Which patients with CRLM could be transplanted?

René Adam

Hopital Paul Brousse, Université Paris Sud
Basic Principle:

Liver Resection is the best treatment of Hepatic Metastases from Colorectal Cancer
Progress in Liver Surgery has increased the Resectability rate...
Downstaging after Chemotherapy: A role for Surgery?
Survival after Liver Resection of Colorectal Metastases
Paul Brousse Hospital - 473 patients (Apr. 88 - Jul. 99)

Survival after Liver Resection of Colorectal Metastases

LiverMetSurvey: Resectable vs initially unresectable

Patient Survival after a 1st hepatectomy for Colorectal Metastases: 18035 patients

Log Rank $p = < 0.0001$

- Resectable: 45% (N=14723) vs 32% (N=3312)
- Initially unresectable: 27% vs 18%

www.livermetsurvey.org
SURVIVAL AFTER CHEMOTHERAPY FOR CRLM


Masi et al, Ann Surg Oncol 2006
OS in patients with KRAS wild-type tumors treated by FolFiri ± Cetuximab

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI</th>
<th>Cetuximab + FOLFIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>20.0 months</td>
<td>23.5 months</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[17.4-21.7]</td>
<td>[21.2-26.3]</td>
</tr>
<tr>
<td>HR [95% CI]</td>
<td>0.796 [0.670-0.946]</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0093 (log-rank)</td>
<td></td>
</tr>
</tbody>
</table>

Median follow up was 46 months

Van Cutsem E et al. GI Cancers Symposium, ASCO 2010 and in press J Clin Onc
Is there a place for Liver Transplantation in these patients?

Lessons from the past...
Evolution of Liver Transplantation for Colorectal Metastases

80% before 1995
Patient Survival after LT for Colorectal Metastases
Centers performing LT for Colorectal Metastases  

<table>
<thead>
<tr>
<th>City</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innsbruck</td>
<td>2</td>
</tr>
<tr>
<td>Wien</td>
<td>25</td>
</tr>
<tr>
<td>Liege</td>
<td>1</td>
</tr>
<tr>
<td>Brussels UCL</td>
<td>2</td>
</tr>
<tr>
<td>Essen</td>
<td>1</td>
</tr>
<tr>
<td>Jena</td>
<td>2</td>
</tr>
<tr>
<td>Hannover</td>
<td>3</td>
</tr>
<tr>
<td>Munchen CUK</td>
<td>1</td>
</tr>
<tr>
<td>Munster</td>
<td>1</td>
</tr>
<tr>
<td>Paris, Villejuif</td>
<td>1</td>
</tr>
<tr>
<td>Rennes</td>
<td>1</td>
</tr>
<tr>
<td>Milano O.N.</td>
<td>1</td>
</tr>
<tr>
<td>Palermo</td>
<td>1</td>
</tr>
<tr>
<td>Pisa</td>
<td>1</td>
</tr>
<tr>
<td>Coimbra</td>
<td>1</td>
</tr>
<tr>
<td>Warsaw</td>
<td>1</td>
</tr>
<tr>
<td>Murcia</td>
<td>1</td>
</tr>
<tr>
<td>Pamplona</td>
<td>1</td>
</tr>
<tr>
<td>Zaragoza</td>
<td>1</td>
</tr>
<tr>
<td>Göteborg</td>
<td>1</td>
</tr>
<tr>
<td>Huddinge</td>
<td>1</td>
</tr>
</tbody>
</table>

Experience of centers have been anecdotal…
## Initial Immunosuppression treatment


<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA + Aza</td>
<td>1</td>
</tr>
<tr>
<td>CsA + Aza + Steroids</td>
<td>3</td>
</tr>
<tr>
<td>CsA + Steroids</td>
<td>1</td>
</tr>
<tr>
<td>CsA + Steroids + ALS</td>
<td>1</td>
</tr>
<tr>
<td>CsA + OKT + Aza + Steroids + ALS</td>
<td>1</td>
</tr>
<tr>
<td>CsA + OKT + Steroids + ALS</td>
<td>13</td>
</tr>
<tr>
<td>CsA + Steroids</td>
<td>11</td>
</tr>
<tr>
<td>Tacro + Steroids + MMF</td>
<td>1</td>
</tr>
<tr>
<td>Tacro + Steroids + MMF + Others</td>
<td>1</td>
</tr>
<tr>
<td>Tacro + Steroids + OKT + ALS + Others</td>
<td>1</td>
</tr>
<tr>
<td>Tacro + Steroids</td>
<td>2</td>
</tr>
<tr>
<td>Tacro + Steroids + Others</td>
<td>1</td>
</tr>
<tr>
<td>Aza + Steroids + Others</td>
<td>1</td>
</tr>
<tr>
<td>OKT + Steroids + ALS</td>
<td>4</td>
</tr>
</tbody>
</table>
## Cause of Death or Graft Failure


