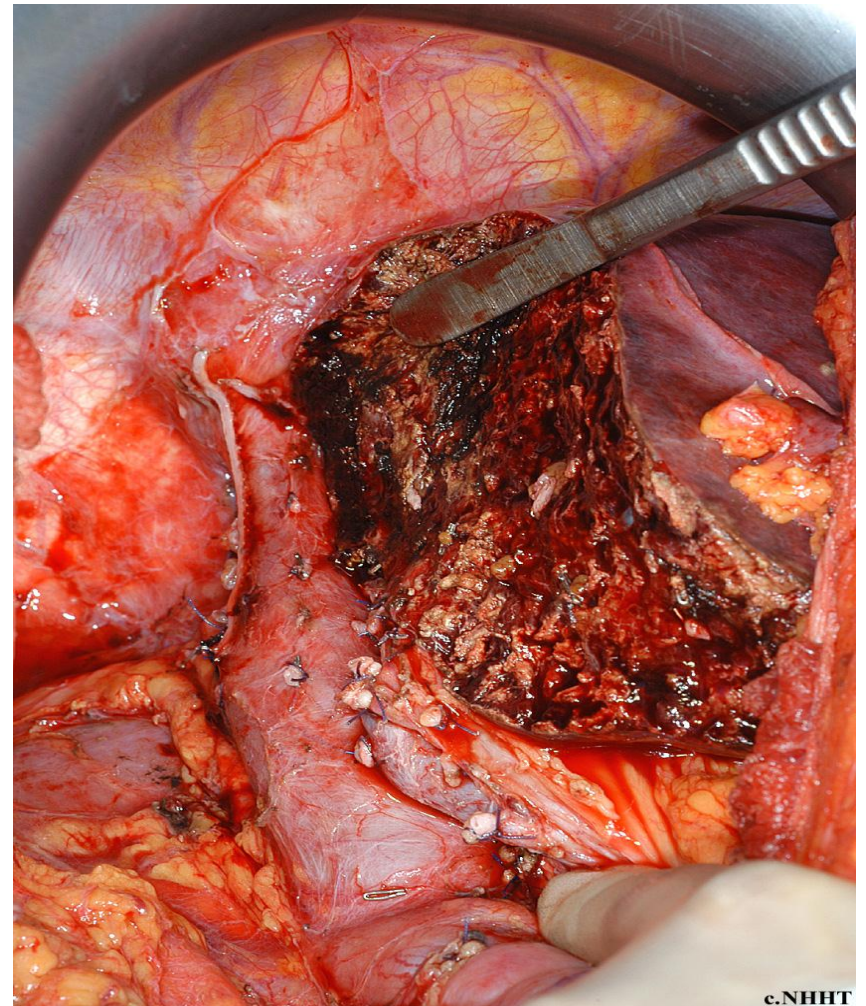


A multidisciplinary team approach



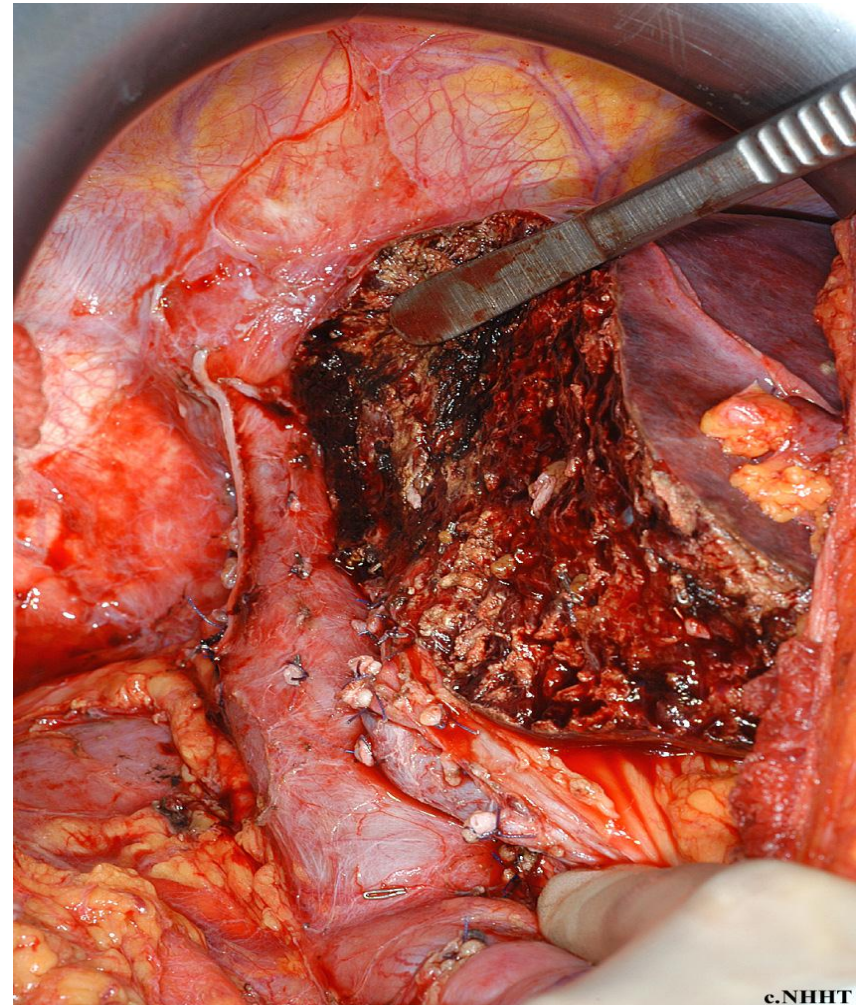
Strategies for managing metastatic colorectal cancer

- Surgical resection
- Chemotherapy
- Radiotherapy
- Tissue ablation
- Liver directed therapy

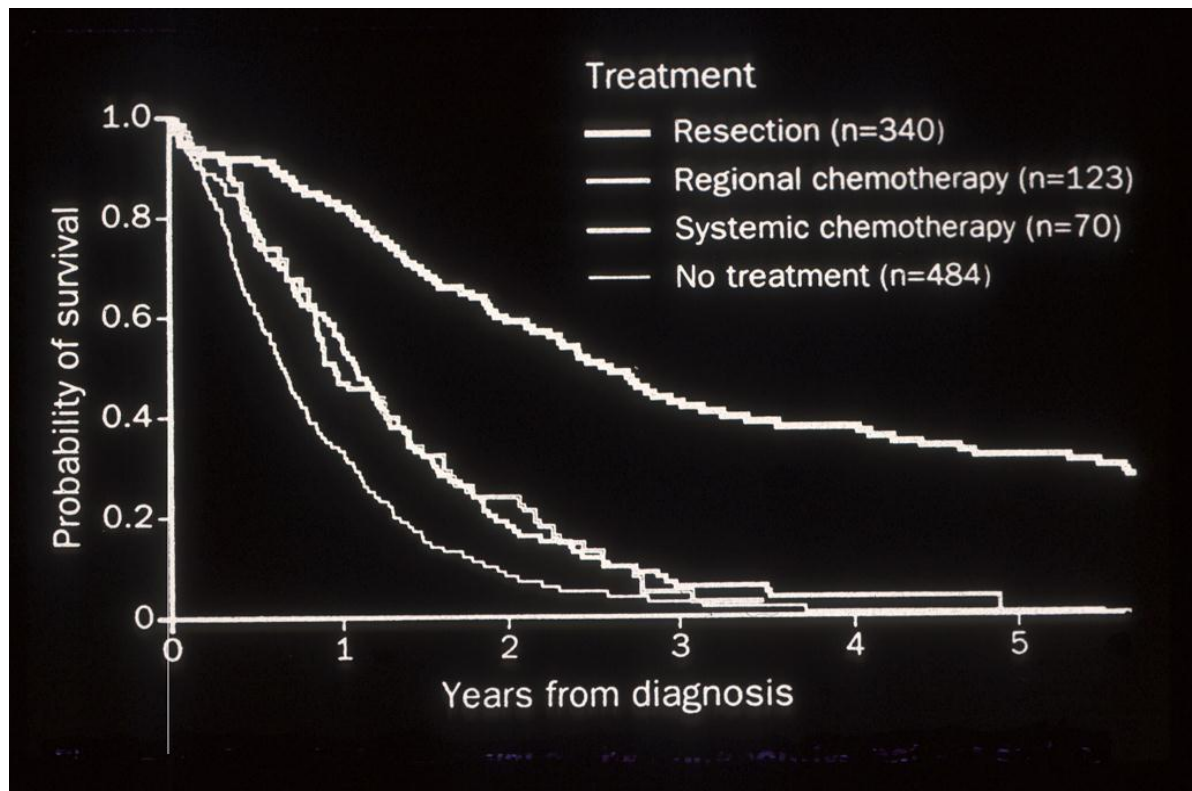


Strategies for managing metastatic colorectal cancer

- Surgical resection
- Chemotherapy
- Radiotherapy
- Tissue ablation
- Liver directed therapy



