XX Riunione Nazionale I.T.M.O.

Monza

6 Maggio 2011

Trattamento medico pre e post-chirurgia delle metastasi epatiche da carcinoma del colon-retto

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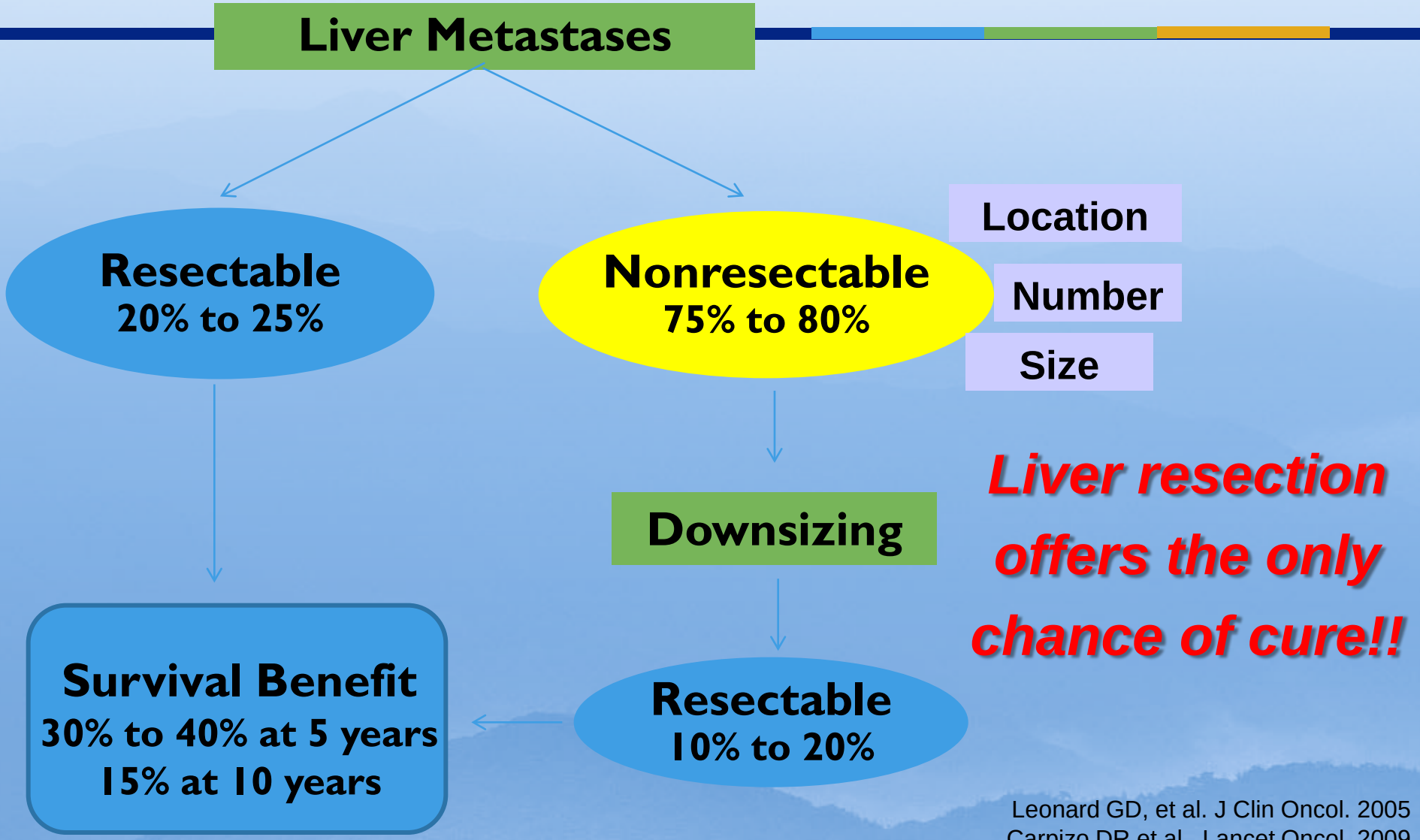
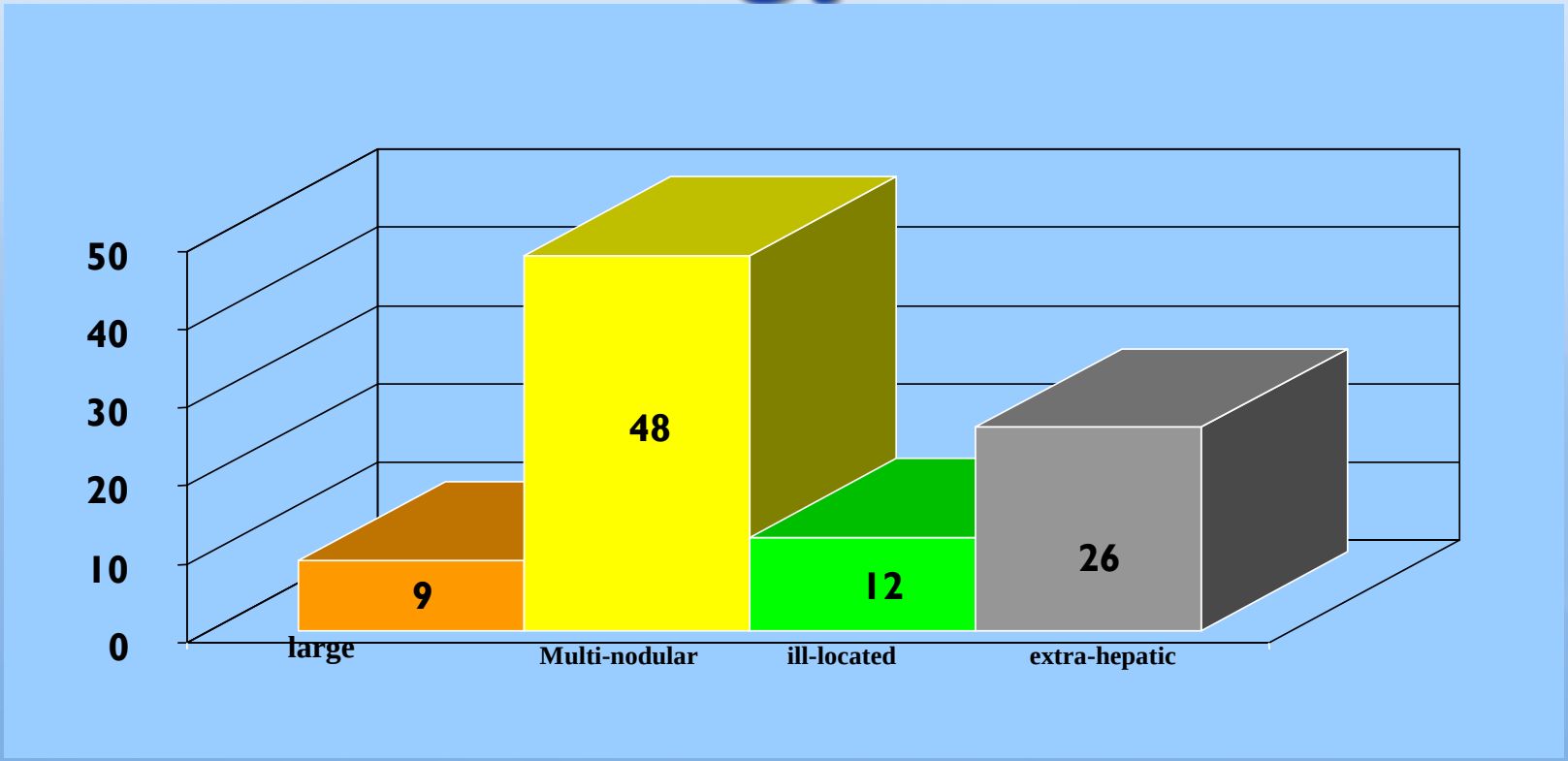
OUTCOMES



Leonard GD, et al. J Clin Oncol. 2005
Carpizo DR et al., Lancet Oncol, 2009

What is non-resectable diseas e?



