Chemotherapy for Colorectal Cancer: What you need to know

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SON Fall Update
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Objectives

- Adjuvant Chemotherapy
  - Benefit, Options, Timing
- Therapy for Advanced CRC – mCRC
  - Benefit, Surgical Implications

Evolution of Adjuvant Therapy

1990	*5-FU/Levamisole better than observation.*
1994	**5-FU/LV better than surgery alone.**
1998	**5-FU/LV better than 5-FU/Levamisole.**
1998	**6 months = 12 months.**
2003	*5-FU/LV plus Oxaliplatin better than 5-FU/LV (FOLFOX)*
2012	*Is 3 months of FOLFOX enough? 3 vs 6 months*

Not Effective
Irinotecan, Bevacizumab (Anti-VEGF), Cetuximab (Anti-EGFR)

Benefit of Chemotherapy

	Recurrence	Death
Stage III		
Fluoropyrimidine	38%	20%
FOLFOX	55%	32%
Stage II		
Fluoropyrimidine	20%	Not Proven
FOLFOX	Not Proven	Not Proven

Standard of Care in Curable CRC

- Adjuvant chemotherapy (AC) is recommended after curative surgical resection of:
  - Stage III colon and rectal cancer
  - Stage II rectal cancer
  - Stage II colon cancer with high-risk features

Clinical Assumptions

1. Chemotherapy should commence as soon as practical after surgical resection

2. Chemotherapy begin ≤ 3 months of surgery, beyond which time the benefit uncertain

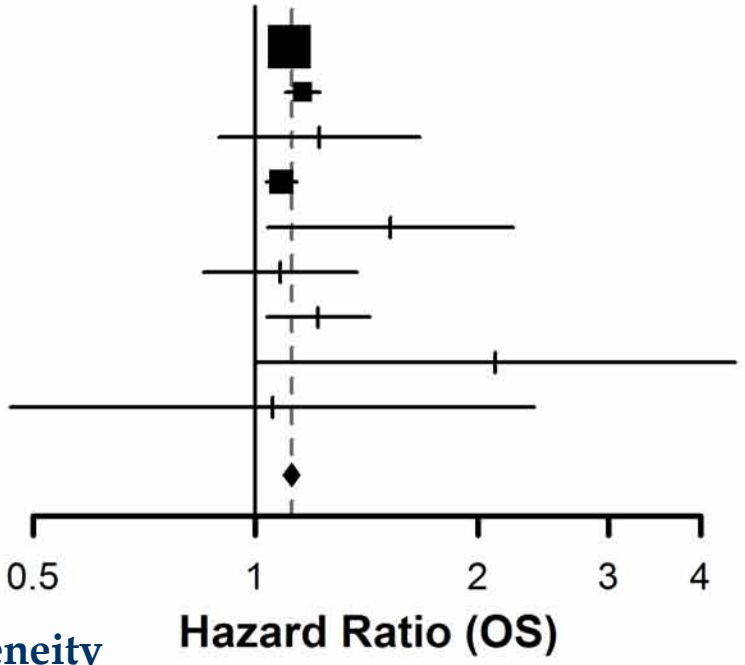
Delay to Start Adjuvant Chemotherapy

In general, two factors that result in delays:

- Patient - post-op complications / recovery
- Logistics - institutional delays / inefficiencies

Meta-Analysis – Overall Survival

Study	*HR (95% CI)*	*Weight (%)*
Cheung, 2009	1.11 (1.07-1.15)	47.37
Hershman, 2006	1.16 (1.10-1.22)	21.34
Zeig-Owens, 2009	1.22 (0.89-1.67)	0.62
Wadd, 2008	1.08 (1.03-1.14)	26.63
Chau, 2005	1.52 (1.04-2.23)	0.41
Ahmad, 2007	1.08 (0.85-1.37)	1.07
Czaykowski, 2007	1.22 (1.04-1.43)	2.36
Bayraktar, 2009	2.11 (1.00-4.45)	0.11
Biagi, 2007	1.05 (0.47-2.38)	0.09
Overall	**1.12 (1.09-1.15)**	



- **Cochrane $\chi 2$ test showed no evidence of heterogeneity (p-value= 0.2629), justifying fixed-effect model**

Biagi et al JAMA 2011

Implications

- For a 65 year old male, good general health, T3N2 mod/diff. colon cancer treated with 5FU-based chemo

  ~60% survival at 5 years with AC
  ~45% survival if no chemotherapy

- Assuming this estimate depends on TTAC of 4 weeks

  ~55% survival at 5 years with delay to 8 weeks
  ~50% survival at 5 years with delay to 12 weeks

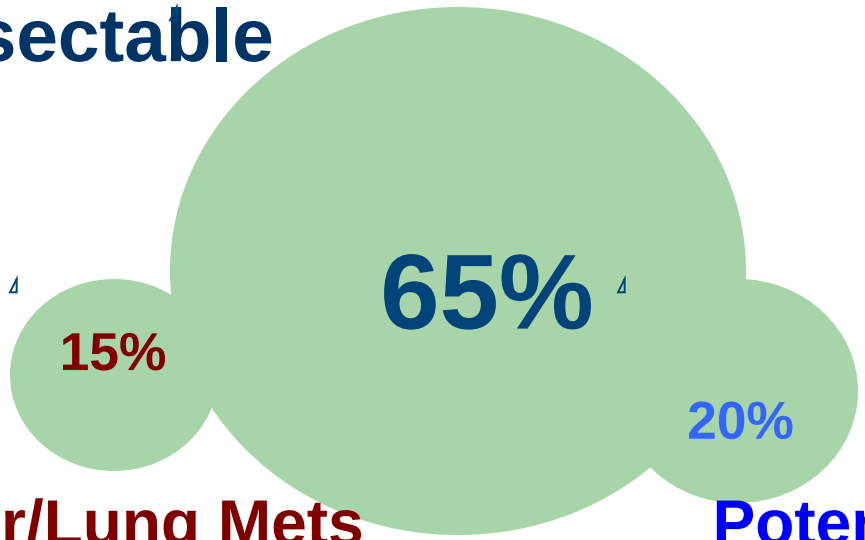
Message

- Adjuvant chemotherapy for:
  - Node Positive Colon
  - Node Negative and Positive Rectal
  - Some T3/T4 Node Negative Colon – pls. refer
- Begin therapy within 2 months of surgery
- Please refer ASAP