<table>
<thead>
<tr>
<th>Cause</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative death</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>Bacterial Infection</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Arterial Thrombosis</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>PNF</td>
<td>3</td>
<td>7%</td>
</tr>
<tr>
<td>Biliary complication</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Massive hemorrhagic necrosis</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>Other liver complication</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Recurrence of original tumor</strong></td>
<td>24</td>
<td>56%</td>
</tr>
<tr>
<td>Recurrence of unrelated tumor</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>De novo solid organ tumor</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Rejection</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

Graft loss was related to non tumoral causes in 44% of cases...
Evolution of Mortality following LT for Colorectal Metastases


- 9 Patients survived > 5 years
- 2 pts alive with NED at 9 and 21 yrs
Liver Transplantation for Colorectal Liver Metastases

Past experience…

5-year survival 18% overall, but…

- Mainly for historical cases (< 1995)
- No real patient selection
- Almost 50% graft loss: non tumoral causes
- No “standard indication” or adjuvant Tt

Survival was possible at long-term
Liver Transplantation for Colorectal Liver Metastases

What has changed?

- Improved expertise in the management of LT
Patient Survival after LT in Europe up to 1985

- Patient mortality decreases significantly within the first year post-LT.
- Survival rates remain relatively stable beyond the first year, with a slight decrease after 5 years.
Patient Survival according to the Year of Liver Transplantation

- <85: 515
- 85-89: 4118
Patient Survival according to the Year of Liver Transplantation
Patient Survival according to the Year of Liver Transplantation

- <85: 515
- 85-89: 4173
- 90-94: 11783
- 95-99: 18038
Patient Survival according to the Year of Liver Transplantation

- <85: 515
- 85-89: 4173
- 90-94: 11783
- 95-99: 18038
- >99: 22015
Patient Survival according to the Year of Liver Transplantation

<85 : 513
85-89 : 4117
90-94 : 11984
95-99 : 18044
2000-2004 : 22573
>2004 : 6157

0 1 2 3 4 5 6 7 8 9 10 Yrs

0 20 40 60 80 100 (%)
Liver Transplantation for Colorectal Liver Metastases

What has changed?

- Improved expertise in the management of LT
- Better knowledge of biology of metastatic disease
Liver Resection for Multiple Mets after Chemo

Overall Survival

- Downstaging: 58
- Stabilization: 39
- Progression: 34

Log Rank: p < 0.0001

**CONCLUSIONS**

*RAS* mutation status is a powerful predictor of OS, RFS, and lung recurrence after curative resection of CLM. These data indicate that the genetic profile of CLM can be used to improve selection of patients with CLM for surgery and predict outcome of patients with CLM. In addition, the finding of a higher rate of pathologic response in patients with wild-type *RAS* sets the stage for further studies focusing on somatic gene mutations and pattern of response associated with preoperative chemotherapy.
BRAF Mutation Predicts for Poor Outcomes After Metastasectomy in Patients With Metastatic Colorectal Cancer

Rona Yaeger, MD\textsuperscript{1}; Andrea Cercek, MD\textsuperscript{1}; Joanne F. Chou, MPH\textsuperscript{2}; Brooke E. Sylvester, PhD\textsuperscript{3}; Nancy E. Kemeny, MD\textsuperscript{1}; Jaclyn F. Hechtman, MD\textsuperscript{4}; Marc Ladanyi, MD\textsuperscript{4}; Neal Rosen, MD\textsuperscript{1}; Martin R. Weiser, MD\textsuperscript{5}; Marinela Capanu, PhD\textsuperscript{2}; David B. Solit, MD\textsuperscript{1,3}; Michael I. D'Angelica, MD\textsuperscript{5}; Efsevia Vakiani, MD\textsuperscript{4}; and Leonard B. Saltz, MD\textsuperscript{1}
Liver Transplantation for Colorectal Liver Metastases

What has changed?

- Improved expertise in the management of LT
- Better knowledge of biology of metastatic disease
- Better imaging: PET/CT
Extrahepatic disease
Liver Transplantation for Colorectal Liver Metastases

What has changed?

- Improved expertise in the management of LT
- Better knowledge of biology of metastatic disease
- Better imaging: PET/CT
- More effective chemotherapy
Treatment of metastatic colorectal cancer

New drugs and new combinations

- Irinotecan (CPT)
- Oxaliplatin (I-OHP)
- Cetuximab / Panitumumab
- Bevacizumab
- Oral 5-FU’s (Capecitabine, UFT…)

Tumor Response rates > 60-80% and even > 90% (FolFox / Cetuximab) (Tabernero et al, 2004)
Liver Transplantation for Colorectal Liver Metastases

What has changed?

