Multidisciplinary treatment of Colorectal Liver Metastases: Surgical perspectives

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Conflicts of interest

• Sanofi
• Merck
Multidisciplinary treatment of CRLM

1- Resection: a real end point of the strategy?
2- For what patients: Definition of Resectability?
3- The role of the surgeon: Extending the indications...
4- The role of the oncologist: Conversion chemotherapy...
5- Still unresectable patients: What the oncologist can do?
6- Still unresectable patients: What the surgeon can do?
7- Definitively unresectable patients: a last chance?
8- The need of a multidisciplinary (MDT) approach
9- A possibility of Cure?
Resection of liver metastases improves survival


- R0, resection with microscopically negative margins.

- Surgical series published after 1980

- Median 5-year survival (range), %
  - R0 resected (16 studies): 30%
  - Resected, R0/R1 unclear (19 studies): 32%
  - Non-radical resection (11 studies): 7%
  - Not resected (6 studies): 0%

R0, resection with microscopically negative margins.
LIVERMETSURVEY: Overall Survival after Liver resection
June 2020: 28,081 Pts - 366 Centers - 63 countries

Patient Survival after a 1st liver operation for Colorectal Metastases: 28081 patients

Log Rank p = <0.0001

43%
26,671 Resected Pts

10%
1410 non Resected

2%

www.livermetsurvey-arcad.org
LIVERMETSURVEY June 2020

29,622 Pts
366 centers
63 Countries

www.livermetsurvey-arcad.org
Main End Point of the Strategy

Resection of Liver Metastases
Multidisciplinary treatment of CRLM

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New definition of resectability

“Pragmatical” rather than “dogmatic”

- All liver metastases that can be completely removed while leaving at least 30% of remnant liver...
- Even in cases with extrahepatic tumors, if these are also resectable...

Adam R et al. Gastrointest Cancer Res. 2009

- NCCN Guidelines criteria for resection suitability:
  “… the likelihood of achieving complete resection of all evident disease with negative surgical margins and maintaining adequate liver reserve”

Multidisciplinary treatment of CRLM

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Long-term Outcome of Patients with ≥ 10 CLM

Allard MA ... Adam R (Br J Cancer 2017)

Overall survival

Time from diagnosis (Months)

Number of metastases: not a contraindication
Overall survival according to surgical margins

R1 Resection: not a contraindication to surgery

Overall Survival according to surgical margins

R1Vasc resection is not adequate for CLMs, because it is associated with a higher local recurrence risk and worse survival. R1Vasc achieves local disease control equivalent to R0 resection and adequate survival.

R0 vs. R1Vasc; $p = \text{n.s.}$

R0 vs. R1Par; $p = 0.034$
LIVERMET SURVEY June 2020
7096 Elderly Patients

Patient Survival after a 1st hepatectomy for Colorectal Metastases: 6980 patients

Global Log Rank p = <0.0001

Age per se: not a contraindication...
1- **Age-related**

2- **Tumor-related**: related to hepatic metastases
   - Number of tumors
   - Tumor Size...

3- **Disease-related**: curative pattern of resection
   - Resection Margin
   - Extrahepatic site

4- **Technical limit of complete tumor resection**: Too small remnant liver (< 30% total funct. liver)
COLO-RECTAL CANCER

LIVER METASTASES

Resectable 10-20% → Surgery

Non resectable 80-90% → Chemotherapy
Multidisciplinary treatment of CRLM

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Metastatic CRC: increasing survival…

- 5-FU/LV bolus: 12.6 months
- 5-FU/LV infusion: 14.1 months
- IFL: 14.8 months
- FOLFIRI: 17.4 months
- FOLFOX: 19.5 months
- IFL + bevacizumab: 20.3 months
- FOLFOXIRI: 22.6 months
- XELOX/FOLFOX + bevacizumab: 21.3 months
- FOLFOX + cetuximab: 22.8* months
- FOLFIRI + cetuximab: 23.5* months
- FOLFIRI + panitumumab: 23.9* months
- FOLFOX or FOLFIRI: 20.6 months
- FOLFOX or FOLFIRI + bevacizumab: 20.6 months
- FOLFIRI + bevacizumab: 25.0 months
- FOLFIRI + cetuximab: 28.7* months
- FOLFIRI + bevacizumab: 25.6 months
- FOLFIRI + cetuximab: 33.1** months


Survival data from various clinical trials and studies.
Recommendation 13: conversion therapy.

- In potentially resectable patients (if conversion is the goal), a regimen leading to high RRs and/or a large tumour size reduction (shrinkage) is recommended [II, A].

