Synchronous liver metastases
Oncosurgical Strategy

How to resect the unresectable?
Epidemiology

- 7129 new cases of Colorectal Cancer *
- 1/3 are rectal cancers
- 3797 mortality cases*

*GLOBOCAN Report 2012 - International Agency for Research on Cancer
Epidemiology

- 25% of patients have metastatic disease at presentation
- 30% develop metastases during the course of their disease
- The liver is the most common site of metastatic disease,
  - Involved in 80% of cases
  - Liver-only mets (40%)

Tzeng CW, Aloia TA. Colorectal liver metastases. J Gastrointest Surg. 2013
Median survival – hepatic metastases

**Untreated** – survival 6 and 12 months

**Systemic chemotherapy** - median survival of 2-year

**Resected R0**  - 5 year survival ranges between 27% to 74%
- 10 Y survival 9- 50%
## Results of hepatic resection for mets CCR

<table>
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<th>Study</th>
<th>n</th>
<th>Survival at 5 Years %</th>
<th>median survival , M</th>
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Resected R0 - 5 year survival ranges between 27% to 74%  
- 10 Y survival 9-50%

Resection is the only chance of long-term survival / cure
Only a minority of patients are suitable for upfront surgery 20% – 25%.

When patients with unresectable disease are downstaged to complete resection, long-term data support 5 and 10-year survival are similar to upfront resectable patients.
Liver metastases in colorectal cancer

Liver metastases

Resectable
20% to 25%

Nonresectable
75% to 80%

downstage

Survival benefit
27% to 74% at 5 Y

Resectable
20% to 30%
Liver metastases in colorectal cancer

How to resect the unresectable?
“Resectable”

1. Appropriate medical candidate for surgery

2. The metastatic liver tumor can be completely resected.

3. Sufficient future remnant liver
Patient selection and Preoperative assessment

- **CT** - scan of the abdomen and chest
- **MRI** - if small lesions, a fatty liver or preop CT
- **PET** - in case of tumor recurrence
  - in patients with a previous liver resection
  - suspected distant metastasis.

- Child Pugh,
- ICGR15
Two management strategies (to improve resectability.)

- **Shrink tumors**
  - Conversion chemotherapy,
  - Hepatic Arterial Infusion Pump Therapy

- **Optimize the FLR**
  - Parenchymal-sparing liver surgery
  - PVE
  - Two-stage hepatectomy
  - (ALPPS)
  - Local ablation techniques
Strategies to Shrink Tumor Burden

- Systemic Chemotherapy
- Hepatic Arterial Infusion Pump Therapy
Systemic Chemotherapy

• In the 5-FU era - **response rates** approximately 20 %

• Modern chemotherapeutic agents (Oxaliplatin, Irinotecan … and new regimens FOLFOX, FOLFIRI …)

  - tumor response rates of >50%
  
  - 6-month stable disease 90–95 %
  
  - long **median survival** (30 months).
N = 872

701 patients with unresectable CRLM (80%)

FOLFOX

14% resectable

5-year survival 39%
Tumor response rate - patients with unresectable CRLM

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<th>Study</th>
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• Modern preop CT allows complete resection in 12-35% of patients

• A strong correlation between the response rates and the resection rates of patients with initially unresectable CLRM

conversion therapy ➔ Resection ➔ 5 year OS (40–50 %)
similar to upfront resectable patients
Hepatic Arterial Infusion Pump Therapy

The concept

- Liver mets larger than 3 mm over 80% of their blood irradiation is by hepatic artery
- Normal hepatocytes derive their blood supply from the PV (75%)
- The tip of the catheter is positioned at the gastroduodenal-hepatic artery junction
Hepatic Arterial Infusion Pump Therapy

- This directed therapy allows an increased amount of cytotoxic drugs without increasing the systemic side effects

- HAIP increased the possibility of tumor response and might improve liver function

- This therapy can be used in combination with systemic chemotherapy
### TABLE 1  Summary of consensus statements