Adam R., et al. Ann Surg Onc 2000

Classical Contraindications to liver resection:

≥4 metastases, size, extraepatic disease, hilar location, resection margin <1 cm, incomplete resection

Changing Defintion of Resecabilit y

Old: What must come out?

1. How many metastases?

- <4 lesions, with unilobar location, resectable

resectable

4. >1 cm resection margin
Extrahepatic disease?

- If none, resectable

New: What will stay in?

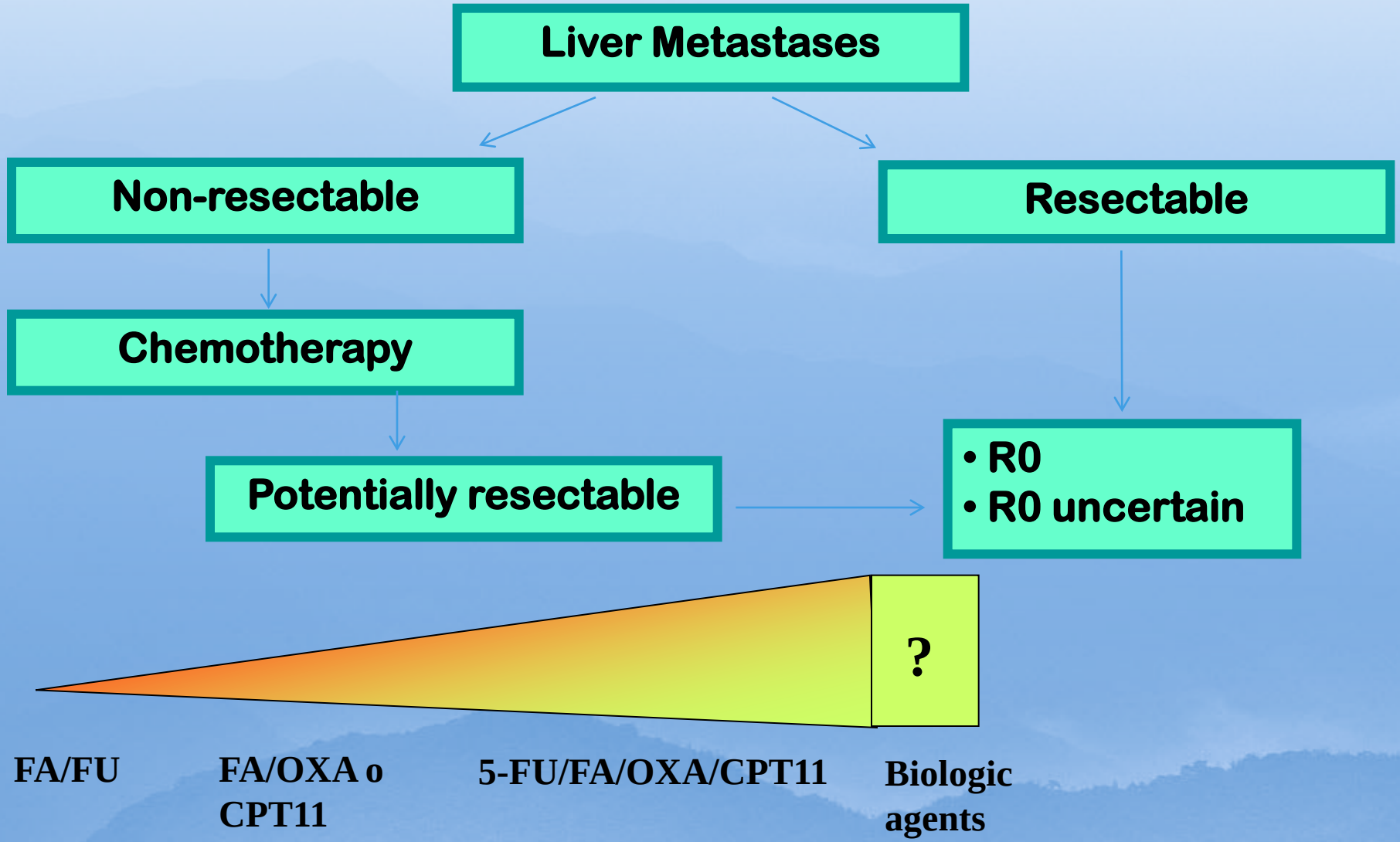
Can R0 resection be achieved?