Prognosis relative to treatment



Traditional resection criteria

- Unilobar disease
- < 2 lesions
- > 1cm margin achievable
- Negative portal node
- No extra-hepatic disease



Traditional resection criteria

- Unilobar disease
- < 2 lesions
- $> 1\text{cm}$ margin achievable
- Negative portal node
- No extra-hepatic disease

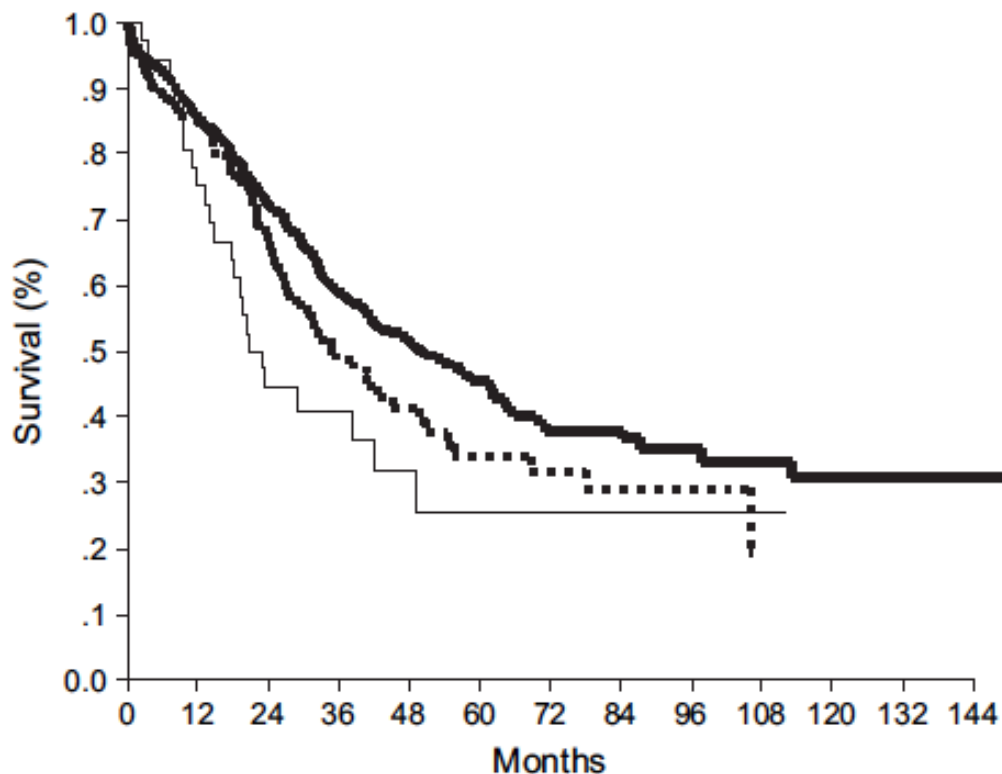


Prognostic influence of multiple hepatic metastases from colorectal cancer

H.Z. Malik, Z.Z.R. Hamady, R. Adair, R. Finch, A. Al-Mukhtar,
G.J. Toogood, K.R. Prasad, J.P.A. Lodge*

HPB and Transplant Unit, St. James's University Hospital, Leeds LS9 7TF, UK

Accepted 28 September 2006

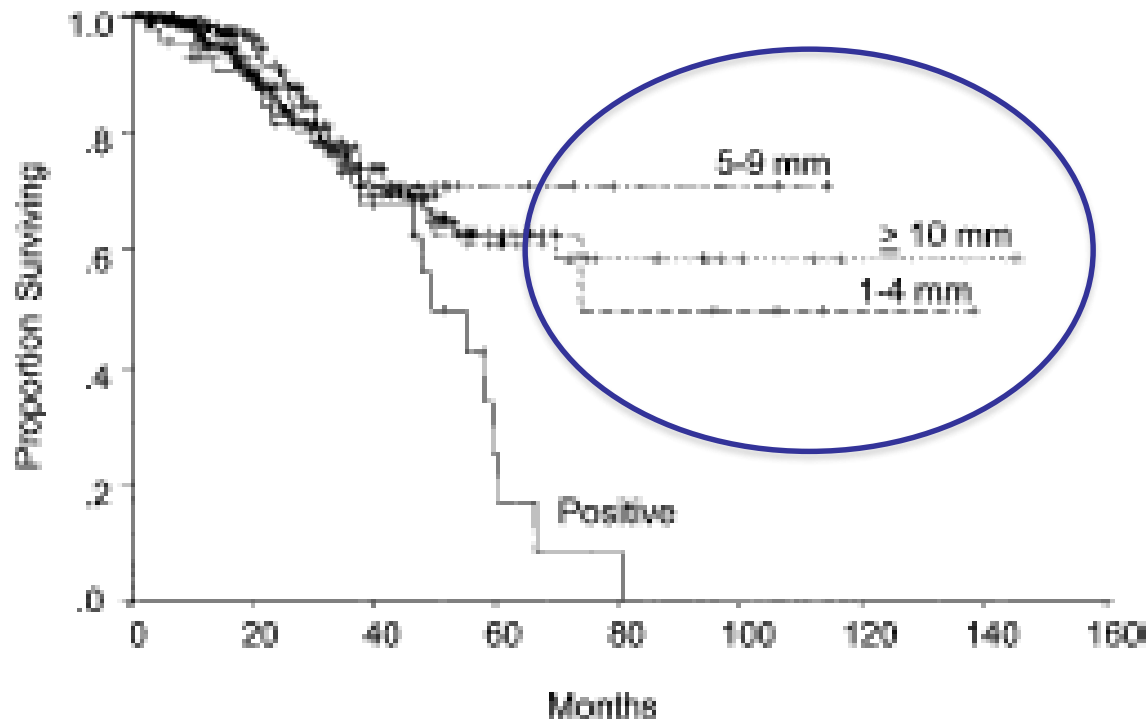


Number	5yr survival:
< 4	44%
4-7	39%
>8	24%

Figure 2. Overall survival comparing the groups for increasing numbers of metastases. Patients with less than 4 metastases, solid bold line; patients with 4–7 metastases, interrupted line; patients with 8 or more metastases, solid thin line. $p = 0.0245$ (comparing 4–7 tumours with 8 or more tumours).

Effect of Surgical Margin Status on Survival and Site of Recurrence After Hepatic Resection for Colorectal Metastases

Timothy M. Pawlik, MD, MPH,* Charles R. Scoggins, MD,* Daria Zorzi, MD,*
Eddie K. Abdalla, MD,* Axel Andres, MD,|| Cathy Eng, MD,† Steven A. Curley, MD,*
Evelyne M. Loyer, MD,‡ Andrea Muratore, MD,§ Gilles Mentha, MD,||
Lorenzo Capussotti, MD,§ and Jean-Nicolas Vauthey, MD*