Metastatic Disease

- 1995 – 1 agents
- 2012 – 6 agents
- Much more complex now:

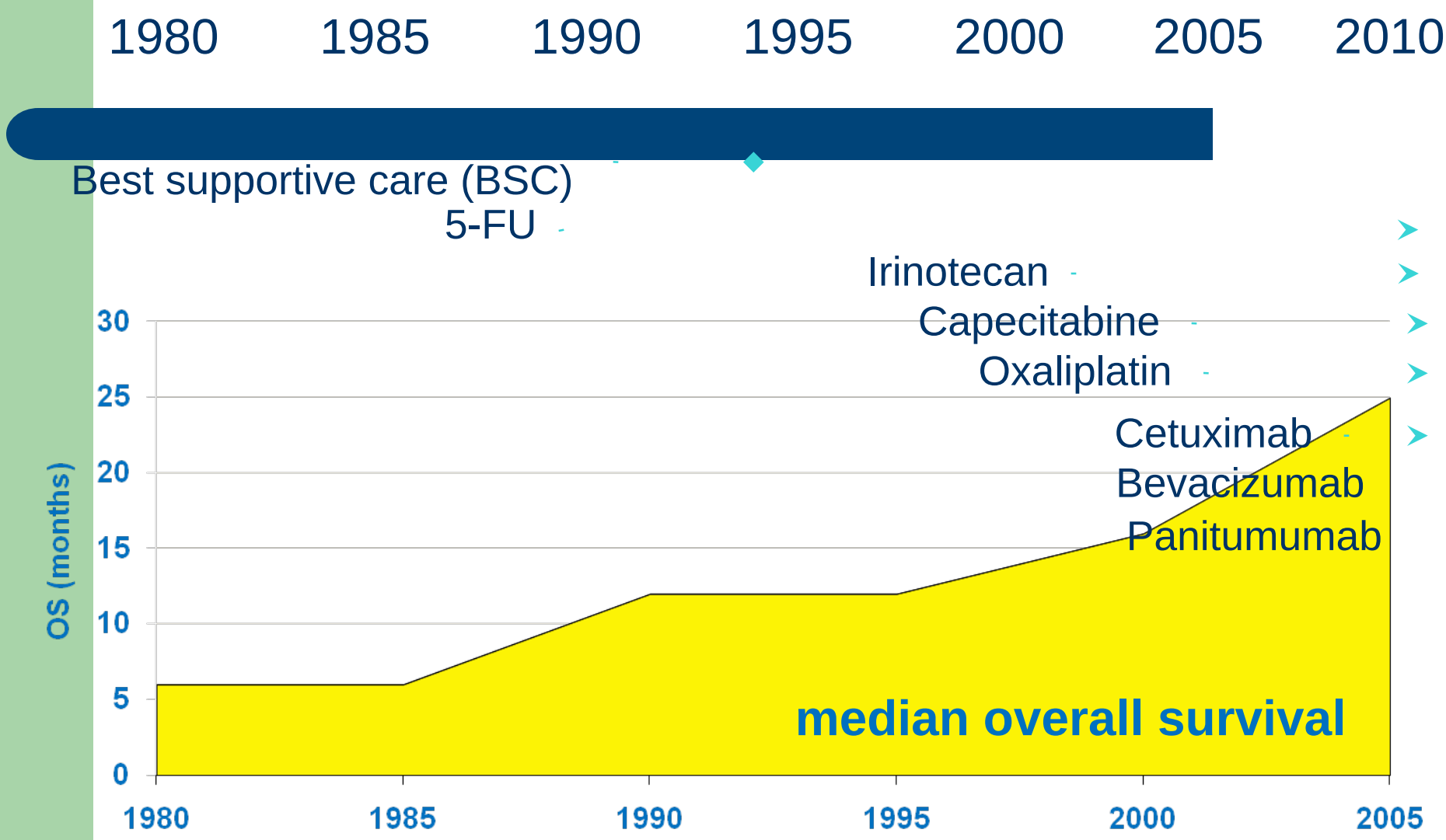
Unresectable



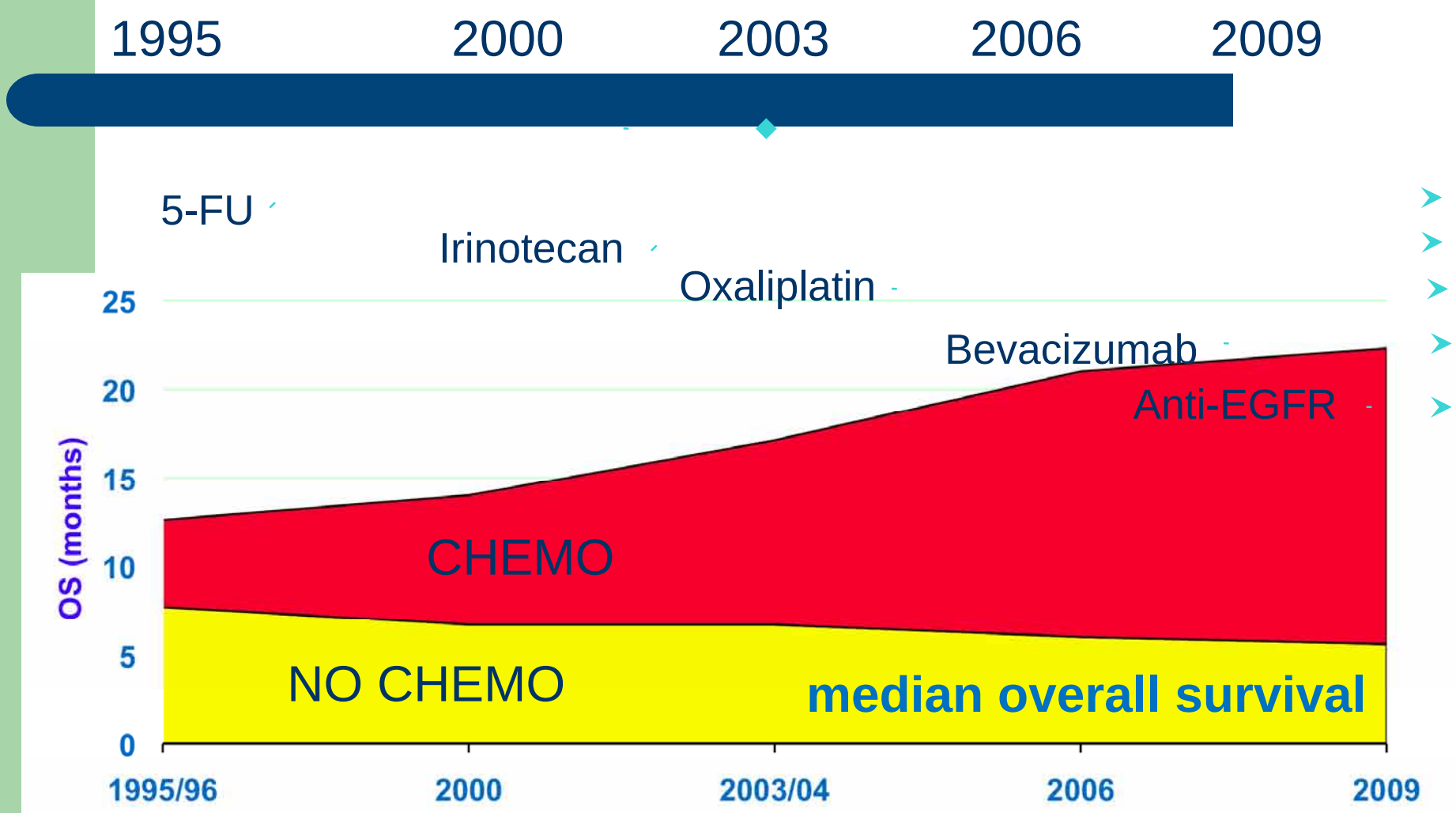
