Treatment of Colorectal Liver Metastases – State of the Art

Eddie K. Abdalla, MD, FACS
Professor and Chairman of Surgery
Chief of Hepatobiliary Surgery

Hilton Metropolitan Palace Hotel – Beirut
16 November, 2012
Improving with time

Survival met CRC phase III trials

Survival met CRC phase III trials

Survival hepatectomy for CLM by era

Kopetz S J Clin Oncol 2009
In 2006, 25% of patients underwent liver resection

*All patients receiving chemotherapy

Kopetz S J Clin Oncol 2009
Metastatic Colorectal Cancer

MD Anderson and Mayo Clinic

Kopetz S J Clin Oncol 2009
Resectable?

16 Lesions:
- 4 left lateral
- 1 Speigel
- 11 right/segment IV
Resectable CLM: *Definition*

**Complete Resection**

of tumor bearing liver sparing adequate hepatic remnant volume (> 20% in normal liver)
Chemotherapy for unresectable CLM

Adam Ann Surg 2004
Chemotherapy for resectable CLM?

- Potential downsizing
  - Increase curative resection rate (97%R0)\(^1\)
  - Enable more conservative surgery

- Identify “responders”
  - Progression may contraindicate surgery if 4 or more metastases\(^2,5\)
  - Tailor postoperative chemo to avoid ineffective treatment in synchronous metastases\(^3\)

- Prolong progression-free survival
  - EORTC Intergroup 40983 phase III Perioperative FOLFOX4\(^4\)

---

\(^1\) Parikh J Gastrointest Surg 2003
\(^2\) Adam Ann Surg 2004
\(^3\) Allen J Gastrointest Surg 2003
\(^4\) Nordlinger ASCO 2007
\(^5\) Chun JAMA 2010
Why both?

*Surgery + Chemotherapy*

- After resection more than 50% of patients develop recurrence(s)

- Chemotherapy can be administered
  - Before: neoadjuvant chemotherapy
  - After: adjuvant chemotherapy
  - Before and after: perioperative chemotherapy
Resectable CLM

Randomized Controlled Trial (EORTC 40983)

- Potentially resectable CLM
- No extrahepatic disease
- No previous chemo with oxaliplatin
- WHO/ECOG 0-2

FOLFOX4
6 cycles (3 months)

Surgery

N=364

FOLFOX4
6 cycles (3 months)

> 50% had SOLITARY metastasis
- Median size of LM < 5 cm
- 2/3 metachronous metastases

Nordlinger Lancet 2008
Trial Profile - EORTC 40983

Randomized: 364

Pre&Postop CTx 182

Resectable on imaging

Surgery 182

Resectable at surgery

Operated/Resected 159/151 = 95%

Operated/Resected 170/152 = 89%

Started pre-op CTx 171

Ineligible

Dz Progression Poor PS/Other

Nordlinger *Lancet* 2008
EORTC 40983:
All Patients: Update May 25, 2009

Progression-free survival
all patients *intent to treat*

Time to first progression
*irrespective of resection*

Periop FOLFOX 4 + Surgery

*p*=0.047

Periop FOLFOX 4 + Surgery

*p*=0.026

POSITIVE TRIAL

Courtesy B. Nordlinger
Who were the patients who benefited from the EORTC 40983 trial

- 333/364 (93%) had 1 to 3 lesions, > 50% had SOLITARY liver metastasis

- Sum of largest diameters of lesions on imaging only 5 cm (before chemo)

- 2/3 were metachronous metastases
Survival: Pathologic Response

305 Resected Patients after 5FU/Irinotecan or 5FU/Oxaliplatin

- Complete Response – no residual tumor
  - P = 0.037

- Major Response – 1 to 49% residual tumor
  - P = 0.028

- Minor Response – > 50% residual tumor

Blazer J Clin Oncol 2008
Cytotoxic Chemotherapy

Irinotecan → Steatosis (11%)\(^1,2\)  
Steatohepatitis (20%)\(^1,2\) → Increased complications/mortality from liver failure

Steatohepatitis associated with ↑ 90-day mortality (15%) vs. non steatohepatitis (2%) (p=0.001); and ↑ risk of death from liver failure (6%)

Oxaliplatin → Sinusoidal Dilation (19%)\(^3,4\) → Increased perioperative transfusions

Vascular alterations associated with RBC transfusion requirements after with > 6 months of preoperative chemotherapy (p=0.04)

\(^1\) Kleiner DE Hepatology 2005  
\(^2\) Vauthey JN J Clin Oncol 2006  
\(^3\) Rubbia-Brandt L Ann Oncol 2004  
\(^4\) Aloia T J Clin Oncol 2006
Toxicity of chemo can be managed with multidisciplinary approach

- Limit chemo $\rightarrow$ limit risk (8.9% steatosis, 8.4% steatohepatitis, 5.4% sinusoidal dilatation)

- In conversion chemo (to render unresectable $\rightarrow$ resectable) restage every 4 cycles and resect as soon as resectable (toxicity increases to 37-58% after 6-9 cycles)