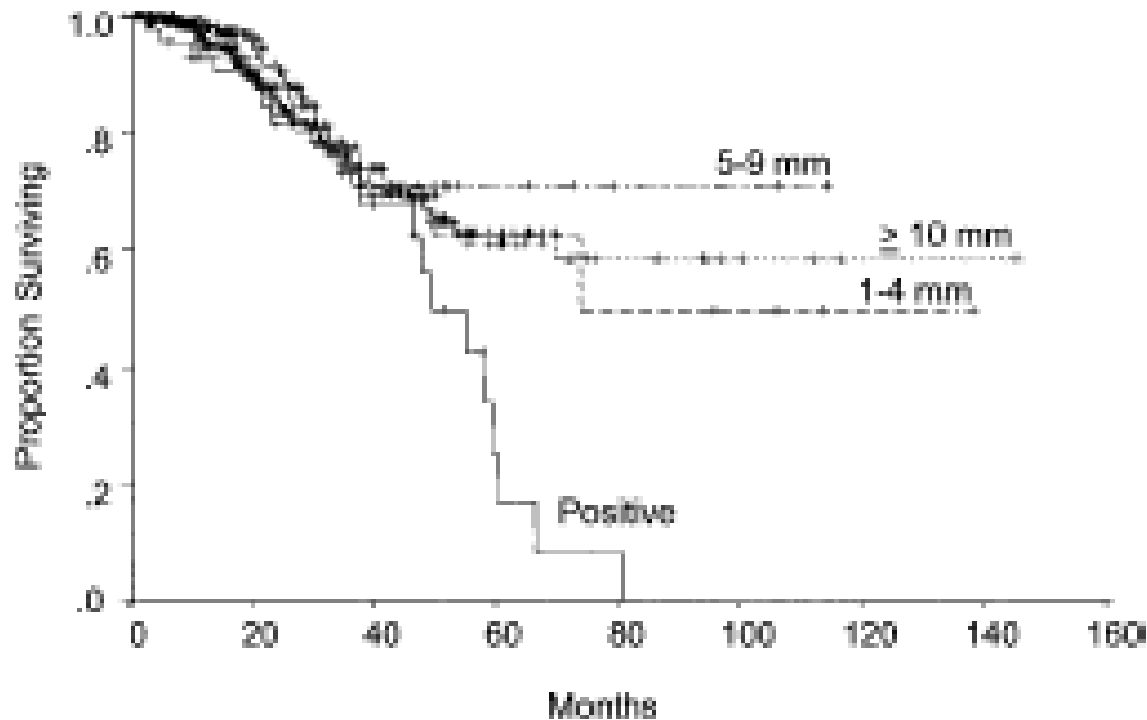


5 year survival:

No difference

Effect of Surgical Margin Status on Survival and Site of Recurrence After Hepatic Resection for Colorectal Metastases

Timothy M. Pawlik, MD, MPH,* Charles R. Scoggins, MD,* Daria Zorzi, MD,*
 Eddie K. Abdalla, MD,* Axel Andres, MD,|| Cathy Eng, MD,† Steven A. Curley, MD,*
 Evelyne M. Loyer, MD,‡ Andrea Muratore, MD,§ Gilles Mentha, MD,||
 Lorenzo Capussotti, MD,§ and Jean-Nicolas Vauthey, MD*



5 year survival:

+ve = 17%

-ve = 64%

P = 0.01

Liver Resection for Colorectal Metastases in Presence of Extrahepatic Disease: Results from an International Multi-institutional Analysis

Carlo Pulitanò, MD^{1,2}, Martin Bodingbauer, MD³, Luca Aldrighetti, MD, PhD², Mechteld C. de Jong, MD⁴, Federico Castillo, MD, PhD¹, Richard D. Schulick, MD⁴, Rowan W. Parks, MD¹, Michael A. Choti, MD⁴, Stephen J. Wigmore, MD, PhD¹, Thomas Gruenberger, MD³, and Timothy M. Pawlik, MD, MPH⁴

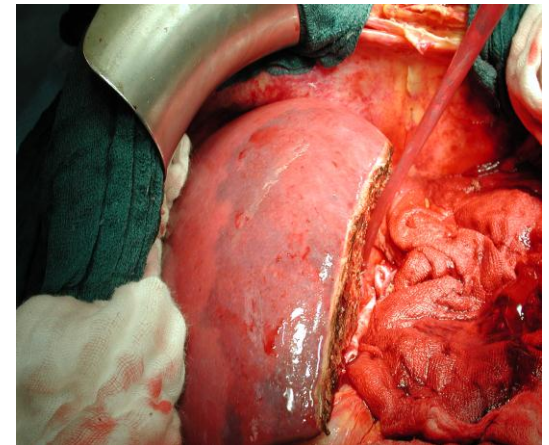
¹Department of Clinical and Surgical Sciences (Surgery), Royal Infirmary of Edinburgh, University of Edinburgh, Edinburgh, UK; ²Department of Surgery, Liver Unit, Scientific Institute San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; ³Department of General Surgery, Hepatobiliary Service, Medical University of Vienna, Vienna, Austria; ⁴Division of Surgical Oncology, Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD

Site	<i>n</i> (%)	Median survival (mo)	3-Year survival (%)	5-Year survival (%)
Lung	62 (36.2)	46	60	33
Peritoneum	25 (14.6)	32	32	26
Hepatic pedicle lymph nodes	41 (23.9)	29	43	27
Aortocaval lymph nodes	14 (8.1)	13	22	7
Other	11 (6.5)	— ^a	— ^a	— ^a
Multiple sites	18 (10.5)	15	26	14

^a Number of patients too small for survival calculations

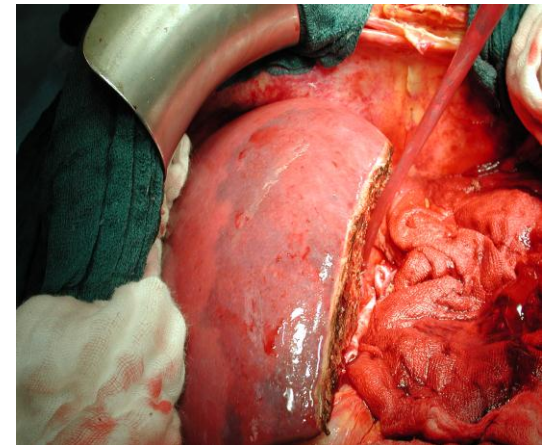
Management of metastatic colorectal cancer

- Simultaneous bowel and metastases
- Hepatectomy after primary
- Primary after hepatectomy
- Chemotherapy prior to either resection



Management of metastatic colorectal cancer

- Simultaneous bowel and metastases
- Hepatectomy after CRCa primary
- CRCa primary after hepatectomy
- Chemotherapy prior to either resection



Order does not appear to be important – need to ensure patient receives both surgery and chemotherapy

Chemotherapy - Important questions

- Is adjuvant chemotherapy beneficial ?
- Is preoperative (downsizing) chemotherapy beneficial in
 - *Unresectable ?*
 - *Bordeline resectable ?*
 - *Unfit ?*
- Is preoperative (neoadjuvant) chemotherapy justified for resectable lesions ?

Chemotherapy - Important questions

- Is adjuvant chemotherapy beneficial ? **PROBABLY**
- Is preoperative (downsizing) chemotherapy beneficial in
 - *Unresectable ?* **YES**
 - *Bordeline resectable ?* **YES**
 - *Unfit ?* **YES**
- Is preoperative (neoadjuvant) chemotherapy justified for resectable lesions ? **UNKNOWN**

Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial

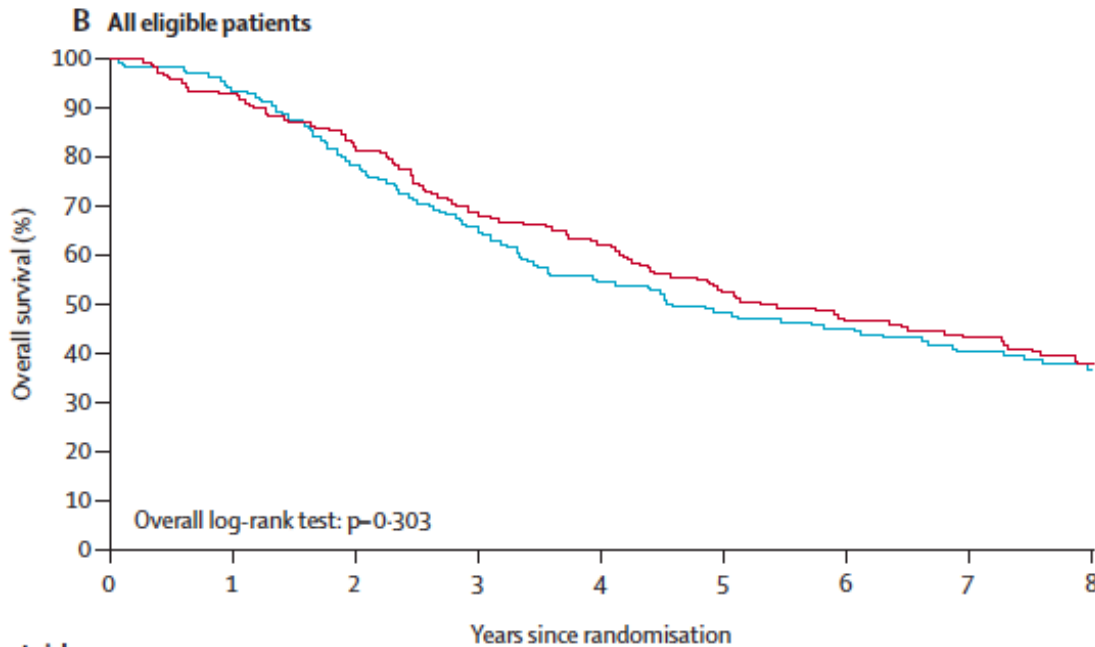
*Bernard Nordlinger, Halfdan Sorbye, Bengt Glimelius, Graeme J Poston, Peter M Schlag, Philippe Rougier, Wolf O Bechstein, John N Primrose, Euan T Walpole, Meg Finch-Jones, Daniel Jaeck, Darius Mirza, Rowan W Parks, Laurence Collette, Michel Praet, Ullrich Bethé, Eric Van Cutsem, Werner Scheithauer, Thomas Gruenberger for the EORTC Gastro-Intestinal Tract Cancer Group, * Cancer Research UK, * Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO), * Australasian Gastro-Intestinal Trials Group (AGITG), * and Fédération Francophone de Cancérologie Digestive (FFCD)**