- Improved expertise in the management of LT
- Better knowledge of biology of metastatic disease
- Better imaging: PET/CT
- More effective chemotherapy
- More adapted immunosuppression
Immunosuppression \neq faster tumor growth

Rapamycin
Figure 12. Actions of various immunosuppressive drugs. T cell below, antigen presenting cell above. Adapted from Rosen 2008.
Meta-analysis: Recurrence and Survival following the use of sirolimus in liver transplantation for hepatocellular carcinoma.

Menon KV, Hakeem AR, Heaton ND.
Institute of Liver Studies, King's College Hospital, London, UK.

BACKGROUND:
The use of sirolimus (SRL)-based immunosuppression protocols have been reported to reduce recurrence rates following liver transplantation (LT) for hepatocellular carcinoma (HCC), although this is still a matter for debate.

AIM:
To undertake a systematic review and meta-analysis of available literature on the usage of SRL as an immunosuppressive agent following LT for HCC, with a view to comparing cancer outcomes with the commonly used calcineurin inhibitors (CNIs).

METHODS:
Systematic review and meta-analysis carried out in line with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. Primary outcomes of interest were tumour recurrence rate and recurrence-free survival (RFS). Secondary outcomes were recurrence-related mortality and overall survival (OS).

RESULTS:
In all, 5 studies met the inclusion criteria (n = 474). The recurrence rate was lower in SRL group (4.9-12.9%) in comparison with CNIs (17.3-38.7%). The 1-, 3- and 5-year RFS was 93-96%, 82-86% and 79-80% for SRL group, which was much better in comparison with the CNIs 70-78%, 64-65% and 54-60% respectively. Similarly, 1-, 3- and 5-year OS was much better for SRL group (94-95%, 85% and 80%) in comparison with CNIs (79-83%, 66% and 59-62%) respectively. Meta-analysis demonstrated lower recurrence (OR = 0.30, 95% CI = 0.16-0.55, P < 0.001), lower recurrence-related mortality (OR = 0.29, 95% CI = 0.12-0.70, P = 0.005) and lower overall mortality (OR = 0.35, 95% CI = 0.20-0.61, P < 0.001) for SRL group.

CONCLUSION:
The review showed lower recurrence rate, longer recurrence-free survival and overall survival and lower recurrence-related mortality in sirolimus-treated patients in comparison with the calcineurin inhibitor-treated patients following liver transplantation for HCC.
Liver Transplantation for Colorectal Liver Metastases

Reasonable hypothesis:
LT for very selected patients with
• Liver-only disease assessed by modern imaging
• Confirmed unresectability by partial hepatectomy
• Preop.control of the tumor by active chemotherapy and routine adjuvant treatment post-transplant
• Adapted immunosuppression

May significantly improve the results and offer long-term survival...
Liver transplantation for colorectal liver metastases: revisiting the concept

Aksel Foss,1,2 Rene Adam3,4 and Svein Dueland5

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Journal compilation © 2010 European Society for Organ Transplantation 23 (2010) 679–685

Figure 1 LT for CRC liver metastases performed before 1995 show a 1- and 5-year survival of 62% and 18%, respectively (n = 50). In the SECA study patient survival is 94% with a median follow-up of 25 months (n = 16).
Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer

Morten Hagness, MD,*† Aksel Foss, MD, PhD,*† Pål-Dag Line, MD, PhD,* Tim Scholz, MD, PhD,*

Tumor characteristics, liver metastases

<table>
<thead>
<tr>
<th>No. metastases, * median (range)</th>
<th>8 (4–40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 and 5</td>
<td>4</td>
</tr>
<tr>
<td>6–9</td>
<td>9</td>
</tr>
<tr>
<td>10–19</td>
<td>3</td>
</tr>
<tr>
<td>20–29</td>
<td>2</td>
</tr>
<tr>
<td>≥30</td>
<td></td>
</tr>
</tbody>
</table>

Diameter of metastases

<table>
<thead>
<tr>
<th>Diameter of metastases</th>
<th>&lt;5</th>
<th>5–10</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>12</td>
<td>14</td>
<td>4</td>
</tr>
</tbody>
</table>

Cancer treatment

Chemotherapies received, n

<table>
<thead>
<tr>
<th>Chemotherapies</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan</td>
<td>16</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>18</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>8</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>5</td>
</tr>
</tbody>
</table>

Preoperative chemotherapy

<table>
<thead>
<tr>
<th>Preoperative chemotherapy</th>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 patients</td>
<td>3</td>
</tr>
</tbody>
</table>

Liver resections

<table>
<thead>
<tr>
<th>Liver resections</th>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 patients</td>
<td>4</td>
</tr>
<tr>
<td>(5 procedures)</td>
<td></td>
</tr>
</tbody>
</table>