- There is uncertainty surrounding the best combination to use as only few trials have addressed this specifically:
  - In patients with RAS wild-type disease, a cytotoxic doublet plus an anti-EGFR antibody seems to have the best benefit risk/ratio, although the combination of FOLFOXIRI plus bevacizumab may also be considered and, to a lesser extent, a cytotoxic doublet plus bevacizumab [II, A].
  - In patients with RAS-mutant disease: a cytotoxic doublet plus bevacizumab or FOLFOXIRI plus bevacizumab [II, A].

- Patients must be re-evaluated regularly in order to prevent the overtreatment of resectable patients as the maximal response is expected to be achieved after 12–16 weeks of therapy in most patients.

Resection of metastases: pivotal role of the strategy?

Chemo ± Targeted

Chemo ± Targeted + Surgery

Survival after Liver Resection of Colorectal Metastases
Paul Brousse Hospital - 473 patients (Apr. 88 - Jul. 99)

91%
66%
48%
30%
23%

P = 0.01

No Surgery

Survival after Liver Resection of Colorectal Metastases
LiverMetSurvey: Resectable vs initially unresectable

Patient Survival after a 1st hepatectomy for Colorectal Metastases 22022 patients

46%
34%
28%

www.livermet surveys-arcad.org


OS in patients with KRAS wild-type tumors treated by FolFiri ± Cetuximab
Downstaging after Chemotherapy: A role for Surgery?
Resectable 10–20%  
Non resectable 80–90%

Survival benefit  
33% at 5 yrs  
15–30 %

Survival benefit  
5% at 5 yrs
Multidisciplinary treatment of CRLM

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**Parameter**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1st line</th>
<th>2nd line</th>
<th>Later lines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rate</strong></td>
<td>38–64%(^1,2)</td>
<td>10–35%(^5,6)</td>
<td>1–13%(^8,9)</td>
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<tr>
<td><strong>Progression-free survival</strong></td>
<td>8–11 months(^3,4)</td>
<td>4–7 months(^5,7)</td>
<td>2–3 months(^8,10)</td>
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</table>

*Range of results for targeted treatment arms of key Phase II and III trials (KRAS wt exon 2 for EGFR inhibitor trials)*

**Conclusion**: 1st line therapy is a critical determinant of overall survival

Resection of colorectal liver metastases after second-line chemotherapy: is it worthwhile? A LiverMetSurvey analysis of 6415 patients

Survival after Hepatectomy

Survival after Diagnosis

Surgery should not be denied after the failure of 1st line chemotherapy
• 55 patients
• 49 IAHC
• IAH FUDR + IV oxaliplatin et irinotecan
• 92% of responses
• 39% secondary resections
Multidisciplinary treatment of CRLM

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Techniques to improve Resectability

Multi Bilobar

Remnant Liver <30%

Portal Vein Embolization
Techniques to improve Resectability

Multi Bilobar

Remnant Liver <30%

Portal Vein Embolization

≤3 nod. ≤30 mm

Hepatectomy ± Local Ablation
Techniques to improve Resectability

Multi Bilobar

Remnant Liver <30%

Portal Vein Embolization

≤3 nod. ≤30 mm

Hepatectomy ± Local Ablation

>3 nod. >30 mm

TSH or ALPPS
LIVERMETSURVEY Dec. 2016
Adjuvant Techniques to increase Resectability

Patient Survival after a 1st hepatectomy for Colorectal Metastases: 21826 patients

Log Rank p = 0.0001

Resection

Resection + Adj. Techn.

46%
32%
COLO-RECTAL CANCER

LIVER METASTASES

Expanding indications

Resectable 20-30%

Non resectable 70-80%

Surgery

Chemotherapy
COLO-RECTAL CANCER

LIVER METASTASES

Expanding indications

Resectable 30-40%

Non resectable 60-70%

Surgery

Rescue Surgery

Chemotherapy
COLO-RECTAL CANCER

LIVER METASTASES

Expanding indications

Resectable #50%

Specific Techniques

Surgery

Rescue Surgery

Targeted therapies

Non resectable 50%

Chemotherapy
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Multidisciplinary approach to the treatment of mCRC in daily practice

The good treatment at the good timing…
Multidisciplinary approach to the treatment of mCRC in daily practice

The medical oncologist needs the surgeon...
- Resectability ?
- Timing of surgery
- Improved long-term survival

The surgeon needs the medical oncologist ...
- Making unresectable patients resectable
- Control the disease before surgery
- improved survival by neoadjuvant chemotherapy
- Preventing recurrence after surgery
Multidisciplinarity Yes...
but MDT with Expertise...
Effect of specialist decision-making on treatment strategies for colorectal liver metastases

R. P. Jones¹,³, J.-N. Vauthey⁶, R. Adam⁷, M. Rees⁴, D. Berry⁵, R. Jackson², N. Grimes³, S. W. Fenwick³, G. J. Poston³ and H. Z. Malik³

Background: One hundred and ten patients were treated with palliative chemotherapy, of whom 53 had liver-only disease and had not been reviewed by a specialist liver surgeon. One scan was excluded.