- 35% vs 24% disease free survival at three years for FOLFOX group
- No overall survival advantage
- More surgery related complications in the FOLFOX group (25% vs 16%)



Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial

Bernard Nordlinger, Halfdan Sorbye, Bengt Glimelius, Graeme J Poston, Peter M Schlag, Philippe Rougier, Wolf O Bechstein, John N Primrose, Evan T Walpole, Meg Finch-Jones, Daniel Jaeck, Darius Mirza, Rowan W Parks, Murielle Maurer, Erik Tanis, Eric Van Cutsem, Werner Scheithauer, Thomas Gruenberger, for the EORTC Gastro-Intestinal Tract Cancer Group, Cancer Research UK, Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO), Australasian Gastro-Intestinal Trials Group (AGITG), and Fédération Francophone de Cancérologie Digestive (FFCD)



5 year survival:
51% vs 48%

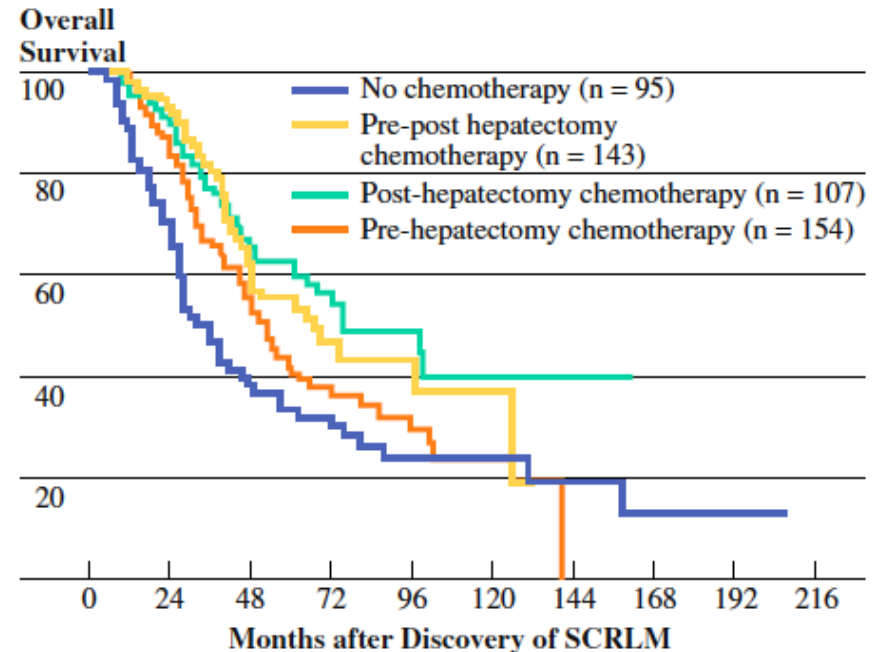
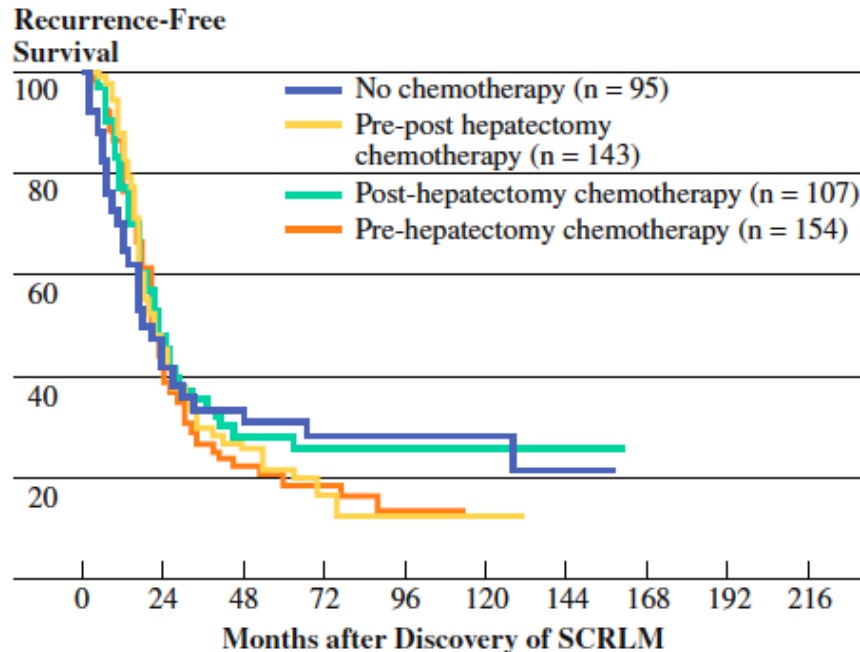
Number at risk

Surgery only	171	159	133	111	91	76	69	56
Perioperative chemotherapy	171	158	139	114	103	86	70	64

Timing of Multimodality Therapy for Resectable Synchronous Colorectal Liver Metastases: A Retrospective Multi-Institutional Analysis

Srinevas K. Reddy¹, Daria Zorzi², Ying Wei Lum³, Andrew S. Barbas¹, Timothy M. Pawlik³, Dario Ribero², Eddie K. Abdalla³, Michael A. Choti², Clinton Kemp³, Jean-Nicolas Vauthey², Michael A. Morse⁴, Rebekah R. White¹, and Bryan M. Clary¹

¹Department of Surgery, Duke University Medical Center, Box 3247, Durham, NC 27710, USA; ²Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; ³Department of Surgery, Johns Hopkins Medical Institutions, Baltimore, MD 21287, USA; ⁴Department of Medicine, Duke University Medical Center, Durham, NC 27710, USA



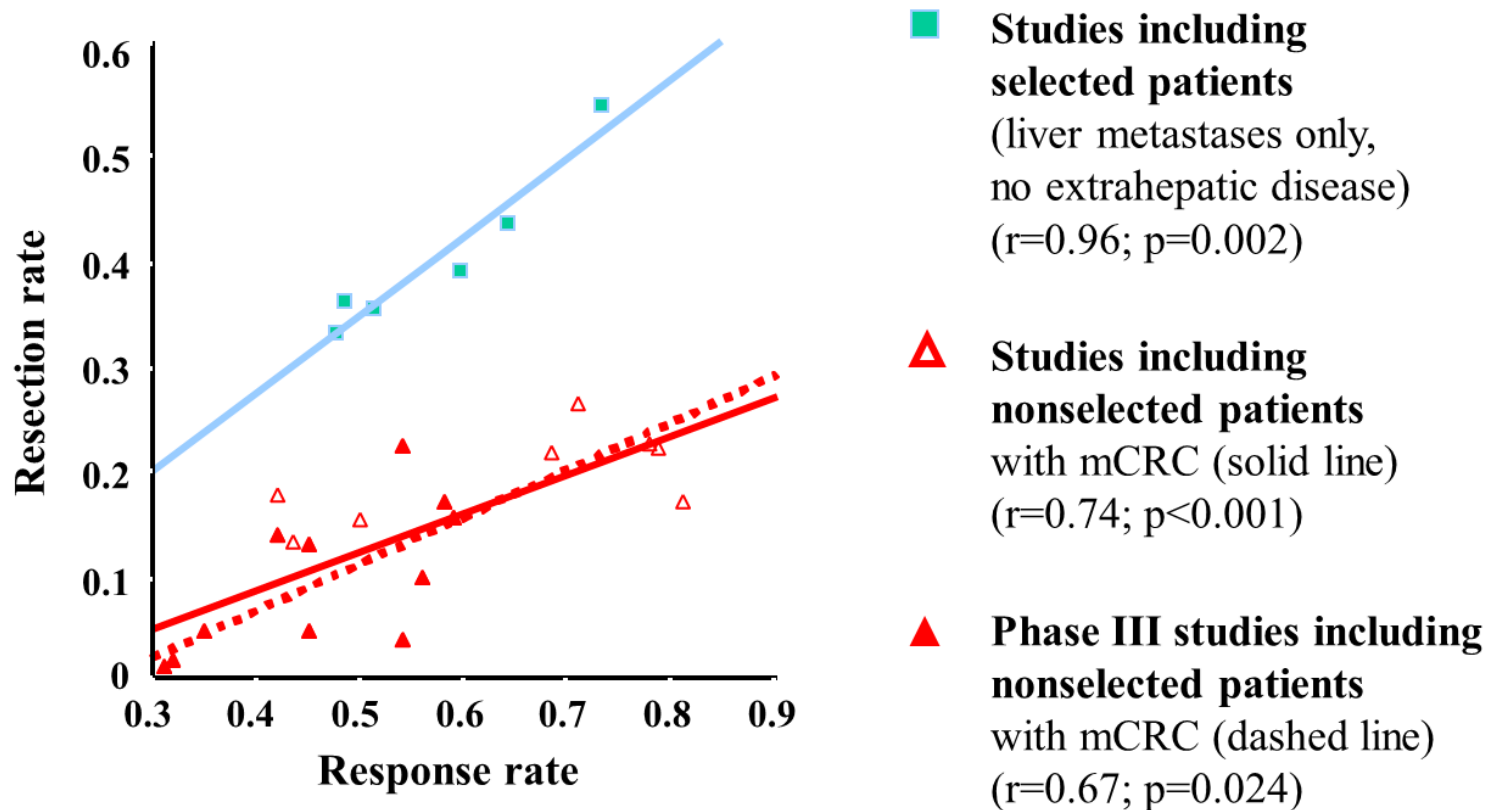
Other issues with chemotherapy:

- Trial of time versus progression on chemotherapy
- Disappearing lesions
- Liver damage post chemotherapy
- Delay to surgery after chemotherapy

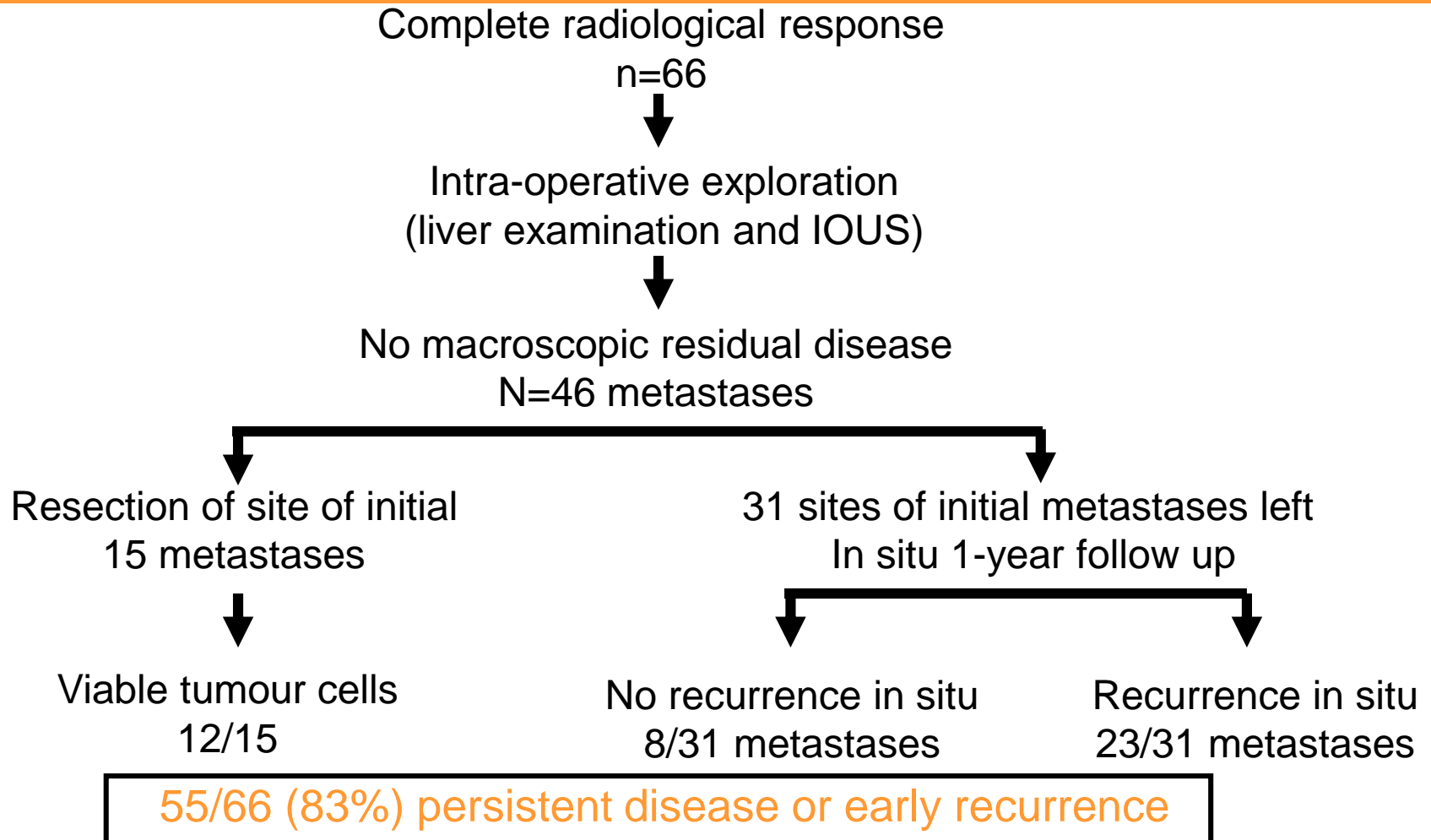


Response on chemo an important predictor

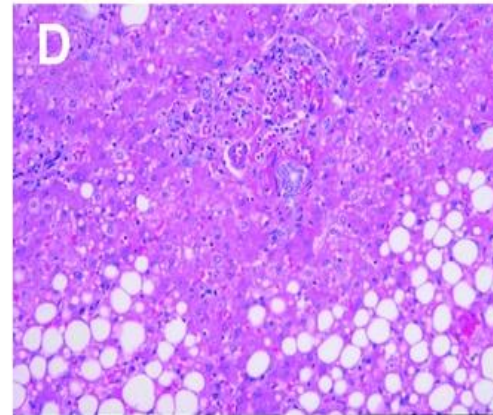
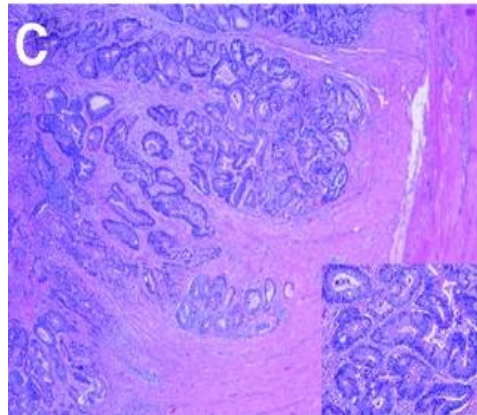
Folprecht G, et al. Ann Oncol 2005;16:1311–1319



Complete response of CRCa liver metastases



Tumour better but liver worse!