Resectable Liver/Lung Mets

Potentially Resectable

Median OS of mCRC on clinical trials

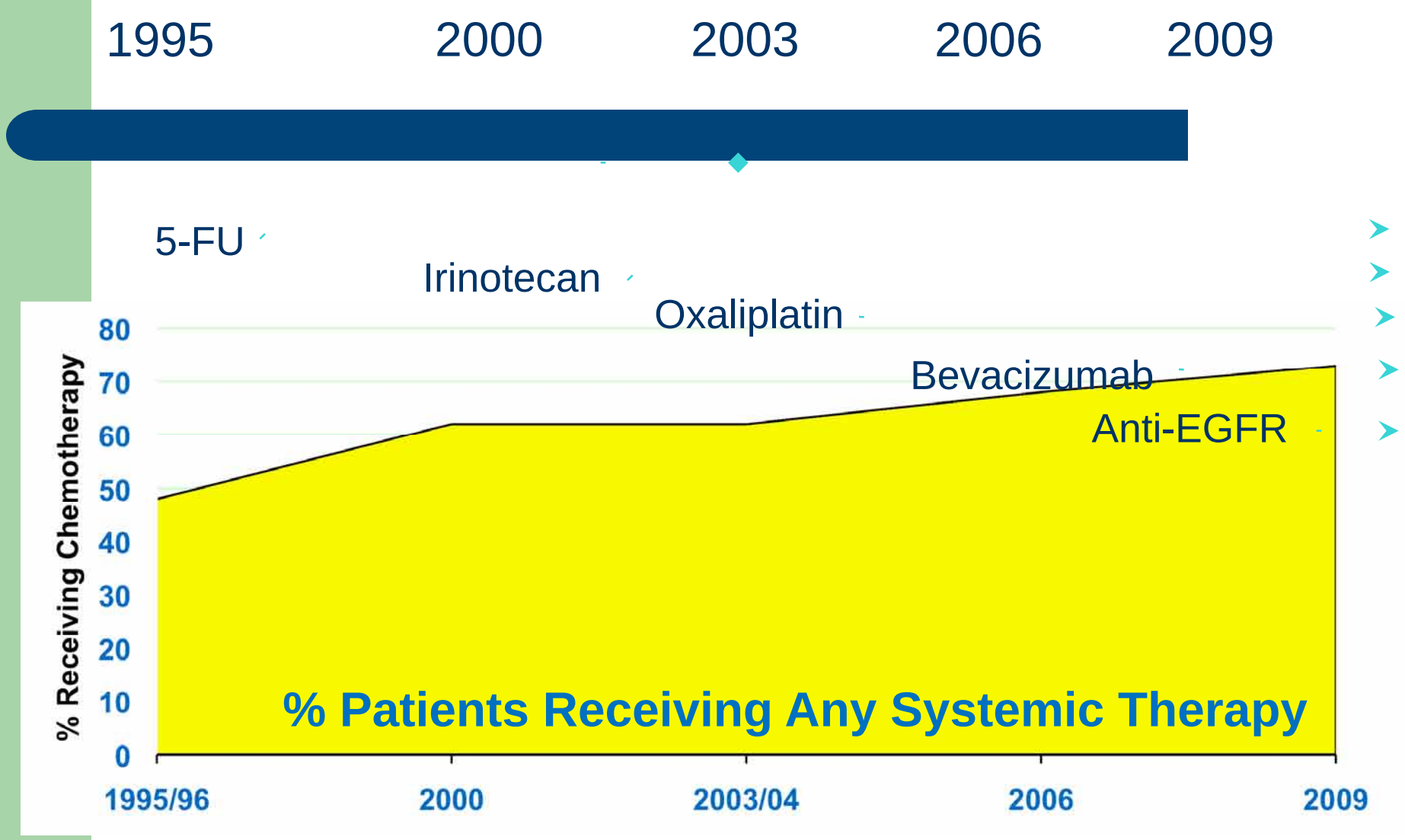


What happens to BCCA patients?

