R1 Liver Resection by necessity: to be blamed or encouraged in the treatment of colorectal metastases?

R Adam

Hôpital Paul Brousse and Université Paris-Sud Villejuif, France
Principles of liver resection

Gold standard recommendation

Safe margin of Non tumoral liver

R0 Resection
Principles of liver resection

R0
1 cm
Gold standard recommendation

R1
0 mm
Remnant lesions

R2
Contraindications
Effect of Surgical Margin Status on Survival and Site of Recurrence After Hepatic Resection for Colorectal Metastases

<table>
<thead>
<tr>
<th>Recurrence type</th>
<th>Positive (N=45)</th>
<th>1-4 mm (N=129)</th>
<th>5-9 mm (N=85)</th>
<th>&gt; 10 mm (N=298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical margin</td>
<td>5 (11%)</td>
<td>7 (5%)</td>
<td>2 (2%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Other intrahepatic</td>
<td>5 (11%)</td>
<td>13 (10%)</td>
<td>9 (11%)</td>
<td>29 (10%)</td>
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<tr>
<td>Extrahepatic</td>
<td>8 (18%)</td>
<td>15 (12%)</td>
<td>14 (16%)</td>
<td>45 (15%)</td>
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<tr>
<td>Intra- + extrahepatic</td>
<td>5 (11%)</td>
<td>15 (12%)</td>
<td>10 (12%)</td>
<td>26 (12%)</td>
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</table>

Positive margin significantly related with surgical margin recurrence \( P = 0.003 \)
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of pts</th>
<th>5-year OS (%)</th>
<th>R0</th>
<th>R1</th>
<th>P</th>
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<tr>
<td>Gayowski</td>
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<td>1001</td>
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<td>Pawlik</td>
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<td>Hamady</td>
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<td>48</td>
<td>36</td>
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<tr>
<td>Welsh</td>
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<td>39.7</td>
<td>17.8</td>
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</table>

R1 liver resection contraindicates surgery for CLM
Genetic and Histological Assessment of Surgical Margins in Resected Liver Metastases From Colorectal Carcinoma

Minimum Surgical Margins for Successful Resection

Norihiro Kokudo, MD; Yoshio Miki, MD; Sachiko Sugai, MS; Akio Yanagisawa, MD; Yo Kato, MD; Yoshihiro Sakamoto, MD; Junji Yamamoto, MD; Toshiharu Yamaguchi, MD; Tetsuichiro Muto, MD; Masatoshi Makuuchi, MD

Micrometastases present in only 2% of patients, all within 4 mm of the tumor border

Margin width: Surgical margin recurrence:
< 2 mm 13.3%
2-4 mm 2.8%
> 4 mm 0%

Arch Surg 2002; 137:833-40
Margin width and survival

Survival

Paul Brousse Hospital – unpublished data

- > 10 mm (N=245)
- 6 - 10 mm (N=59)
- 0 - 5 mm (N=162)
- 0 mm (N=154)

R0

R1

P = 0.002
Should we avoid such type of R1 resection?

Our policy: Inability of R0 resection: no surgical contraindication provided a complete macroscopic resection.
Should R1 liver resection by necessity be blamed or encouraged in the treatment of colorectal metastases?

**Rationale**

Increasingly effective chemotherapies and repeat surgery may render Survival after R1 liver resection still be more valuable than palliative treatment.
Study population

Hepatectomy for CRM
Jan 1990 – Jan 2006
840 consecutive Pts

R2 liver resection: N=57 (7%)
Concomitant EHD: N=134 (16%)
Concom. local treatment: N=85 (10%)
No exhaustive margin information for all nodules: N=128 (15%)

Liver only metastases
Completely resected
Only surgically treated with evaluable margins

R0
N=234 (28%)