Not observed <6 cycles

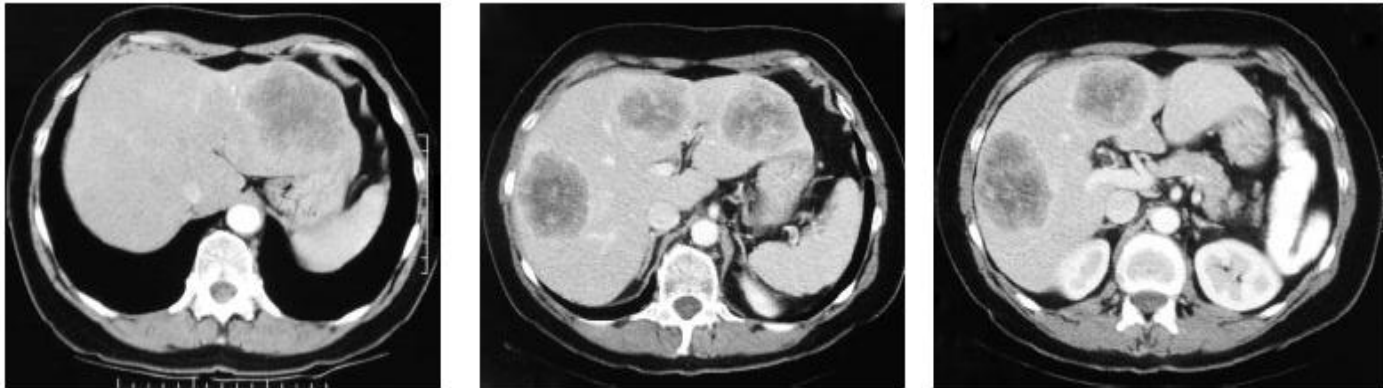
Recommendation

Resectable hepatic
disease with other
favorable factors



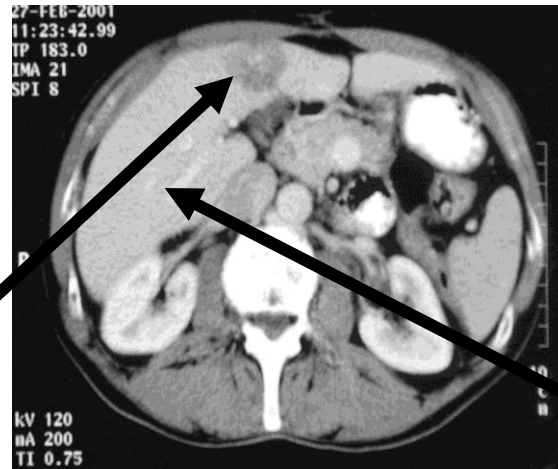
Straight to resection

Reality for most patients



Disease is beyond resectability

Strategies to improve resectability



Reduce size index lesion
remnant

Chemotherapy

Targeted ablation

Liver directed therapy

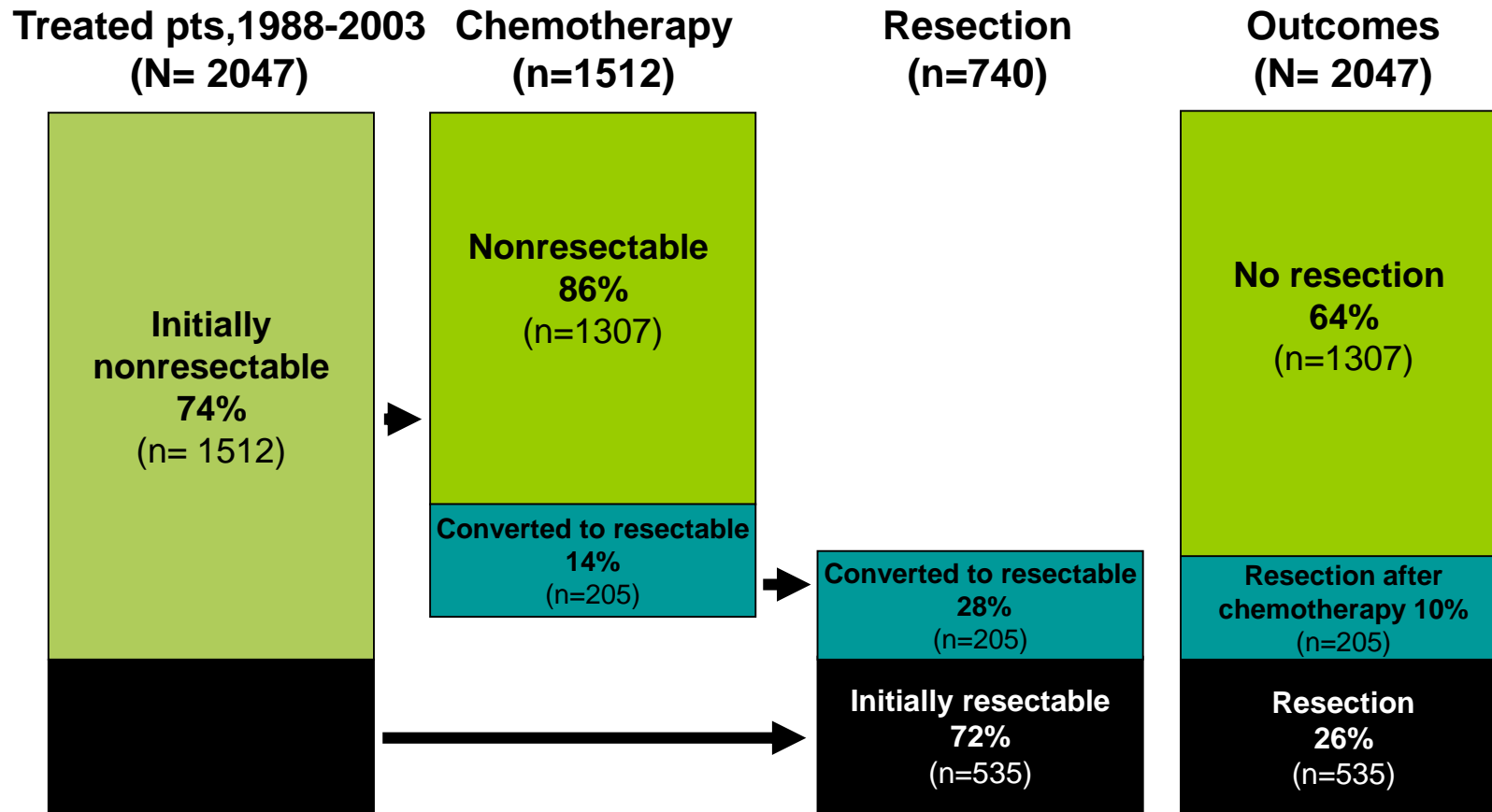
Increase size future liver

Portal vein embolisation

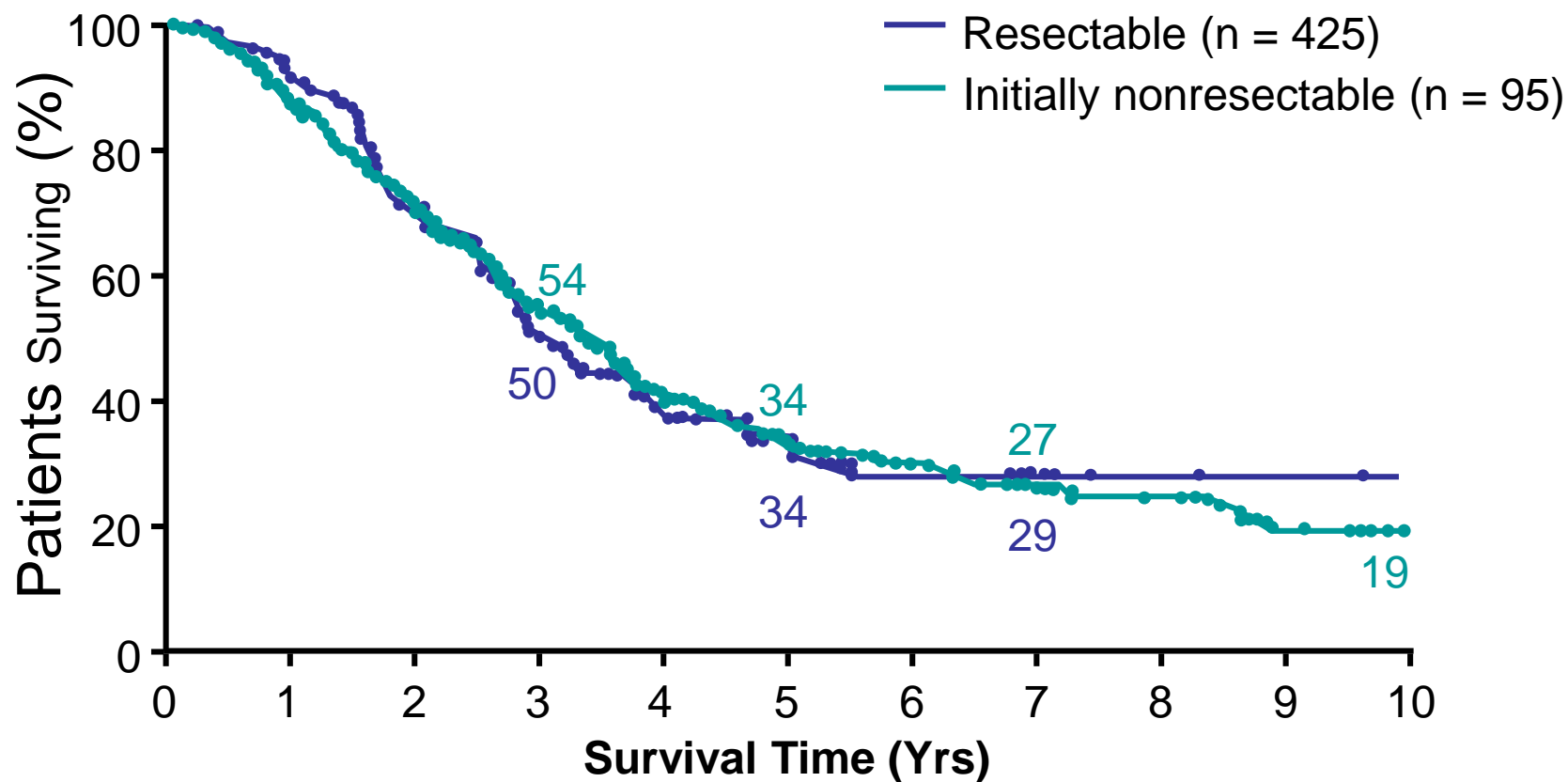
2-stage hepatectomy

ALPS resection

Neoadjuvant Oxaliplatin: Paul Brousse Hospital study



Survival of Liver Metastases based on initial resectability



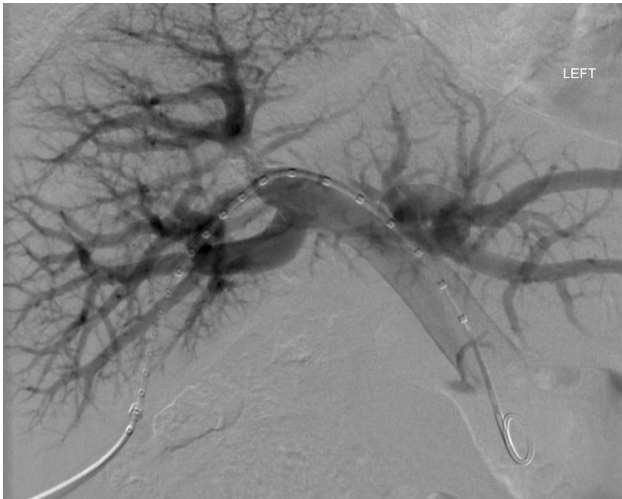
Portal vein embolisation (PVE)



“... to initiate compensatory hypertrophy of the future remnant liver, thus preventing postoperative liver failure.”

Makuuchi et al. Surgery 1990; 107: 521-7

PVE of right portal vein



Portogram