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<thead>
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<td><strong>HAIP</strong> chemotherapy should be given in combination with systemic chemotherapy.</td>
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<td><strong>HAIP</strong> chemotherapy should be offered in the context of a multidisciplinary program that includes expertise in hepatobiliary surgery, medical oncology, interventional radiology, nursing, and nuclear medicine.</td>
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<tr>
<td><strong>HAIP</strong> chemotherapy in combination with systemic therapy should be considered in patients with unresectable colorectal liver metastases who have progressed on first-line systemic treatment. In addition, <strong>HAIP</strong> chemotherapy is acceptable as first-line treatment in patients with unresectable colorectal liver metastases.</td>
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<td><strong>HAIP</strong> chemotherapy is not recommended in the setting of extrahepatic disease outside the context of a clinical trial.</td>
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<td><strong>HAIP</strong> chemotherapy in combination with systemic therapy is an option for select patients with resected colorectal liver metastases.</td>
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</table>
49 patients with unresectable CRLM

combined HAIP and systemic CT including bevacizumab

47% achieved conversion to resection at a median of 6 months from treatment initiation

3-year OS – resected patients 80% / not resection 26%
Two management strategies (to improve resectability.)

- **Tumor**
  - Shrink tumors
    - Conversion chemotherapy,
    - Hepatic Arterial Infusion Pump Therapy

- **Liver**
  - Optimize the FLR
    - Parenchymal-sparing liver surgery
    - PVE
    - Two-stage hepatectomy
    - (ALPPS)
    - Local ablation techniques
Strategies to optimize FRL

The objective

- Resection of all detectable lesions with tumor-free margins

- Parenchymal-sparing liver surgery

- PVE

- Two-stage hepatectomy

- (ALPPS)

- Local ablation techniques
Preoperative Planning and Volumetric Assessment

To achieve a safe hepatic resection with an adequate FLR

- Evaluation of the underlying parenchymal status and function
- Evaluation of liver tumors (the proximity to critical structures)
- Evaluation of liver volumes (FRL)
Makuuchi's criteria

Ascites

No or controllable

Total bilirubin

Normal

ICG 15'

Normal

Trisegmentectomy
Rt hepatectomy

10%-19%

Lt hepatectomy
Rt segmentectomy

20%-29%

Subsegmentectomy

30% ≤

Limited resection

Incontrollable

Limited resection

No hepatectomy
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Total

Volume total = 1,533
volume 234 = 33,1%
Volume 23 = 18,9%
Parenchymal-sparing liver surgery
(One-Stage Ultrasonically Guided Liver Resection)

- A profound knowledge of liver patient’s anatomy
- Expert IOUS skills

- This technique allow radical but conservative liver resections
- Avoiding the unnecessary sacrifice of functional parenchyma
- Reducing the risk of developing postoperative liver failure
- Avoiding the necessity of PVE / two stage heptectomy

with equal or better perioperative and long-term outcomes than non-PSLS
“Prophylactic” large resections were useless in preventing intra or extra-hepatic recurrence

- increased patient risk
- less chances of future repeated resection
- poorer prognosis after major resection than after multiple minor resections
S7 resection

S7 partial resection of RHV reconstruction by running suture
S4a
PVE (portal vein embolization)

- Introduced in the 1980s by Makuuchi

- Tumor is technically resectable but the FRL is too small

- Is embolized the PV supplying the portion of liver to be resected

- Induce ipsilateral atrophy and contralateral compensatory hypertrophy of the FRL up to 40% over a median period of approximately 4 weeks*

*Azoulay, Ann. Surg. April 2000 Vol. 231, No. 4,
PVE → Surgery

- Surgery 2 to 6 weeks after PVE
- Resectability 60% to 82%
  - progression of hepatic or extrahepatic disease
  - Insufficient hypertrophy 9%
Impact of portal vein embolization on long-term survival of patients with primarily unresectable colorectal liver metastases

D. A. Wicherts¹,², R. J. de Haas¹,², P. Andreani¹, D. Sotirov¹, C. Salloum¹, D. Castaing¹,²,³, R. Adam¹,²,³ and D. Azoulay¹

¹Centre Hépato-Biliaire, Assistance Publique—Hôpitaux de Paris, Hôpital Paul Brousse, ²Institut National de la Santé et de la Recherche Médicale, Unité 785, and ³Université Paris-Sud, Unité Mixte de Recherche-8755, Villejuif, France, and ⁴Department of Surgery, University Medical Centre Utrecht, Utrecht, The Netherlands

n = 364 hepatectomias major

PVE = 67 (18%)

Morbilidade: 41 % não PVE / 55% PVE
PVE

PVE in bilobar disease
PVE may increases tumor growth rate


Two stage hepatectomy
Two stage hepatectomy

In patients with bilobar, multinodular tumor

- **the first stage** - clearing the FLR
- PVE to increase the volume of the tumor-free FLR.
- **second stage** - resection of the remaining disease