Can 2 contiguous liver segments

Consensus on the definition of resectability criteria and surgical attitude varies among centers!

Charnsangavej C et al. Ann Surg Oncol 2006

MANAGING
scenario



ROLE OF CHEMOTHERAPY

ASCO 2006

- **Neoadjuvant therapy**

Preoperative systemic therapy for *resectable* hepatic metastases followed by *post resection* therapy (perioperative therapy? *JCO Editorial 2008*)

- **Adjuvant therapy**

Systemic/regional therapy *post hepatic resection*

- **Conversion therapy**

Systemic/regional therapy for patients with *nonresectable* hepatic metastases in an attempt to make the metastases *resectable*

ROLE OF CHEMOTHERAPY

Resectable disease

- Peri-operative trials
- Adjuvant chemotherapy
- Hepatic Artery Infusion therapy (HAI)

PERIOPERATIVE TRIALS

Author	Therapy	Phase	N Pts	Pros	OR rate (%)	Survival (% or median)	Resectability (%)
Gruenberger (2004)	Xelox Folfox-4	2	50	yes	70	48% at 1 y	100
Taeib (2005)	Folfox-7	2	22	Yes	77	89% at 2 ys	91
Gruenberger (2008)	Bev+Xelox	2	56	yes	73	NR	95
Nordlinger (2007)	Folofox-4	3	182	yes	43	Not reached	93

- **EORTC 40051 BOS***: Randomized phase II trial
  Folfox+Cetuximab+/- Bevacizumab

- **COI-E**: non-randomized phase II trial (Fondazione IRCCS INT, Milan)

*www.cancer.gov/clinicaltrials/search

Rationale of pre-operative chemotherapy

Benefit

- Improved PFS
- Chemoresponsiveness
- Selection of surgery
- Fewer «open and close»
- Low operative mortality

Potential negative impact

- Delayed surgery
- Reversible surgical complications
- Chemotherapy-associated liver injuries
- Complete response making metastases difficult to find
- Cost

REQUIRE ACCURATE RISK/BENEFIT EVALUATION!!!

- ✓ Sinusoidal dilation (oxaliplatin)
- ✓ Regenerative nodular hyperplasia (oxaliplatin)
- ✓ Steatohepatitis (irinotecan)

ADJUVANT TRIALS

- **FFCD-ACHBTH-AURC 9002 TRIAL***: Bolus 5-FU/LV vs surgery. 171 pts. RFS 33.5% vs 26.7% at 5 ys, OS 51.1% vs 41.1% at 5 ys

- **EORTC-NCIC-GIVIO****: Bolus 5-FU/LV vs surgery. 129 pts. RFS 45% vs 35% at 4 ys, OS 57% vs 47% at 4 ys