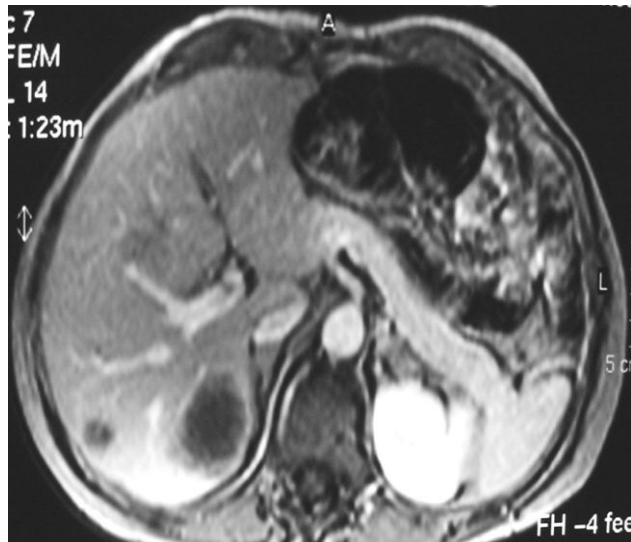


Embolisation



Post embolisation

Effect of PVT on CT follow-up imaging

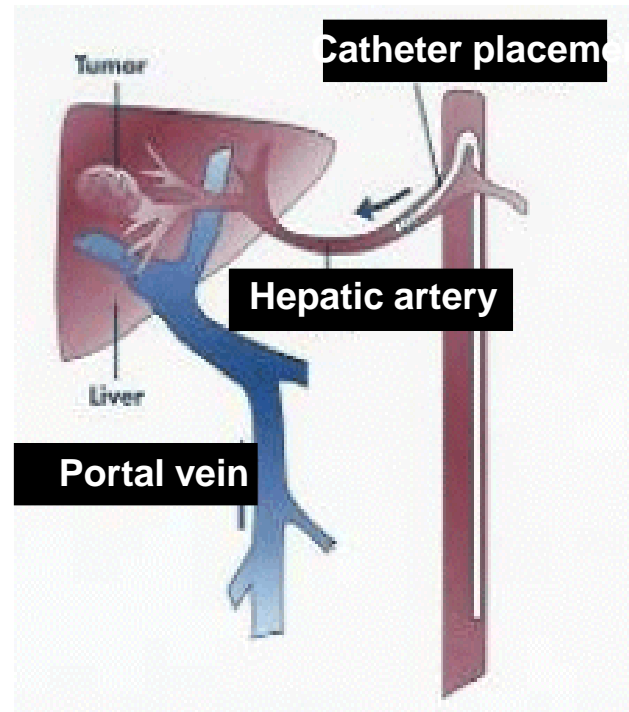


Pre-PVE



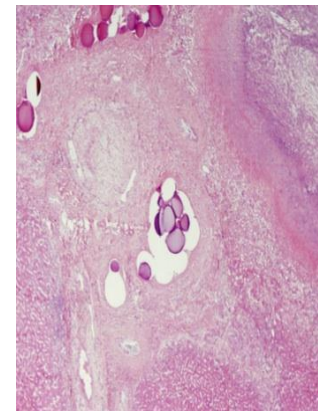
Post-PVE

Liver directed therapies



Irinotecan loaded Microspheres (DEBIRI)

- Catheter minimally invasive therapy
- Polyvinyl alcohol microspheres
- Ischaemia and drug delivery
- Single treatment event
- No systemic effects



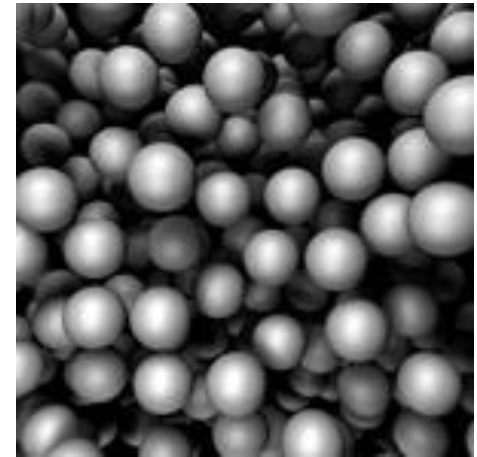
Response

Response	3-months	6-months	12-months
Complete	8	9	12
Partial	35	22	22
Stable	19	30	36
Progression	3	13	18

Compared to best supportive care, RR 2-5% at 3-6 months

Radio-embolisation (SIRT)

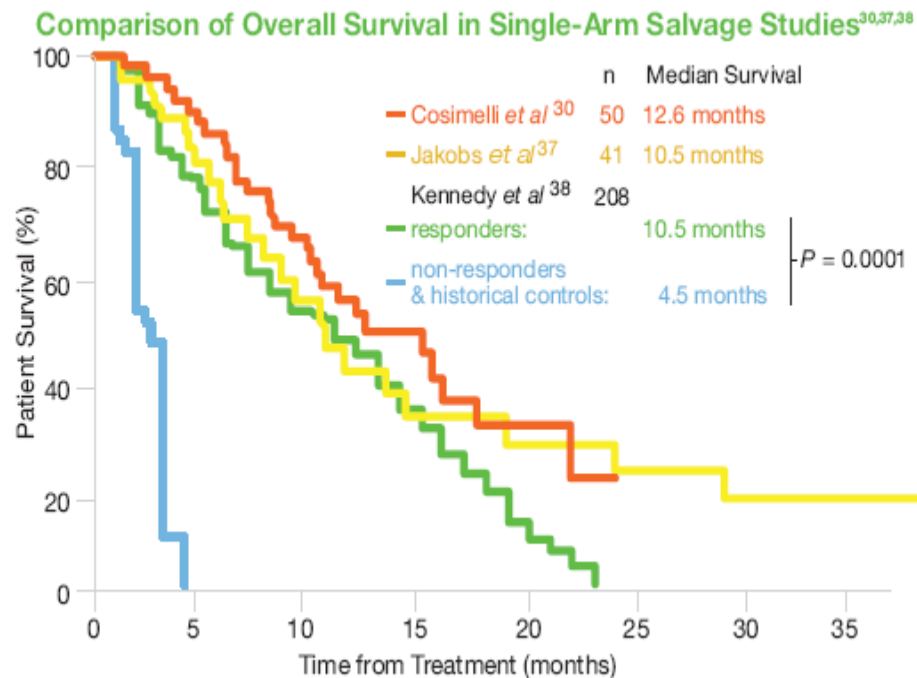
- Yttrium-90 is a beta emitter with $t_{1/2}$ 64 hours
- Maximum range of penetration 11mm (mean 2.5m)
- Normal liver poor tolerance to DXR
- Blood supply of liver tumors almost entirely arterial
- Able to administer selectively by a minimally invasive technique