Radio-frequency ablations

<table>
<thead>
<tr>
<th>Radio-frequency ablations</th>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 patients</td>
<td></td>
</tr>
</tbody>
</table>

Results: Kaplan-Meier estimates of the OS rate at 1, 3, and 5 years were 95%, 68%, and 60%, respectively. Metastatic recurrence of disease was common (mainly pulmonary). However, a significant proportion of the recurrences were accessible for surgery, and at follow-up (after median of 27 months; range, 8–60), 33% had no evidence of disease. Hepatic tumor load before liver transplantation, time from primary surgery to liver transplantation, and progressive disease on chemotherapy were identified as significant prognostic factors.
Waiting list

The mean time on waiting list in the study population was 17 days, which reflects the short waiting list in Norway. However, longer waiting list figures will affect patient survival and thus the effectiveness of the treatment.
Prognostic Factors:

- Max T diameter $\geq 5.5$
- CEA $> 80$ ng/ml
- < 2 yrs interval (CRC-LT)
- Tumor progression
Liver Transplantation for Colorectal Liver Metastases

- Place of LT in other Liver Malignancies
- Results of LT for validated indications
- What room for improvement?
PHRC 2013 INCA : TransMet

• Chemotherapy and LT vs Chemotherapy alone in the treatment of definitively non resectable colorectal liver metastases:
  Prospective randomised multicentric Trial
Figure 3 Explanted liver from study patient.

Female 54 years at time of transplantation, body weight 58 kg. The weight of the liver is 4.6 kg. The liver/body weight ratio is 8% which was the highest ratio in the study population. The histology showed breaching of liver capsula at several places. She was the patient with shortest survival in the study, 6 months post transplantation.
Pulmonary recurrence after LT: an « indolent » pattern (72% 5yr OS)

Hepatic recurrence after LT: Very poor prognosis (Median OS 14 Mo)
« At the time of liver transplantation, 16 of 21 patients (76%) had progressed on first or later lines of chemotherapy… »

Hagness et al; Ann Surg 2013
PHRC : Multicentric Randomised Trial

Towards a better Patient Selection …
- \( \leq 65 \) years
- Confirmed non resectable liver metastases of colorectal cancer,
- High standard carcinological resection of the primary (\( \geq 12 \) lymph N)
- No extrahepatic tumor localisation
- Treatment by \( \geq 3 \) months of optimal chemotherapy
- Stable or Partial Response while on \( \leq 3 \) lines of chemotherapy
- No BRAF mutation
- Serum CEA levels < 100 ng/ml or 50% decrease from baseline

Independant Validation of the indication…
by the steering committee of the study including oncologists, radiologists and hepatologists / Transplant surgeons

Tailored Immunosuppression…

OncoSurgical Approach…
Independent Steering Committee

- **Oncologists**: E. Van Cutsem (Belgium)
  J. Tabernero (Spain)
  F. Lévi (France)
  M. Ducreux (France)

- **Radiologists**: M. Lewin (France)
  F. Kunstlinger (France)

- **Surgeons**: J. Lerut (Belgium)
  P. Majno (Switzerland)
  P. Muiesan (UK)
  R. Adam (France)

- **Hepatologist**: D. Samuel (France)
Safety Control Committee

- **Oncologists**: Ph Rougier (France)
- **Surgeons**: J Figueras (Spain)
- **Hepatologist**: P. Burra (Italy)
PHRC: Multicentric Randomised Trial

- 1\textsuperscript{ry} End Point: 5-yr OS
- Objective: $\geq 50\%$ with LT
- 80 Pts (40 in each group) to demonstrate a 40\% diff (50 vs 10\%)
- 14 French centres
- 10 European centres
- Additional centres…
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*††

**Results:** DFS/PFS in both groups were 8 to 10 months. However, a dramatic difference in OS was observed. The 5-year OS rate was 56% in patients undergoing liver transplantation compared with 9% in patients starting first-line chemotherapy. The reason for the large difference in OS despite similar
Conclusions

• LMCR: CI to LT owing to experience acquired 20 yrs ago…
• The changes occurred in the management of LT, in imaging, in chemotherapy, immunosuppression and in prognostic factors of outcome open the way for a significant improvement of the results
• This concept is partially validated by the Norwegian study
• The French/European randomised trial is designed to definitively validate or invalidate the current contraindication for LT…
Points of discussion

• No of Grafts: ≤ 10 per year in each country...
• Priorisation: LT ideally between 3 to 5 weeks after the last course...
• Which grafts: conventional, NHBD, Marginal, Domino Living…?
• Informed Consent of patients…
• Ancillary studies: molecular biology, immunohistological markers …