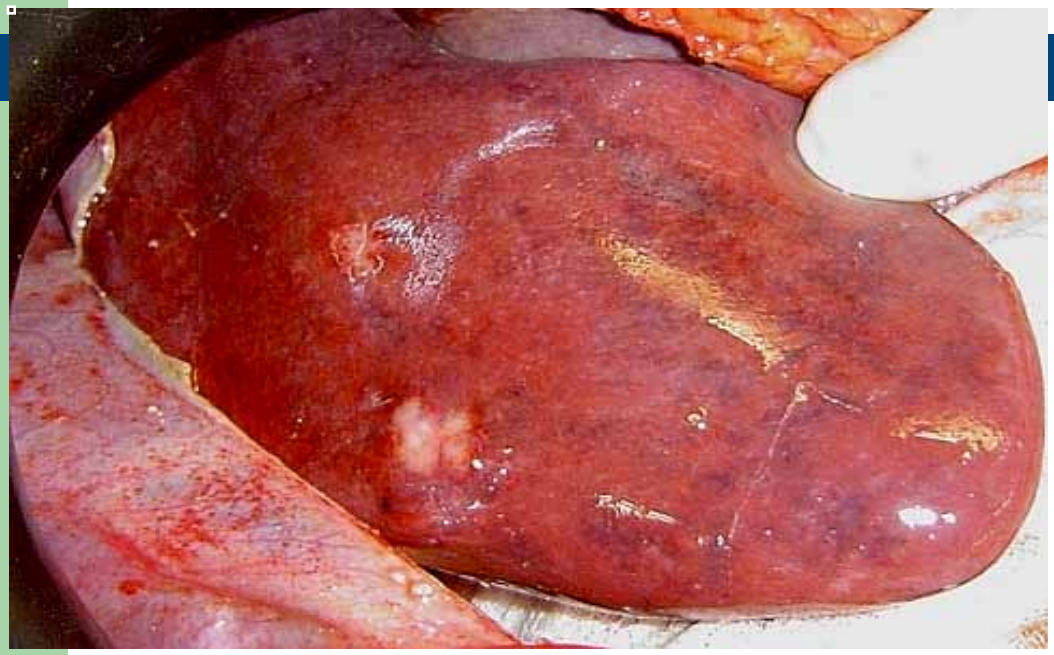


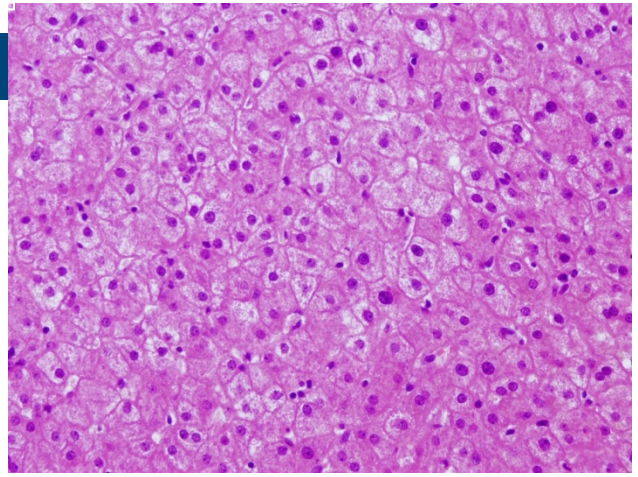
H Lim JOP 2009, D Renouf Clin Colon Cancer 2009, M Ho Submitted to ASCO 2013