R1
N=202 (24%)
## Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>R0 Group N=234</th>
<th>R1 Group N=202</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>62 ± 11</td>
<td>59 ± 11</td>
<td>0.01</td>
</tr>
<tr>
<td>Male</td>
<td>60%</td>
<td>58%</td>
<td>0.77</td>
</tr>
<tr>
<td>Primary tumor</td>
<td>Colon / Rectum</td>
<td>77% / 23%</td>
<td>0.95</td>
</tr>
<tr>
<td>Synchronous CLM</td>
<td>107 (46%)</td>
<td>118 (58%)</td>
<td>0.008</td>
</tr>
<tr>
<td>No. of CLM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>116 (50%)</td>
<td>61 (32%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2-3</td>
<td>82 (36%)</td>
<td>61 (32%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 3</td>
<td>32 (14%)</td>
<td>69 (36%)</td>
<td></td>
</tr>
<tr>
<td>Mean max. size (mm)</td>
<td>39 ± 29</td>
<td>56 ± 32</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bilateral</td>
<td>77 (33%)</td>
<td>118 (58%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Initial unresectability</td>
<td>72 (31%)</td>
<td>113 (56%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
In conclusion, despite a higher intrahepatic recurrence rate, OS, PFS and DFS rates were almost similar for patients with R0 and R1 resections for CLM, treated by an aggressive strategy consisting of chemotherapy and surgery. As chemotherapy regimens are nowadays increasingly effective, the inability to obtain microscopically free surgical margins as a contraindication to hepatic resection for CLM should be revisited.
Overall Survival according to surgical margins

Overall survival

- **R0 (N=234)**
  - 1 yr: 61%
  - 3 yrs: 57%
  - 5 yrs: 43%
  - 8 yrs: 37%
  - 10 yrs: 37%

- **R1 (N=202)**
  - 1 yr: 43%
  - 3 yrs: 37%
  - 5 yrs: 61%

**P = 0.27**
Progression-Free Survival according to surgical margins

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Total</th>
<th>1 yr</th>
<th>3 yrs</th>
<th>5 yrs</th>
<th>6 yrs</th>
<th>8 yrs</th>
<th>10 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>234</td>
<td>119</td>
<td>50</td>
<td>33</td>
<td>26</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>R1</td>
<td>201</td>
<td>102</td>
<td>24</td>
<td>16</td>
<td>13</td>
<td>8</td>
<td>7</td>
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</tbody>
</table>

Progression-free survival

R0 (N=234)  
R1 (N=202)

P = 0.11
Disease-Free Survival according to surgical margin

P = 0.12

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Total</th>
<th>1 yr</th>
<th>3 yrs</th>
<th>5 yrs</th>
<th>6 yrs</th>
<th>8 yrs</th>
<th>10 yrs</th>
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</thead>
<tbody>
<tr>
<td>R0</td>
<td>232</td>
<td>160</td>
<td>74</td>
<td>46</td>
<td>34</td>
<td>22</td>
<td>14</td>
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<tr>
<td>R1</td>
<td>201</td>
<td>131</td>
<td>47</td>
<td>24</td>
<td>17</td>
<td>9</td>
<td>7</td>
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</table>
### Impact of Repeat Resection

**Patients at risk**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>1 yr</th>
<th>2 yrs</th>
<th>3 yrs</th>
<th>4 yrs</th>
<th>5 yrs</th>
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</thead>
<tbody>
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<td>131</td>
<td>72</td>
<td>47</td>
<td>35</td>
<td>24</td>
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<tr>
<td>PFS</td>
<td>201</td>
<td>102</td>
<td>44</td>
<td>24</td>
<td>20</td>
<td>16</td>
</tr>
</tbody>
</table>

**Survival**

- **DFS**
  - 1 yr: 72%
  - 2 yrs: 55%
  - 3 yrs: 32%
  - 4 yrs: 20%
  - 5 yrs: 14%

- **PFS**
  - 1 yr: 20%
  - 2 yrs: 19%
  - 3 yrs: 14%
  - 4 yrs: 13%
  - 5 yrs: 10%

**Changes**

- DFS: +17%
- PFS: +13%
- Total: +6%
Independent predictors of poor overall survival (OS):

- Preoperative CEA level $> 10$ ng/ml (HR 2.0; $P < 0.001$)
- Major hepatectomy (HR 1.6; $P = 0.02$)

Surgical margin status did not influence overall survival rates.
Independent predictors of R1 resection

Multivariate analysis:

- Max. size of CLM at diagnosis $\geq 30$ mm (RR 3.6; $P < 0.001$)
- Bilateral distribution of CLM (RR 2.8; $P < 0.001$)
- Intraoperative RBC transfusion (RR 2.4; $P = 0.001$)
Conclusions

1. Patients treated by R1 resection are more likely to have initially unresectable, multinodular, large, bilateral metastases than R0 treated population.