These studies were closed early for slow accrual

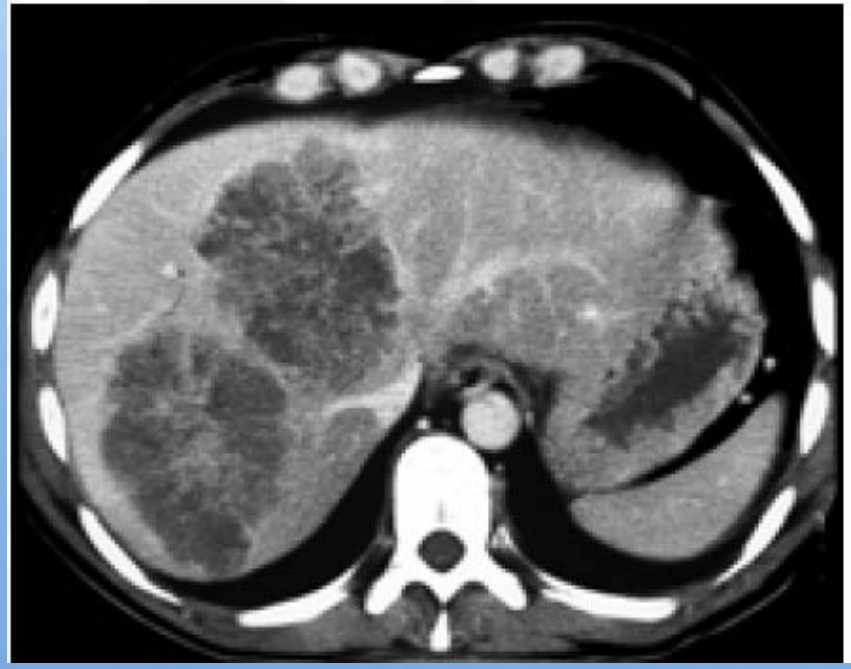
Was performed a *pooled analysis* of data from these studies reported by E. Mitry JCO on 2008, which showed a trend in favor of chemotherapy both in the RFS (27.9 months vs 18.8) that the OS (62.2 months vs 47.3).

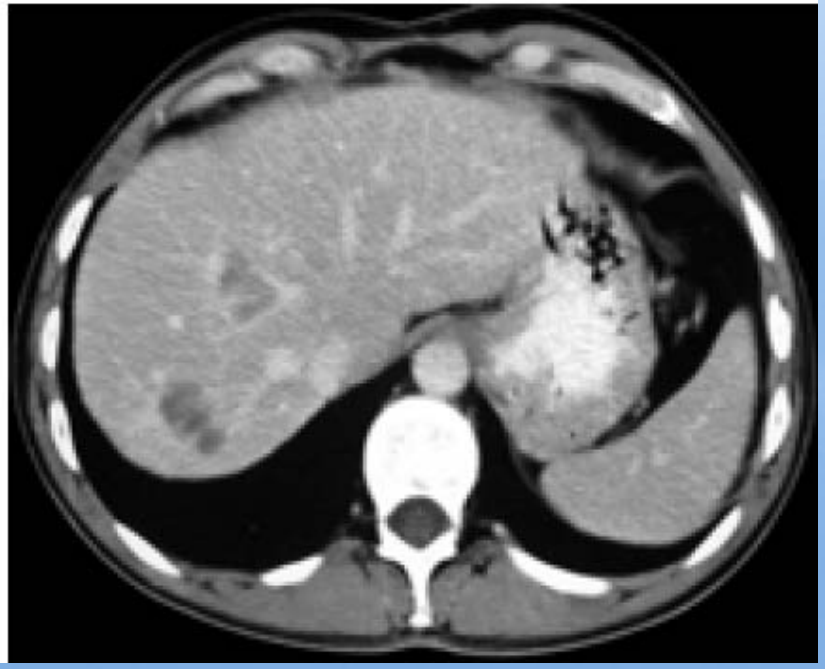
* Portier J. JCO 2006;24:4976
** Langer B. JCO 2002;20:592