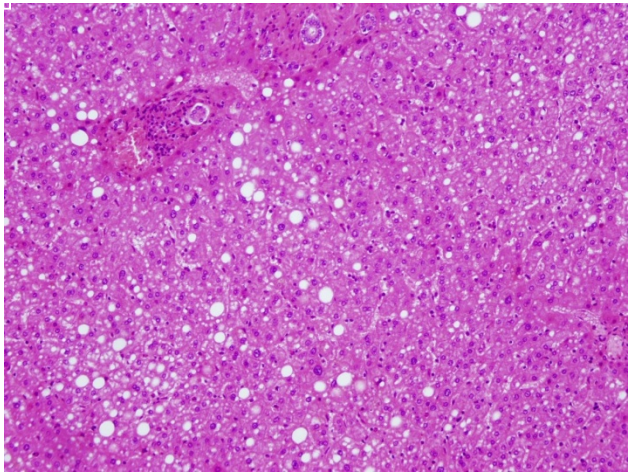
% BCCA who received any chemotherapy



Chemo Considerations







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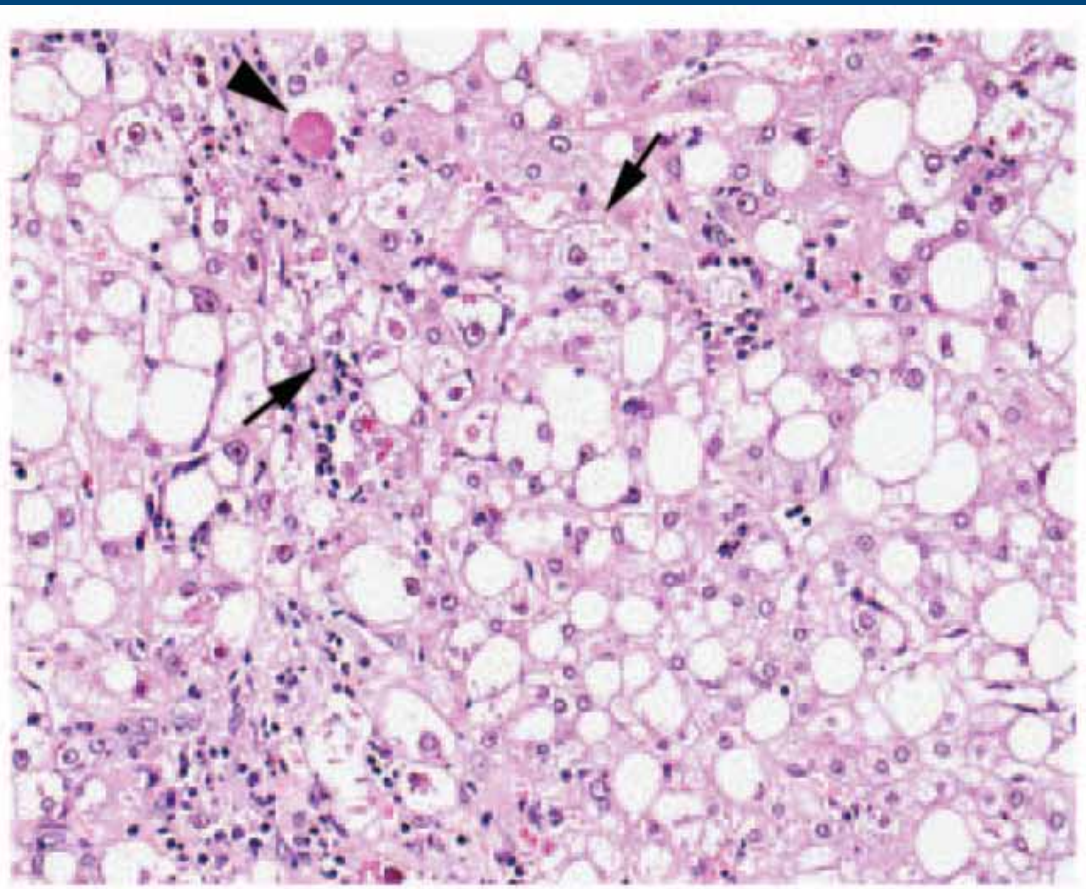
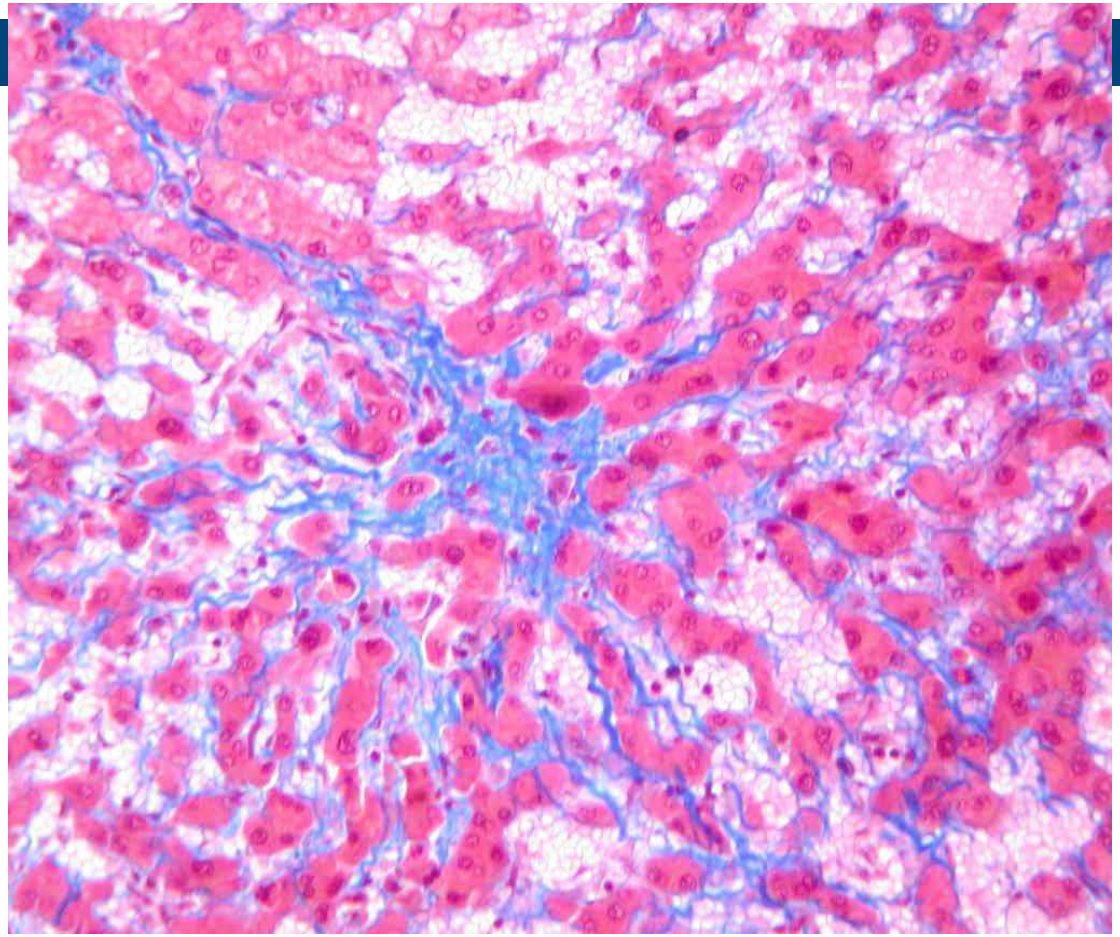
Steatosis and Steatohepatitis: Irinotecan