Salvage therapy of treatment refractory disease

Lead Author	n	Treatment	Cohort	ORR	SD	Median TTP ^A or PFS [†]	Median Survival
Salvage Therapy of Treatment-Refractory Disease							
Hendlishz ²⁷	44	SIR-Spheres [†] + 5FU vs. 5FU (> SIR-Spheres [†] at PD)	LO	10%	76%	5.5 months ^{ΔL} HR: 0.38 2.1 months ^{ΔL} P = 0.003	10.0 months ns 7.3 months
			LO	0%	35%		
Seidensticker ²⁸	29	SIR-Spheres [†] vs. BSC matched pairs	LD	41.4%	17.2%	5.5 months [‡] nr 2.1 months [‡]	8.3 months HR: 0.26 3.5 months P < 0.001
			LD	nr	nr		
Bester ²⁹	224	SIR-Spheres [†] vs. conventional therapy or BSC	LD	nr	nr	nr	11.9 months HR: 0.50 6.6 months P < 0.001
			LD	nr	nr		
Cosimelli ³⁰	50	SIR-Spheres [†]	LD	24%	24%	4 months [‡]	12.6 months
Sofocleous ³¹	19	SIR-Spheres [†]	LD		70.6% ^{DCR}	6 months [‡]	16.0 months
Kennedy ³²	606 [§]	SIR-Spheres [†]	LD	nr	nr	nr	9.6 months
Sofocleous ³³	18 [§]	SIR-Spheres [†]	LD		40.0% ^{DCR}	5.1 months [‡]	7.4 months
Leoni ³⁴	51 [§]	SIR-Spheres [†]	LD	24% ^c		nr	8.0 months
Nace ³⁵	51 [§]	SIR-Spheres [†] (+ FUDR HAC) ^{33%}	LD	12.9%	64.5%		10.2 months
			LO				17.0 months
Cianni ³⁶	41 [§]	SIR-Spheres [†]	LD	46%	36%	9.3 months [‡]	11.8 months
Jakobs ³⁷	41 [§]	SIR-Spheres [†]	LD	17%	61%	5.9 months ^{ΔL}	10.5 months
Kennedy ³⁸	208 [§]	SIR-Spheres [†] responders non-responders & historical controls	LD	35.5% ^w	55%	nr	10.5 months P = 0.0001 4.5 months

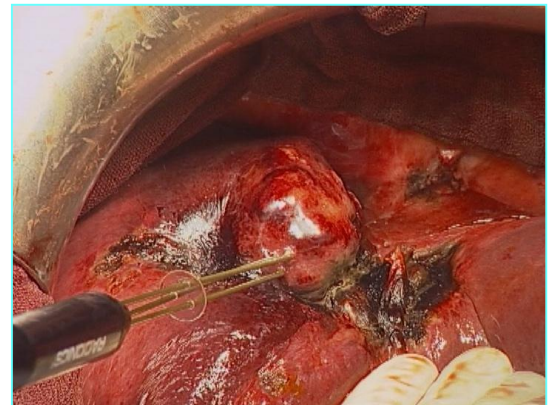
Chemo-refractory liver dominant disease



Appears to be a clear benefit in survival for unresectable, heavily pre-treated CRCa liver metastases

Local ablative therapies

- Percutaneous ethanol injection (PEI)
- Cryotherapy
- Microwave coagulation therapy (MCT)
- Laser induced thermotherapy (LITT)
- Radiofrequency ablation (RFA)
- Microwave ablation (MWA)
- Nano-knife



Radiofrequency ablation of CRCa liver metastases

- Systematic review¹ 2 comparative studies, 11 case series
- Post procedure complication rate 0-33%
- Shorter survival than surgical resection
- Local recurrence rate 4-55%

	RFA	Resection
Survival (months)	44 (median)	54 (mean)
5-year survival (%)	40	53

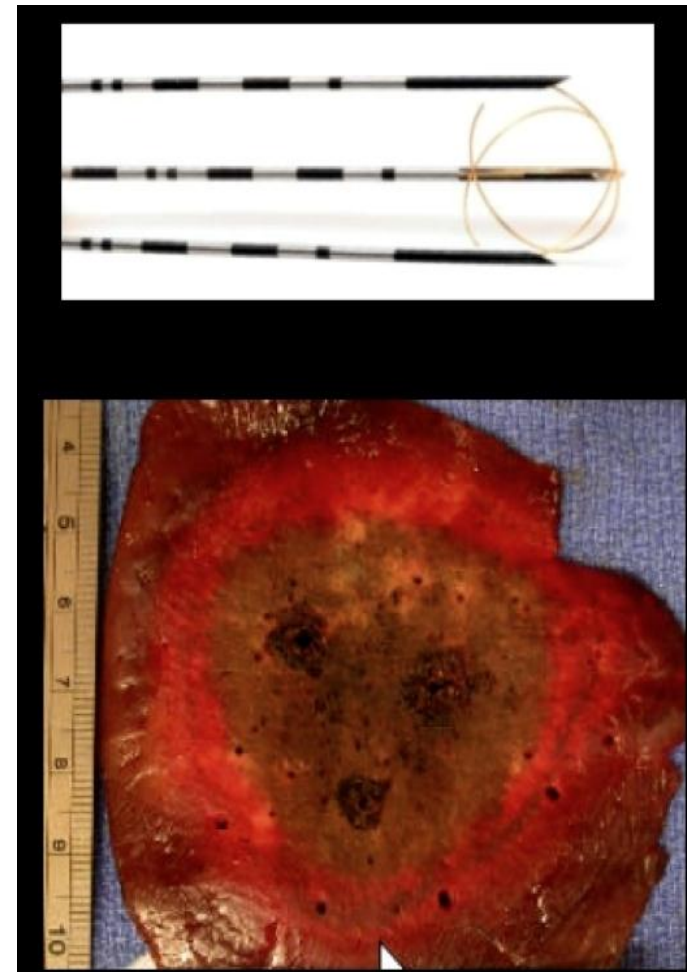
For lesions <3 cm, RFA and resection probably equivalent²

¹Sutherland et al., Arch Surg 2006; 141:181-90

²Mulier S et al., Dig Surg 2009; 25(6):445

Microwave ablation of liver tumours

- MWA zones larger than for RFA
- Rapid heating
- Local vessels cause less deflection
- No pathological difference in degree of necrosis
- (Lower recurrence rates)

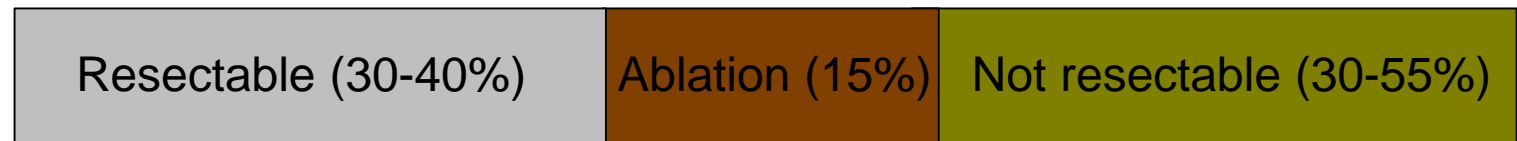


Summary: An evolving paradigm

The Past 2000



The Present 2013



Overall summary

- Too few patients with potentially curable disease referred
- Definition of resectability has changed
- Chemotherapy does improve long-term outcome (perioperative or adjuvant)
- Risks of prolonged systemic therapy must be weighed against benefits
- Liver targeted therapies (DEBIRI, SIRT) appear to offer survival benefit, but need to better define treatment group
- Minimally invasive tissue ablation complements resection
- Individualized, multidisciplinary approach required to optimize outcomes