ROLE OF CHEMOTHERAPY

Unresectable liver disease

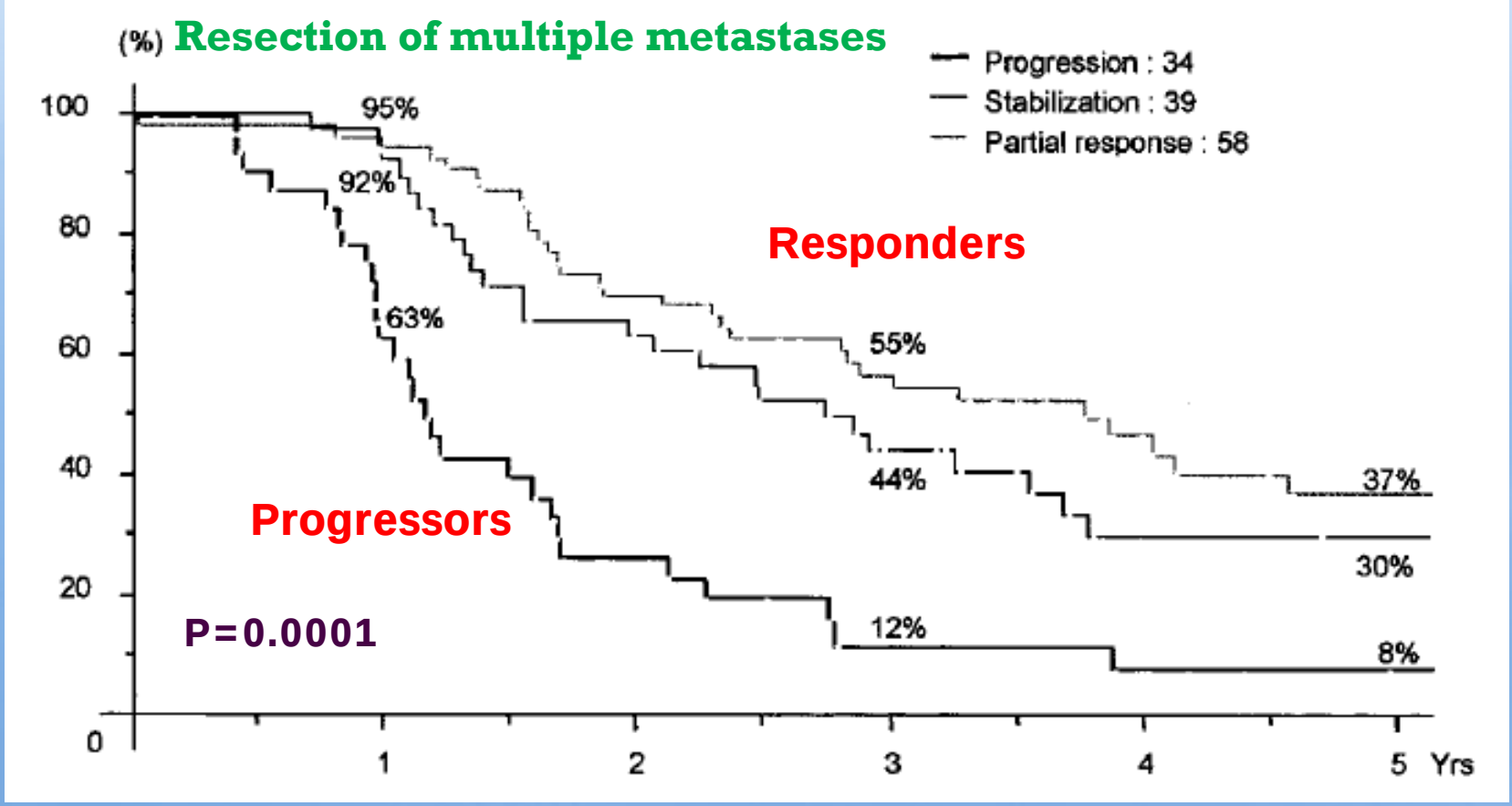
Down-staging to resectable disease





Neoadjuvant therapy: is it a realistic option?