Sinusoidal Obstruction: Oxaliplatin

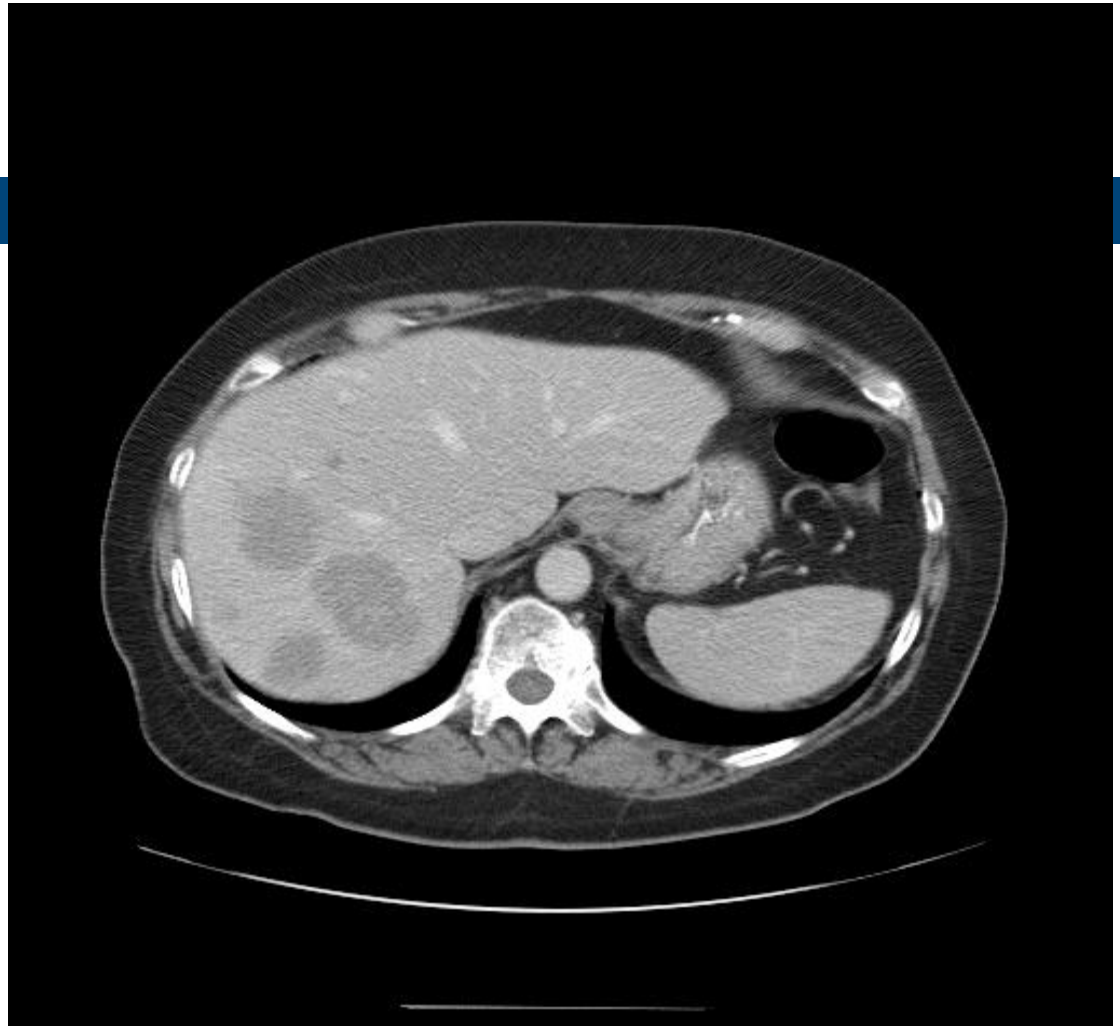


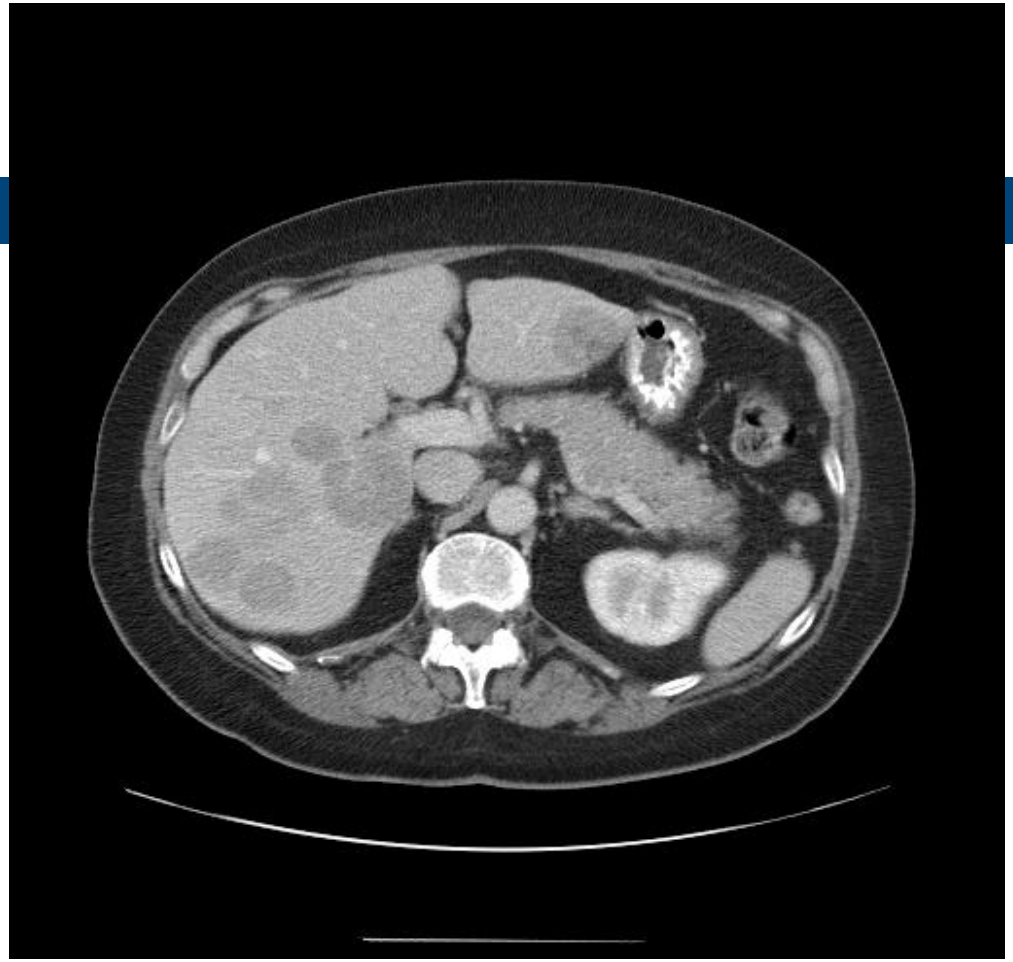
Potentially Resectable MCRC

- 62-year-old female elementary school teacher presented with increased abdominal girth and malaise for several months
- No change in bowel habit
- Liver enlarged
- ECOG 1
- Mild hypertension

Investigations

- **Labs**
  - CBC: normal
  - LDH: 2000 IU/L
  - AST: 250 U/L
  - CEA: 550 ng/mL
  - Bilirubin: N
  - ALT: 200 U/L
  - ALP: 256 U/L
- **CT Scan – Cecal mass, bulky liver mets**
- **PET Scan – Liver mets, no extra-hepatic disease**





EORTC European Organization for Research and Treatment of Cancer

ALM CAO

AGITG

FFCD

CANCER RESEARCH UK

Peri-operative FOLFOX4 chemotherapy and surgery for resectable liver metastases from colorectal cancer

