

## Synchronous resectable metastasis with asymptomatic colon cancer: Upfront chemotherapy vs. surgery

### CHEMOTHERAPY

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## Colo-rectal Cancer at Diagnosis

- 39% localized stages <sup>(1)</sup>
- 37% Regional extension
- 19% Distant stages
- 5% unknown
- Incidence in Europe in 2008 <sup>(2)</sup> :
  - 436 000 cases
  - ~ 82 000 at stage IV at diagnosis

1-JNCI News August 19 2009 (1114)

2- J Ferlay et al Eur J Cancer 2010 46 765-781

## Resectable liver metastasis from CRC

- Surgery is the only way to potentially cure patients with resectable metastasis, most often in the liver
  - 5 year-survival rates range from 25 to 55%
  - EORTC 40983: PFS at 3 years: 28% with surgery alone
- Cancer relapse occurs in most of the patients
- How could these results be improved:
  - By using a systemic treatment for a systemic disease

## Up-front chemotherapy for synchronous resectable metastasis in asymptomatic colorectal cancer

- Advantages of up-front chemotherapy (+/- targeted agents)
  - Systemic treatment of a systemic disease
  - No need for immediate resection in asymptomatic primary tumor
  - Early treatment of metastatic disease
  - Test for chemosensitivity and post-operative use of chemotherapy
  - Eradication of micro-metastatic disease
  - Avoid unneeded surgery in patients progressing under treatment
  - Important prognostic factor
  - Allow better patient selection to undergo surgery

## Up-front chemotherapy for synchronous resectable metastasis in asymptomatic colorectal cancer

- Disadvantages of up-front chemotherapy (+/- targeted agents)
  - Delay immediate surgery in a totally resectable patient
  - Risk of PS deterioration compromising surgical approach
  - Drug-associated toxicity:
    - Vascular, sinusoidal liver lesion with Oxaliplatin
    - Steatosis or steatohepatitis with Irinotecan
  - Total disappearance of metastasis
  - Risque of early progression under treatment?
  - Risk of primary tumor perforation, bleeding, obstruction

## Clinical data on Neo-adjuvant chemotherapy

- EORTC Intergroup trial 40983 <sup>(1)</sup>
  - 364 patients with  $\leq 4$  liver metastasis from CRC (34% synchronous)
  - 342 eligible, 303 resected:
    - 152 up-front (84%)
    - 151 after 6 cycles of Folfox4 (83%)
      - 115 received additional Folfox4 after surgery (63%)
  - Primary End-point: PFS

Nordlinger B. et al The Lancet 2008; 371: 1007-16

## EORTC Intergroup trial 40983

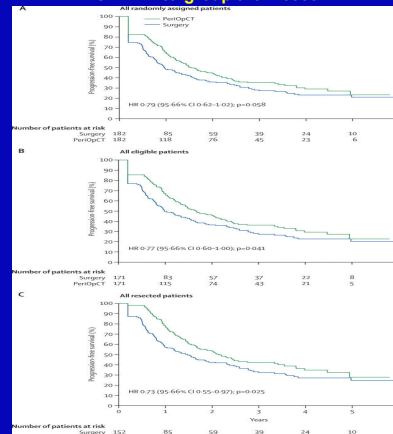
### SURGERY ALONE

- Median time to surgery: 2 w
- Response rate: -
- Operated on: 93%
- Curative resection: 83%
- Post-op complications: 46%
- Post-op death: 1%

### NEO-ADJUVANT CT + SURGERY

- 16 w
- 43%
- 87%
- 84%
- 78% p=0.04
- 1%

## EORTC Intergroup trial 40983



## EORTC Intergroup trial 40983: tolerance

### PRE-OPERATIVE FOLFOX: usual toxicity profile (G3/4)

- Diarrhea: 8%, Neurotoxicity: 8%, Neutropenia: 11%

### POST-OPERATIVE TOXICITY:

	Peri-op	vs.	Surgery
Reversible post-op complications:	25	vs.	16%
Biliary fistula:	8	vs.	4%
Hepatic failure	7	vs.	5%
Intra-abdominal infection	7	vs.	2%
Post-operative death	1	vs.	1%

## EORTC Intergroup trial 40983

- Peri-operative Folfox is feasible without adding major toxicity, slight increase in morbidity, no increase in post-op mortality
- Potentially curative resection similar in both groups
- Improved PFS with:
  - a 23% reduction of the risk of progression in eligible patients (+ 8% at 3 years, p=0.04)
  - A 27% reduction of the risk of progression in resected patients (+ 9% at 3 years p=0.02)
- Overall survival not available yet

## Peri-operative chemotherapy for resectable mCRC: Further possible directions

### Intensification of chemotherapy:

- Triple cytotoxic combination
  - Folfirinox, Folfoxiri:
    - Higher response rate: 60-70%
    - Increased toxicity

### Randomized study FOLFOXIRI vs. FOLFIRI<sup>1</sup>: n=122

- All types of patients 1st line
- RR: 60 vs. 34%
- Resection rate liver met only: 36 vs 17%

Falcone A et al ASCO GI 2006 (abst. 227)

## Peri-operative chemotherapy for resectable mCRC: Further possible directions

### Combination with targeted therapies

- Bevacizumab
  - Folfiri-Bevacizumab (BICC C: 63% RR)
  - Folfox-Bevacizumab (N016966: 47%)
- Cetuximab for wild-type Kras
  - Folfiri Cetuximab (Crystal 57%)
  - Folfox Cetuximab (OPUS 61%)