Survival related to response to preoperative CT (Retrospective Analysis of 131 pts)



Overall survival was much lower for pts with progressive disease to preoperative chemotherapy than for those with responsive or stable disease

Adam R et al, Ann Surg 2004

Author (y)	Therapy	Phase	N Pts	Prosp	OR rate	Survival (% or median)	Resectability (%)
Bismuth (1996)	FU/FA/oxa	2	53	NO	NR	40% at 5 ys	16
Giacchetti (1999)	Oxa regimens	2	151	NO	59%	48 m	38
Adam (2001)	FU/FA/oxa	2	95	NO	cCR: 4/95 pCR: 6/95	35% at 5 ys	14
Alberts (2003)	FOLFOX4	2	42	YES	62%	31.4 m	33
Tournigand (2004)	FOLFOX6-FOLFIRI	3	220	NO	54 – 56%	20.6 – 21.5 m	13 – 7
Goldberg (2004)	FOLFOX-IFL-IROX	3	795	NO	45 – 31 – 35%	19.5 – 15 – 17.4 m	4.1 – 0.75
Quenet (2004)	FU/oxa/IRI	2	34	YES	72%	NR	37.5
Pozzo (2004)	FOLFIRI	2	40	YES	47.5%	Not reached after 30.4 m	32.5
Benoist (2006)	FU/FA - FU/FA/oxa - FU/FA/IRI	2	38	YES	NA	72% recurred in situ at 1 y	NA
Adam (2009)	Different schedules	2	184	NO	62%	33% at 5 ys	Not applicable
CRYSTAL (2009)	FOLFIRI FOLFIRI+ Cetuximab	3	599 vs 599	YES	39 vs 47%	19.9 - 18.6 m	3.7 – 7
OPUS (2009)	FOLFOX4 FOLFOX4+Cetuximab	2	168 vs 169	YES	36 vs 46%	Not applicable	2.4 – 4.7
Celim (2009)	FOLFOX6/FOLFIRI + Cetuximab	2	56 vs 55	YES	75 vs 79% in K-ras wt	Not applicable	40 – 43
Folfoxiri (2007)	FOLFOXIRI/FOLFIRI	3	122 vs 122	YES	60 vs 34%	22.6 – 16.7 m	36 – 12

ROLE OF CHEMOTHERAPY

Biologic agents?

BEVACIZUMAB

- **BEAT study***: phase IV

Safety and efficacy of BEV plus first-line chemotherapy (Folfox, Folfiri, Xelox) in a general cohort of patients with mCRC. 1927 pts: 63 had undergone metastasectomy and 60 had liver resection

- **NO16966 study****: randomized phase III

XELOX – FOLFOX4 +/- BEV in mCRC. 44/699 (6.3%) pts receiving CT + BEV underwent RO resection vs 34/701 (4.9%) pts receiving placebo