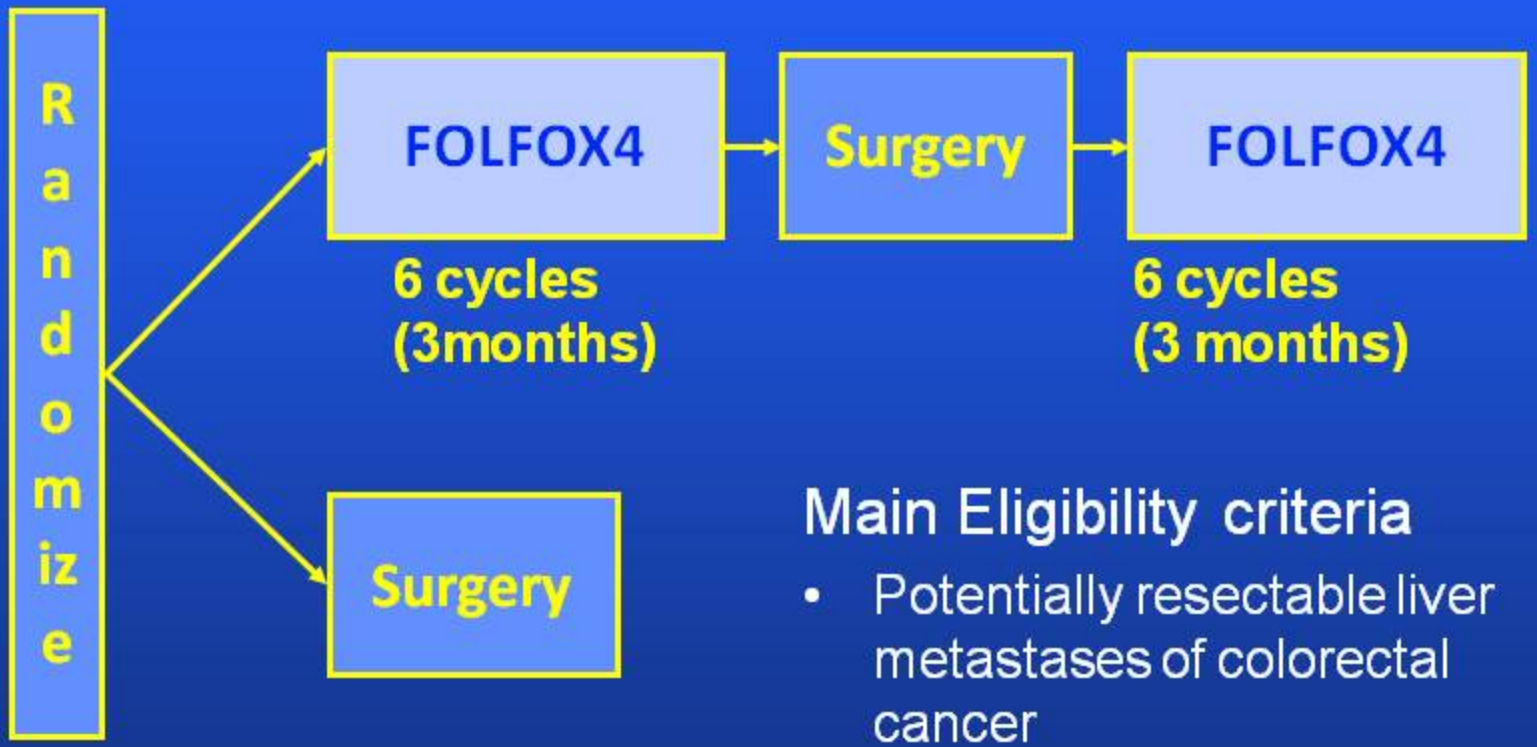
Long-term survival results of the EORTC Intergroup phase III study 40983.

B. Nordlinger, H. Sorbye, B. Glimelius, G.J. Poston, P.M. Schlag, P. Rougier, W.O. Bechstein, J. Primrose, E.T. Walpole, M.E. Mauer, T. Gruenberger

For the EORTC GI Group, CR UK, ALMCAO, AGITG and FFCD

Aim and design

Demonstrate that chemotherapy combined with surgery is a better treatment than surgery alone