2. Despite devoted to more aggressive disease, R1 liver resections bear similar long-term outcome as RO resection.

3. The higher risk of liver (but no local...) recurrence could be managed by an aggressive oncossurgical approach including chemotherapy and repeat surgery.
Questions

1- Why a similar outcome between R1 and R0 resections?

2- Should R1 resection be reconsidered as a contraindication to surgery?
Questions

1- Why a similar outcome between R1 and R0 resections ?

2- Should R1 resection be reconsidered as a contraindication to surgery ?
Aspiration hepatic tissue by ultrasonic dissector

Additional rim of 1-2 mm

Potential overestimation of proportion of real R1 resection on pathology...
Remnant cut section treated with argon beam

‘Sterilization’ of an extra 1-2 mm of hepatic tissue
3. Perioperative chemotherapy is able to prevent recurrence…

Less satellite nodules might develop by using the currently available more effective chemotherapies

Current study:

- 74% of patients received preoperative chemotherapy
- 83% of patients received postoperative chemotherapy
Conclusions: In the era of modern chemotherapy, negative margins remain an important determinant of survival and should be the primary goal of surgical therapy. The impact of positive margins is most pronounced in patients with suboptimal response to systemic therapy.
4. Repeat surgery for intrahepatic and/or extrahepatic recurrences is associated with good survival...

Current study:
- 182 patients (42%) developed an intrahepatic recurrence
- 99 (54%) underwent repeat hepatectomy
- 234 patients (54%) developed an extrahepatic recurrence
- 85 (36%) underwent repeat surgery

Adam R et al, Ann Surg 2003
Questions

1- Why a similar outcome between R1 and R0 resections?

2- Should R1 resection be reconsidered as a contraindication to surgery?
R1- The alternative: Absence of surgery?

No 5-year survivors


"The resection margin width is an independent predictor of OS. **To ensure a clear margin, wide margins should be attempted in all cases when this is safe and feasible.** The improved outcome observed with a submillimeter margin width is likely a microscopic surrogate for the biologic behavior of a tumor. Thus, liver resection should not be precluded from any patient who is expected to undergo a resection with narrow margin, as cure can be achieved and an unpredictable submillimeter margin clearance is associated with improved survival."
Should R1 liver resection by necessity be blamed or encouraged in the treatment of colorectal metastases?

**Summary**

Although R0 resection should remain the gold standard, R1 resection by necessity should be considered…

The dogma: R1 resection as an absolute contraindication to surgery should be revisited…
Should R1 liver resection by necessity be blamed or encouraged in the treatment of colorectal metastases?

In the past
Should R1 liver resection by necessity be blamed or encouraged in the treatment of colorectal metastases?
Is Cure possible after R1 Resection?
Paul Brousse Hospital (2000-2009)
Total no. of resected patients
n= 628

Remaining study population
n=428 (100%)

R0 resection
n=219 (51%)
R0 resection
more than 5 years follow-up
n=130 (30%)

R1 resection
n=209 (49%)
R1 resection
more than 5 years follow-up
n=141 (33%)

n=200 patients excluded:
• Concomitant extrahepatic disease: n=126
• Concomitant local treatment: n=57
• R2 resection: n=45

*14 patients were performed concomitant local treatment with concomitant extrahepatic disease.
** 8 patients were R2 resection with concomitant extrahepatic disease and 6 patients were R2 resection with concomitant local treatment.
Overall Survival Curves of Patients with More Than 5 Years Follow-Up According to Surgical Margin Status

Survival Rate, %

<table>
<thead>
<tr>
<th>Time, yr</th>
<th>R0 (n=130)</th>
<th>R1 (n=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 yr</td>
<td>34%</td>
<td>48%</td>
</tr>
<tr>
<td>3 yrs</td>
<td>56%</td>
<td>35%</td>
</tr>
<tr>
<td>5 yrs</td>
<td>48%</td>
<td>34%</td>
</tr>
<tr>
<td>6 yrs</td>
<td>56%</td>
<td>35%</td>
</tr>
<tr>
<td>8 yrs</td>
<td>48%</td>
<td>34%</td>
</tr>
<tr>
<td>10 yrs</td>
<td>35%</td>
<td>34%</td>
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</tbody>
</table>