Results: Tumours in 33 patients (63 per cent) were considered potentially resectable, with a high level of interobserver agreement (κ = 0.577). When individual approach to management was considered, interobserver agreement was less marked (κ = 0.378).

Conclusion: Management of patients with colorectal liver metastases without the involvement of a specialist liver multidisciplinary team can lead to patients being denied potentially curative treatments. Management of these patients must involve a specialist liver surgeon to ensure appropriate management.
Evaluation for surgical treatment in metastatic colorectal cancer (mCRC)  
A Retrospective, central evaluation of FIRE-3  
by 8 visceral surgeons and 3 medical oncologists

<table>
<thead>
<tr>
<th>N=448</th>
<th>Retrospectively considered resectable at baseline</th>
<th>Retrospectively considered resectable at best response</th>
<th>Secondary resection</th>
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<td>97 (21.7%)</td>
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<td>58 (96.7%)</td>
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<td>48 (67.7%)</td>
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<td>14.8%</td>
<td>16.8%</td>
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In FIRE-3, surgery is a treatment option for approximately half of the pts. The discrepancy between possible and de facto done resections highlights the need for a multi-disciplinary decision making. The inclusion of dedicated surgeons or other interventionalists in addition to medical oncologists appears as mandatory, not only before start of treatment, but also more importantly during systemic treatment on a regular and preplanned basis.
2016 - FIRE3: Blinded review for resectability:
The Gap between Resectability and Resection...

Neumann et al, ESMO 2016
In summary, many patients with CRLM are not being offered appropriate surgery, despite the preponderance of evidence that metastasectomy is an important life-extending therapy. A major obstacle is the assessment of resectability by nonexperts. It is simply not possible to translate principles of resectability into simple criteria. Now, the decision-making process for resectability is more complex than ever as knowledge of disease biology grows and advanced surgical techniques evolve. There is an even greater need to involve experienced HPB surgeons and medical oncologists early in the care of these patients. We should ensure that all patients with isolated CRLM have a formal review of resectability—at a minimum in a multidisciplinary cancer conference staffed by surgeons knowledgeable in liver surgery, but optimally via consultation with an experienced HPB surgeon. This is an achievable aim that will improve access to metastasectomy for all patients who are eligible.
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LIVERMETSURVEY: Overall Survival after Liver resection
June 2020: 28,081 Pts - 366 Centers - 63 countries

Patient Survival after a 1st liver operation for Colorectal Metastases: 28081 patients

Log Rank p = <0.0001

www.livermetsurvey-arcad.org
Patients With Initially Unresectable Colorectal Liver Metastases: Is There a Possibility of Cure?

René Adam, Dennis A. Wicherts, Robbert J. de Haas, Oriana Ciacio, Francis Lévi, Bernard Paule, Michel Dureux, Daniel Azoulay, Henri Bismuth, and Denis Castaing

**Fig 1.** Overall and disease-free survival curves of patients with initially unresectable disease who underwent resection after downsizing chemotherapy.
LIVERMETSURVEY Dec. 2016
Repeat Hepatectomy

Patient Survival after the last hepatectomy of the patient for Colorectal Metastases: 24795 patients

Global Log Rank p = <0.0001

From the time Of last hepatectomy

40%
31%

Number of exposed patients

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<th>No_of_hep</th>
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<th>1 yr</th>
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</table>
5-year survival of English colorectal cancer patients first diagnosed 1998–2004 (n=114,155)

Morris EJA, ..., Poston G. Brit J Surg 2010

All stage 4 resected n=3116
Main End Point of the Strategy

- Extend Indications
- Conversion Chemo 1st/2nd line
- Specific Techniques
- MDT management
- Expertise

Personalization through Molecular Biology
Take Home messages

1. Resection upfront or after chemo: the objective with...

2. Optimal 1st line Chemo using anti-EGFR in Ras WT

3. As short as needed to induce resectability…

4. Expert MDTeam, well defined criteria resectability…

5. Fighting spirit from oncologists…

6. And surgeons…

7. Even for locally advanced disease (LLD) and recurrence…

Never Give up !!!