- **BOXER study***:** non-randomized phase II

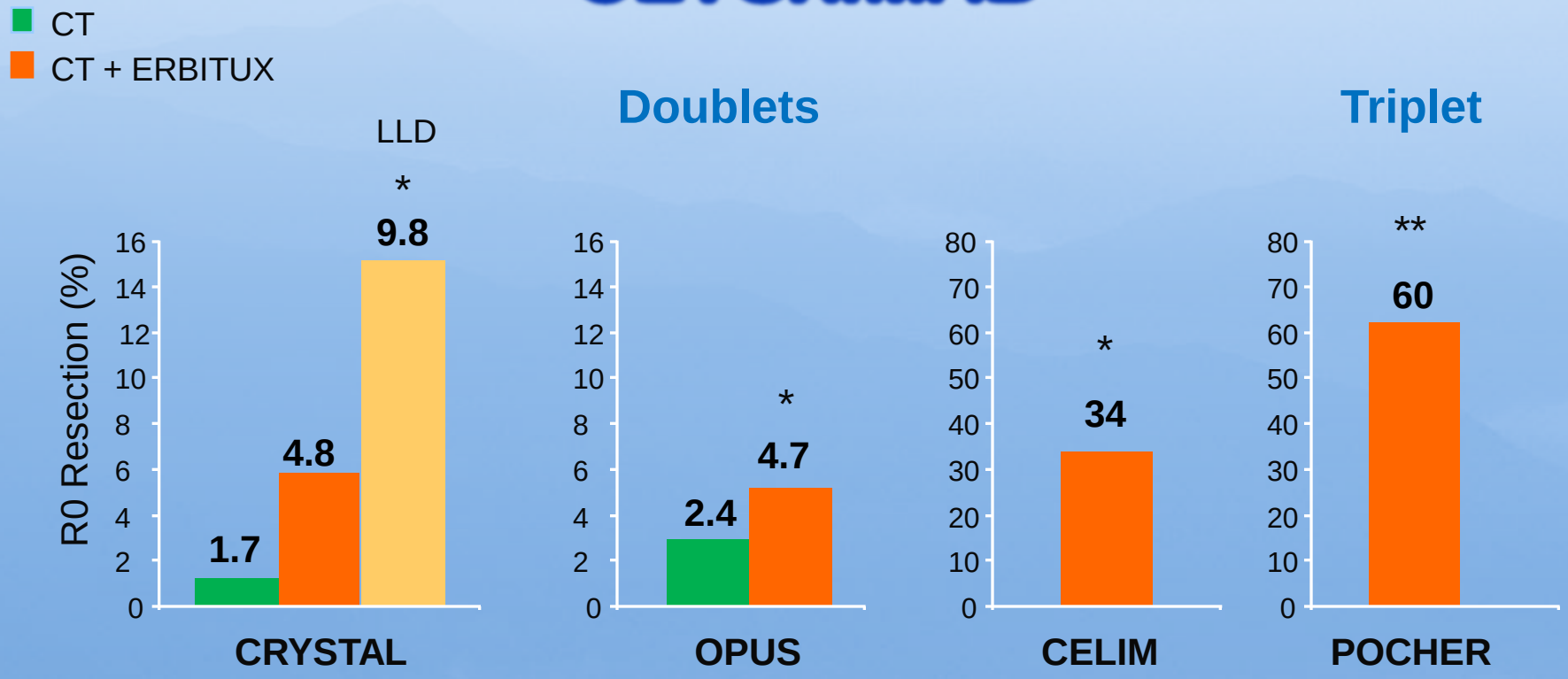
XELOX+BEV in mCRC. 45 pts. RR: 78%, R0 resection: 32%.

* Michael M et al. Abs 3523 JCO 2006; 24.
** Saltz LB et al. JCO 2008; 26: 2013.
*** Wong R et al. Abs ECCO ESMO 2009. Eur J Cancer 2009; 7: 334.

ROLE OF CHEMOTHERAPY

Biologic agents?

CETUXIMAB



***KRAS wt, **ITT**
LLD=liver-limited disease

Van Cutsem E, et al. ECCOESMO 2009 Abs 6077
Van Cutsem E, et al. N Engl J Med 2009;360:1408–1417
Van Cutsem E, et al. Ann Oncol 2008;19(Suppl.8):viii4 [Update to 710]
Bokemeyer C, et al. J Clin Oncol 2009;27:663–671
Bechstein WO, et al. J Clin Oncol 2009;27(Suppl. 15): Abstract No. 4091
Garufi C, et alECCO/ESMO, Berlin, 2009

Managing liver metastases in colorectal cancer

10% to 25% of patients with mCRC are considered resectable for cure

the 5-year survival in this population approaches 35%

relapse can occur in 75% of patients, generally occurring within the first 2 years after surgery

50% of relapses are in the liver

Key issues

- ✓Optimal chemotherapy regimen
- ✓Role of targeted therapy
- ✓Iatrogenic Liver Damage
- ✓Treat to best response or resectability? (Duration of therapy)

Grazie!