### No randomized data available

- Phase II on potentially resectable liver met. N=66
- Xelox+Bevacizumab X 5 + Xelox X 1
- RR: 72%, STB 20%, PD 8%
- Resection rate: 79% (11 pts with synchronous primary)
- Morbidity: 11% Mortality 0%
- PFS directly correlated to response (25 m in OR, 8 m in stb, 3 m in PD)

Gruenberger B et al BMC cancer 2008 8 120

### Peri-operative chemotherapy for resectable mCRC: Ongoing clinical trials

- ⊙ EORTC 40051 BOS trial
  - 50 pts accrued
  - Terminated early based on Cairo 2 and Pacce
- ⊙ EORTC 40091 BOS 2 trial (planned)
  - Randomized phase II
  - Resectable liver met from CRC wild-type Kras
  - Folfox vs. Folfox Panitumumab vs Folfox Bevacizumab
  - Primary EP: PFS
  - 360 patients

### Peri-operative chemotherapy for resectable mCRC: Unanswered questions

1. **Should Chemotherapy be given as neo- or adjuvant only?**
  - Never evaluated in clinical trial
  - Neo-adjuvant CT should be short enough to avoid toxicity
  - Neo-adjuvant CT provide rationale for further adjuvant in responders
2. **Pseudo-adjuvant, post-resection chemotherapy**
  - Benefit not formally demonstrated, used by analogy with adjuvant setting results
  - Few randomized post-resection trials:
    - FFC0902: bolus 5FU vs Observation
    - EORTC/NCIC CTG/GIVIO: bolus 5FU vs. Observation
    - CPT GMA 301 (Ychou et al.): FOLFIRI vs. LV5FU2
  - **Trend in favor of 5FU vs. Observation for PFS and OS**
  - **Trend in favor of FOLFIRI vs. LV5FU2 for PFS and OS**

### Peri-operative chemotherapy for resectable mCRC: The specific situation of Rectal cancer

- ⊙ Most of primary rectal cancer are symptomatic
- ⊙ Neo-adjuvant Chemoradiation on the primary is the standard of care
- ⊙ Chemotherapy backbone in combination with radiation may be safely used (Oxali-based)
- ⊙ Chemotherapy used in the neo-adjuvant setting will have efficacy on metastatic disease as well and may be intensified (Oxali-based) in combination with radiation and continued after radiation and before surgery.

### Peri-operative chemotherapy for resectable mCRC: Decision making

- ⊙ **Each case should be discuss before any treatment by a multidisciplinary team:**
  - GI surgeon experienced in liver surgery
  - Medical Oncologist, Gastro-enterologist
  - Radiologist
  - Pathologist

### Peri-operative chemotherapy for resectable mCRC: Decision making recommendations

- ⊙ Prognostic factors should be considered: <sup>(1)</sup>
  - **Poor tumor-associated prognostic factors include:**
    - Undifferentiated histology
    - Multiple metastasis, size > 5cm, synchronous
    - High tumor markers
- ⊙ All patients with > 1 poor prognostic factor should receive neo-adjuvant treatment <sup>(1)</sup>
- ⊙ Chemotherapy efficacy should be evaluated early before total disappearance of lesions <sup>(1)</sup>

<sup>1</sup> Expert Panel recommendations Annals Oncol 2009 20 985-992

### Peri-operative chemotherapy for resectable mCRC: Decision making recommendations

- ⊙ Chemotherapy should not exceed 6 cycles to avoid liver damages <sup>(1)</sup>
- ⊙ Post-operative chemotherapy should be used in resected patients to reach a total of 12 cycles. <sup>(1)</sup>
- ⊙ In patients with good prognostic factors:
  - Single, 2cm liver metastasis, well differentiated may go straight to surgery <sup>(1)</sup>

<sup>1</sup> Expert Panel recommendations Annals Oncol 2009 20 985-992

### Peri-operative chemotherapy for resectable mCRC

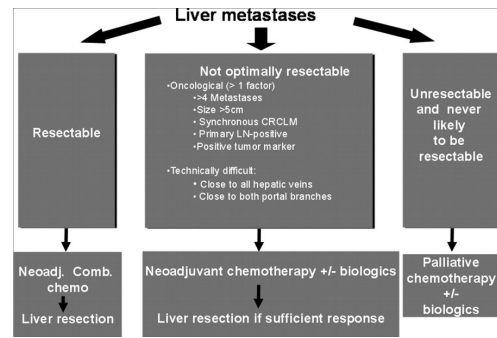
⊙ Peri-operative chemo+/- targeted therapy should be delivered in patients with resectable, asymptomatic or pauci-symptomatic primary tumor with synchronous metastasis of colo-rectal cancer

⊙ Such combined modality has multiple advantages:

- Improved Disease-Free Survival
- Treat micrometastatic disease
- Test for chemosensitivity
- Select patients with aggressive disease and avoid unneeded surgery
- Facilitate limited hepatectomy

⊙ Without increasing post-operative mortality

Treatment choices for patients with colorectal liver metastases, bearing in mind the type of chemotherapy maybe the same in all three clinical situations.



Nordlinger B et al. Ann Oncol 2009;20:985-992

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