 Patients at risk

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Total</th>
<th>1 yr</th>
<th>3 yrs</th>
<th>5 yrs</th>
<th>6 yrs</th>
<th>8 yrs</th>
<th>10 yrs</th>
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</thead>
<tbody>
<tr>
<td>R0</td>
<td>130</td>
<td>121</td>
<td>90</td>
<td>73</td>
<td>56</td>
<td>22</td>
<td>7</td>
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<tr>
<td>R1</td>
<td>141</td>
<td>126</td>
<td>88</td>
<td>68</td>
<td>42</td>
<td>24</td>
<td>14</td>
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</table>

\( P = 0.37 \)
Potential Cure after R0 Resection for CLM

R0 resection more than 5 years follow-up
n=130 (100%)

n=9 (7%) patients excluded:
• 90-day mortality: n=1
• Disease-free interval of less than 5 years after last resection: n=8

Cured patients
n=30 (23%)

Cured after resection of initial disease
n=24 (18%)

Cured after resection of disease recurrence
n=6 (5%)

Noncured patients
n=91 (70%)
Potential Cure after **R1** Resection for CLM

R1 resection more than 5 years follow-up  
\[ n=141 \ (100\%) \]

n=9 (6%) patients excluded:  
• 90-day mortality: \[ n=1 \]
• Disease-free interval of less than 5 years after last resection: \[ n=8 \]

Cured patients  
\[ n=26 \ (18\%) \]

Noncured patients  
\[ n=106 \ (70.5\%) \]

Cured after resection of initial disease  
\[ n=18 \ (13\%) \]

Cured after resection of disease recurrence  
\[ n=8 \ (5.6\%) \]
Disease Free Survival and Progression Free Survival Curves of Patients with More Than 5 years Follow-Up after R1 Resection

Survival Rate, %  

- Time to last unresectable recurrence
- Recurrence-free survival

Patients at risk

<table>
<thead>
<tr>
<th>Time to last unresectable recurrence</th>
<th>Total</th>
<th>1 yr</th>
<th>3 yrs</th>
<th>5 yrs</th>
<th>6 yrs</th>
<th>8 yrs</th>
<th>10 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>141</td>
<td>106</td>
<td>65</td>
<td>45</td>
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<table>
<thead>
<tr>
<th>Recurrence-free survival</th>
<th>Total</th>
<th>1 yr</th>
<th>3 yrs</th>
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<td>Time</td>
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<td>79</td>
<td>28</td>
<td>20</td>
<td>16</td>
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## Univariate and Multivariate Analysis of Predictive Factors of Cure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cured Patients (n=26)</th>
<th>Noncured Patients (n=106)</th>
<th>Univariate P</th>
<th>Multivariate P</th>
<th>RR</th>
<th>95% CI</th>
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<tr>
<td>1</td>
<td>21 84</td>
<td>62 63</td>
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<tr>
<td>&gt;1</td>
<td>4 16</td>
<td>36 37</td>
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<tr>
<td>Total no. of cycles</td>
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<tr>
<td>≤10</td>
<td>24 96</td>
<td>52 53</td>
<td>&lt;0.001</td>
<td>0.005</td>
<td>20.1</td>
<td>2.5 to 160.6</td>
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<tr>
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<td>46 47</td>
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<td>Clinical response at CT scan</td>
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<tr>
<td>Response</td>
<td>19 76</td>
<td>51 52</td>
<td>0.03</td>
<td>0.03</td>
<td>3.2</td>
<td>1.0 to 9.8</td>
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<tr>
<td>Nonresponse</td>
<td>6 24</td>
<td>47 48</td>
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<tr>
<td>CEA level at hepatectomy, ng/mL</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤9</td>
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<td>51 49</td>
<td>0.02</td>
<td>NS</td>
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<td>-</td>
</tr>
<tr>
<td>&gt;9</td>
<td>7 27</td>
<td>54 51</td>
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<tr>
<td>≤55</td>
<td>24 92</td>
<td>64 64</td>
<td>0.005</td>
<td>NS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&gt;55</td>
<td>2 8</td>
<td>36 36</td>
<td></td>
<td></td>
<td>-</td>
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<tr>
<td>No. of resected metastases</td>
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<td></td>
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</tr>
<tr>
<td>1</td>
<td>10 38</td>
<td>21 20</td>
<td>0.04</td>
<td>NS</td>
<td>-</td>
<td>-</td>
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<tr>
<td>&gt;1</td>
<td>16 62</td>
<td>85 80</td>
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<td>Pathological tumor size, mm</td>
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<tr>
<td>≤35</td>
<td>17 65</td>
<td>50 47</td>
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<td>NS</td>
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<td>-</td>
</tr>
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<td>&gt;35</td>
<td>9 35</td>
<td>56 53</td>
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</table>
Overall Survival Curves of Patients after R1 Resection According to Clinical Response to Preoperative Chemotherapy