The second stage resection is completed in 69-77% of patients **

Patients who complete two-stage procedure had an overall 5 Y survival of 42%

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**Oncology, Vol 5, No 5 October 2014
Annals of surgery 248, dec 2008**
Two stage hepatectomy-strategy

Preop CT

First-stage resection + PVE

CT (3 w after liver resection)

Second-stage resection

Postop CT

compensatory hypertrophy

Two-Stage Hepatectomy: A Planned Strategy to Treat Irresectable Liver Tumors
Conclusions: Two-stage hepatectomy provides a 5-year survival of 42% and a hope of long-term survival for selected patients with extensive bilobar CLM, irresectable by any other means.
ALPPS - Associated Liver Partition and Portal vein ligation for Staged hepatectomy

- Is a novel two-stage technique for optimizing FLR

- **First stage** - Portal vein ligation is combined with an in situ liver transection

- Results in a pronounced short-term parenchymal hypertrophy over approximately 1 week

- **Second stage** (1 week), a second laparotomy to remove the pre-divided liver
ALPPS - Associated Liver Partition and Portal vein ligation for Staged hepatectomy

- The increase in FLR with ALPPS ranges form 63-87%

- Advantage of ALPPS over PVE is the short interval to completion surgery

  hypertrophy of the FLR - in less than 10 days (ALPPS)
  - compared to over 3 weeks for PVE

Morbidity 53-71% / mortality of 0-22%

The benefit of ALPPS over conventional PVE is heavily debated.
Locoregional Therapies - RFA

- RFA thermally ablate tumors
- Can be performed percutaneously, laparoscopically, or during laparotomy
Locoregional Therapies - RFA

Indications:

✓ Patients who are not candidates for surgical resection (co-morbidities)

✓ May be used in combination with resection in order to optimize FLR
Locoregional Therapies - RFA

Disadvantage / limits

✓ Tumors greater than 30 mm  (high recurrence rate)

✓ Contact with major biliary structures (risk for bile duct stricture and fistula)

✓ Contact with major vascular structures (risk of an inadequate ablation)
- 141 patients treated with multiple resections
- 95 patients treated with ablation + resection techniques
- 5-year OS was statistically similar - ablation-resection (56 %) - multiple resection (49 %)

**Conclusions and Relevance** Treatment of bilateral, multiple hepatic metastases with combined resection and ablation was associated with improved perioperative outcomes without compromising long-term survival compared with bilateral resection. Ablative therapies extend the capability of delivering potentially curative treatment for bilateral hepatic colorectal metastases.
What about liver transplantation?

Nonresectable liver-only metastases → Standard treatment option → Palliative chemotherapy
comparison of results in 2 prospective studies SECA / NORDIC VII
- CRC nonresectable metástases
- liver-only metástases

SECA study - patients undergoing liver transplantation

NORDIC VII study - patients receiving chemotherapy
- Nordic FLOX with or without cetuximab
Chemotherapy or Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer?

Svein Dueland, MD, PhD,* Tormod K. Guren, MD, PhD,* Morten Hagness, MD, PhD,††
Bengt Glimelius, MD, PhD,§ Pål-Dag Line, MD, PhD,† Per Pfeiffer, MD, PhD,¶ Aksel Foss, MD, PhD,††
and Kjell M. Tveit, MD, PhD*††

5-year OS
-56% in patients undergoing liver transplantation
-9% in patients starting firstline chemotherapy
Autor recomendations

- Selecting patients for liver transplantation based on
  
  - CEA < 80 μg/L
  - metastases < 5.5 cm
  - no progressive disease at the time of transplantation
  - more than 2 years from diagnosis of CRC

May be obtained a 5-year OS rate of 75%
Liver metastases in colorectal cancer

Liver metastases

Resectable
20% to 25%

Nonresectable
75% to 80%

donstage

Survival benefit
27% to 74% at 5 Y

Resectable
20% to 30%

Medical therapies
Surgical techniques
Conclusion

- Surgical resection remains the treatment of choice for resectable CLM

- Surgical techniques and medical therapies, are currently utilized in to improve resectability.

- Treating hepatic metastases requires a knowledge of all treatment options

- Patients with unresectable disease are downstaged to complete resection, long-term data support 5 and 10-year survival are similar to upfront resectable patients

- Liver Transplantation for Unresectable CRCLM? …

Will the paradigm change in the future?
Obrigado