Vauthey J Clin Oncol 2006
Duration of Chemotherapy

**Morbidity**

<table>
<thead>
<tr>
<th>Duration</th>
<th>Morbidity %</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CT</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>≤ 5 cycles</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>6-9 cycles</td>
<td>45</td>
<td>11</td>
</tr>
<tr>
<td>≥ 10 cycles</td>
<td>61</td>
<td>13</td>
</tr>
</tbody>
</table>

Karoui  *Ann Surg* 2006
Hepatic resection after 2\textsuperscript{nd} line chemotherapy

Brouquet..Abdalla *Cancer* 2011
Limits of safe resection
Liver volume and liver function

- ↓ Major Complications
- ↓ ICU & hospital stay
- Improved liver function

Abdalla Arch Surg 2002
Portal Vein Embolization (PVE)

Overcoming volumetric limits

- Deliberate occlusion of the portal branches to the liver to be resected (diverting flow to the FLR)

- These studies indicated that
  1) PVE is safe
  2) PVE leads to increased FLR volume and function
  3) PVE does not complicate surgical resection
  3) liver insufficiency is less common after resection following PVE

Abdalla Br J Surg 2001
Portal Vein Embolization

Pre-chemo, pre-PVE

Post-chemo, post-PVE
301 Consecutive Extended Right Hepatectomies

Outcome based on systematic liver volumetry

<table>
<thead>
<tr>
<th>FLR</th>
<th>Pre PVE &lt; 20%</th>
<th>Post PVE &gt; 20%</th>
<th>Have postop course no different from native FLR &gt; 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLR ≤ 20</td>
<td>13/38 (34%)</td>
<td>15/144 (10%)</td>
<td>16/108 (15%)</td>
</tr>
<tr>
<td>sFLR 20.1 - 30 (%)</td>
<td>P = 0.010</td>
<td>P = 0.001</td>
<td></td>
</tr>
<tr>
<td>sFLR &gt; 30</td>
<td>P = 0.293</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kishi..Abdalla Ann Surg 2009
Liver and tumor changes after PVE

$n=104$

Ribero..Abdalla Br J Surg 2007
Chemo and Regeneration after PVE

Zorzi..Abdalla Ann Surg Oncol 2008
Strategies – Bilateral Tumors

- Resect + Resect (one stage)
  - In case of limited disease

- Resect + Resect (two-stage)
  - Chemo $\rightarrow$ response
  - 1st stage minor resection $\rightarrow$ recovery
  - PVE $\rightarrow$ hypertrophy
  - 2nd stage completion resection

- Resect + RFA (one stage)
  - +/- Chemo $\rightarrow$ response
  - Resect dominant disease
  - Ablate small lesions in remnant
Preop chemo plus 2-stage resection
median 6 tumors per patient

Intention-to-treat

Completed 2-stage: 64%

Brouquet..Abdalla JCO 2011
Unresectable disease → RFA?

Solitary CLM – Local Recurrence

All Patients

% Local Recurrence

<table>
<thead>
<tr>
<th>% Local Recurrence</th>
<th>Resection</th>
<th>RFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>P=.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall

Proportion Surviving

<table>
<thead>
<tr>
<th>Years</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
<td>.8</td>
<td>.6</td>
<td>.4</td>
<td>.2</td>
<td>.0</td>
<td></td>
</tr>
</tbody>
</table>

P=0.0004

Resection

RFA

Aloia..Abdalla Arch Surg 2006
**Bilateral CLM**

**Resection plus RFA or 2-stage resection?**

- **Resection + RFA**
  - (mean 4 tumors)
  - Cumulative Survival < 30 mo

- **2-stage Resection**
  - (mean 6 tumors)
  - Median OS not reached at 51 mo f/u

---

1. Abdalla Ann Surg 2004
2. Brouquet..Abdalla JCO 2011
Resectable?

- 48 yo referred after transverse colectomy for obstructing cancer, complicated by leak
- Found at surgery to have multiple bilateral liver metastases
- 16 tumors in 7 of 8 anatomic segments
Chemotherapy, 2-stage resection with PVE

4 years NED
Synchronous CLM

- 156 consecutive patients with synchronous resectable CLM and intact 1°
  - Combined (simultaneous resection of 1° and CLM)
  - Classic (1° before liver)
  - Reverse (liver before 1°)
Synchronous CLM

*Reverse the strategy when needed*

Brouquet..Abdalla *J Am Coll Surg* 2010
Summary

Changing the standard of care

- Preop chemo improves selection for resection
  - Even in patients with limited disease
- Chemotherapy and surgery are compatible
  - Improved selection, improved outcomes
- Complete resection is key to best outcome
  - Resection of all lesions ever present is standard
Summary

Changing the standard of care

- Portal vein embolization increases safety of major resection
  - Perform for proper indications
- Staged resection → selection → excellent outcome
  - When chemotherapy used first and response assessed
- In situ ablation is adjunctive tool
  - Higher local recurrence, lower survival – use with care
- Synchronous CLM
  - Classical, simultaneous and reverse approaches
Metastatic Colorectal Cancer

60% 5-year survival