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Total</th>
<th>1 yr</th>
<th>3 yrs</th>
<th>5 yrs</th>
<th>6 yrs</th>
<th>8 yrs</th>
<th>10 yrs</th>
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</thead>
<tbody>
<tr>
<td>Response</td>
<td>77</td>
<td>71</td>
<td>53</td>
<td>41</td>
<td>26</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Stabilization</td>
<td>45</td>
<td>38</td>
<td>24</td>
<td>21</td>
<td>13</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Progression</td>
<td>9</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td></td>
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</tr>
</tbody>
</table>

$P = 0.001$
Conclusions

• Potential cure can be achieved overall in 18% of patients after R1 vs 23% after R0 resection for CLM.

• The best conditions to achieve long-term survival after R1 resection rely on a good response to an efficient and relatively short first-line chemotherapy.

• No hope of cure after R1 resection in patients not responding to chemotherapy.
Thank You

Merci
Figure 1  Survival of patients classified into group 1 (-----, n = 921), group 2 (---; n = 62) and group 3 (----; n = 226), including operative deaths. The number at the end of the curve indicates the number of patients surviving beyond 10 years. P < 0.0001
Remnant cut section treated with argon beam
Why was R1 resection not considered a contraindication for surgery at the Paul Brousse Hospital?

2. Application of argon beam or bipolar coagulation on remnant cut section

‘Sterilization’ of an extra 1-2 mm of hepatic tissue
Aspiration hepatic tissue by ultrasonic dissector
1. Long-term outcome after R0 and R1 liver resections for CLM almost similar when treated by an aggressive oncosurgical approach

2. Long-term outcome after R1 resection closer to that observed after R0 resection than to that observed after R2 resection

3. In the era of effective chemotherapies, R1 resection as contraindication to surgery for CLM should be revisited
OS after 1st hepatectomy (N=243)  OS after 2nd hepatectomy (N=64)

To resect with positive surgical margin (R1) or to treat with palliative chemotherapy?

Vascular proximity

Before chemotherapy

After chemotherapy

To resect with positive surgical margin (R1) or to treat with palliative chemotherapy?
Should R1 liver resection by necessity be blamed or encouraged in the treatment of colorectal metastases?

Paul Brousse Policy for CLM

Inability of R0 resection but complete macroscopic resection: no surgical contraindication
Should R1 liver resection by necessity be blamed or encouraged in the treatment of colorectal metastases?

**Methods**

**Statistical analysis:**

- Comparison R0 and R1 liver resection:
  1. Patient, tumor, and heptatectomy characteristics
  2. Progression-free survival (period until first recurrence)
  3. Disease-free survival (disease-status at last follow-up)
  4. Overall survival
  5. Predictors overall survival and R1 liver resection
Impact of surgical margin status in hepatic resection for CLM
Conclusions: A positive margin after resection of CLM is associated with adverse biologic factors and increased risk of surgical-margin recurrence. The width of a negative surgical margin does not affect survival, recurrence risk, or site of recurrence. **A predicted margin of 1 cm after resection of CLM should not be used as an exclusion criterion for resection.**
“Although an R1 resection should clearly be avoided, the actual margin width of an R0 resection does not impact on outcome after resection of CLM.”