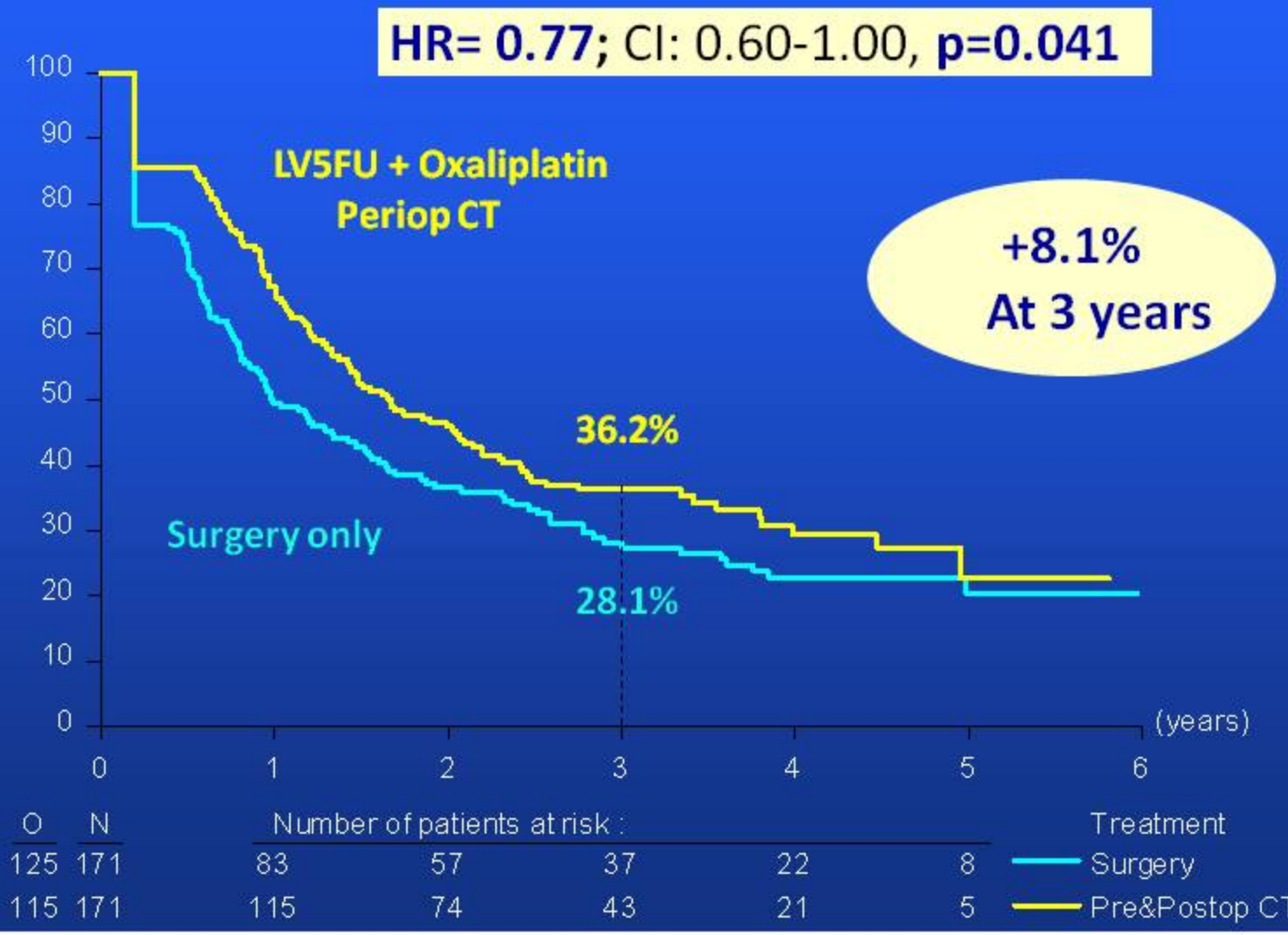
N=364 patients

Main Eligibility criteria

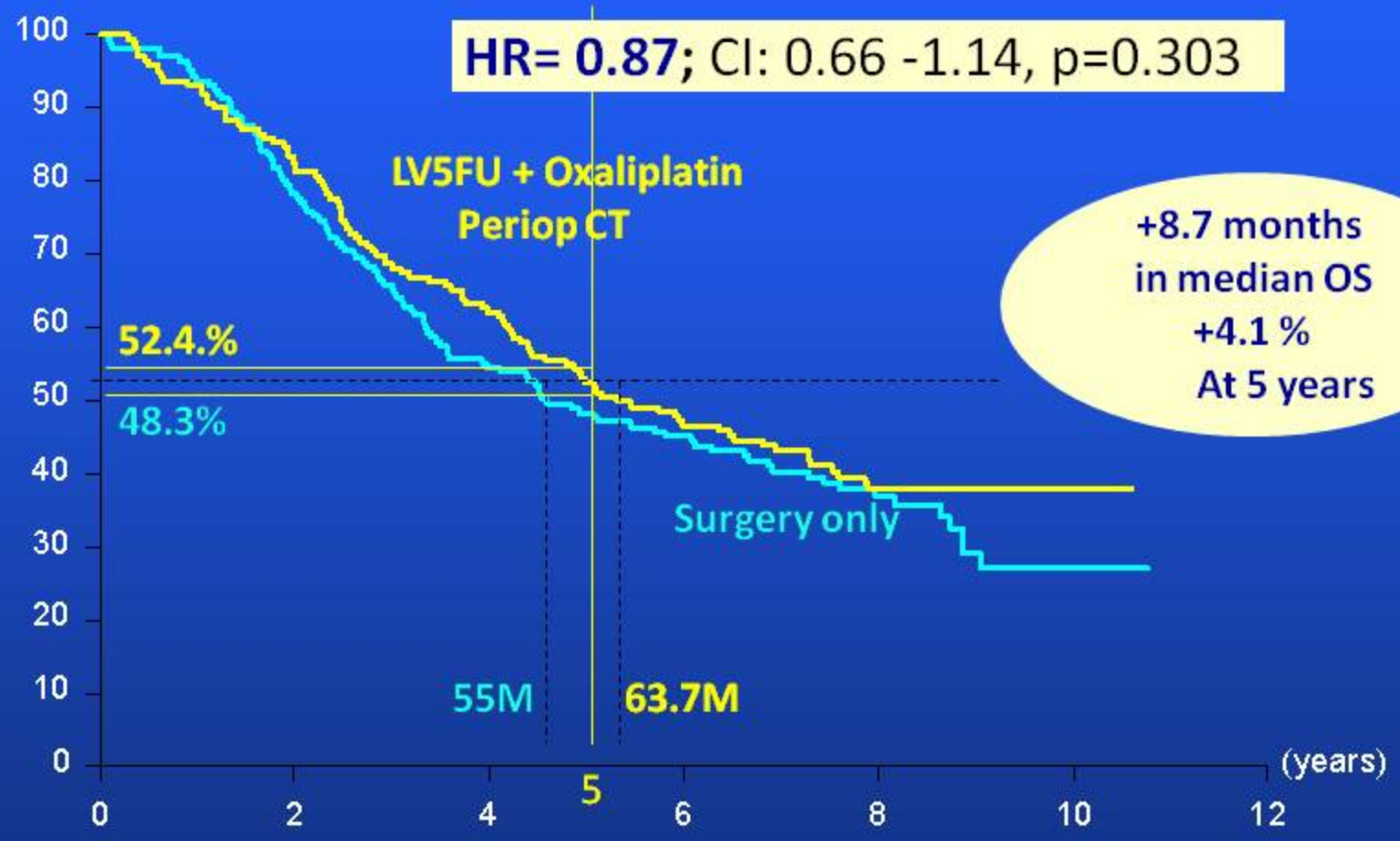
- Potentially resectable liver metastases of colorectal cancer
- Up to 4 deposits (on CT-scan, at randomization)

Progression-free survival in eligible patients

Nordlinger et al. Lancet 2008



Overall survival in eligible patients



Messages

- Most patients eligible for palliative chemo
- Palliative chemo increases survival
- Patients with “liver or lung only” mCRC should be considered for surgical resection and chemotherapy.