Peri-operative FOLFOX4 chemotherapy and surgery for resectable liver metastases from colorectal cancer

Long-term survival results of the EORTC Intergroup phase III study 40983.


For the EORTC GI Group, CR UK, ALMCAO, AGITG and FFCD
Aim and design

Demonstrate that chemotherapy combined with surgery is a better treatment than surgery alone

Main Eligibility criteria
- Potentially resectable liver metastases of colorectal cancer
- Up to 4 deposits (on CT-scan, at randomization)

Randomize

N=364 patients
Objectives of the trial

Primary endpoint: to demonstrate an improvement in progression-free survival (PFS) with peri-operative chemotherapy) compared to surgery alone.

Secondary endpoints: overall survival, tumor resectability, tumor response, safety.

364 patients (182 x 2) recruited from September 2000 to July 2004.

PFS results reported at ASCO 2007.
## Patient population (N=364)

<table>
<thead>
<tr>
<th></th>
<th>Peri-op CT (N=182)</th>
<th>Surgery (N=182)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range)</strong></td>
<td>62 (29-79)</td>
<td>64 (25-78)</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td>69.8%</td>
<td>62.6%</td>
</tr>
<tr>
<td>1-3 liver mets on CT-scan</td>
<td>93.4%</td>
<td>91.2%</td>
</tr>
</tbody>
</table>
Compliance and tolerance to chemotherapy

**Compliance to preo-operative CT** was high with 143/182 pts (78.6%) who received the 6 cycles. Median relative dose intensity was above 90%.

There was **no unexpected toxicity**; no toxic death during preop CT. One patient was not resected due to liver damage probably due to CT.

Only 115/182 (63.2%) pts received **post-operative CT**. **Compliance was lower** with 80 pts (43.9%) who received the 6 cycles.
Size of lesions after pre-operative CT

Relative change (SUM of the largest diameter): - 29.5%

RECIST Response after pre-operative CT:
- Complete response: 7 (3.8%)
- Partial response: 73 (40.1%)
- Stable disease: 64 (35.2%)
- Progressive disease: 12 (6.6%)
Patient Flow in summary

Informed consent

Randomized: 364

Pre&Postop CT 182

Started pre-op CT 171

Resected 152

Resectable on imaging

_started pre-op CT_ 171

Resectable at surgery

Resected 152

Started post-op CT 115

Surgery 182

Ineligible 11

Resectable on imaging 11

Ineligible 11

Started post-op CT 115

Resectable at surgery 152

Resectable on imaging 11

Ineligible 11
Progression-free survival in eligible patients


**HR = 0.77; CI: 0.60-1.00, p=0.041**

- **LV5FU + Oxaliplatin Periop CT**
  - 36.2%
- **Surgery only**
  - 28.1%

+8.1% At 3 years

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ON</th>
<th>Number of patients at risk:</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV5FU + Oxaliplatin Periop CT</td>
<td>125</td>
<td>83, 57, 37, 22, 8</td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td>171</td>
<td>115, 74, 43, 21, 5</td>
<td>Pre&amp;Postop CT</td>
</tr>
</tbody>
</table>
Progression-free survival in randomized patients


HR = 0.79; CI: 0.62-1.02, p=0.058

LV5FU + Oxaliplatin Periop CT

+7.2%
At 3 years

Surgery only

<table>
<thead>
<tr>
<th>Year</th>
<th>Surgery</th>
<th>Pre&amp;Postop CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>131</td>
<td>182</td>
</tr>
<tr>
<td>1</td>
<td>123</td>
<td>182</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>6</td>
</tr>
</tbody>
</table>

Number of patients at risk:

EORTC
European Organisation for Research and Treatment of Cancer
Conclusions on PFS analysis

Peri-operative chemotherapy with FOLFOX4

• improved PFS over surgery alone in patients with resectable liver metastases
• was safe
• Has been adopted as the reference treatment in many institutions
We now report on the secondary endpoint overall survival (OS) results, after a median follow-up of 8.5 years.
## Survival status (18-01-2012)

<table>
<thead>
<tr>
<th>Survival status</th>
<th>Pre+Postop CT (N=182)</th>
<th>Surgery alone (N=182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*29 patients lost to follow-up at the time of the analysis (13 in the Pre+Postop CT arm and 16 in the Surgery alone arm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive*</td>
<td>75 (41.2)</td>
<td>68 (37.4)</td>
</tr>
<tr>
<td>Death</td>
<td>107 (58.8)</td>
<td>114 (62.6)</td>
</tr>
<tr>
<td>Main cause of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>progression of disease</td>
<td>85 (46.7)</td>
<td>99 (54.4)</td>
</tr>
<tr>
<td>surgical complication</td>
<td>2 (1.1)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>other</td>
<td>16 (8.8)</td>
<td>11 (6.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (2.2)</td>
<td>2 (1.1)</td>
</tr>
</tbody>
</table>
Overall survival in eligible patients

HR = 0.87; CI: 0.66 - 1.14, p = 0.303

LV5FU + Oxaliplatin Periop CT

+8.7 months in median OS
+4.1%
At 5 years

Surgery only

Number of patients at risk:

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Number of patients at risk</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>109</td>
<td>171</td>
<td>133</td>
<td>91</td>
</tr>
<tr>
<td>101</td>
<td>171</td>
<td>139</td>
<td>103</td>
</tr>
</tbody>
</table>

EORTC European Organisation for Research and Treatment of Cancer
Overall survival in randomized patients

HR = 0.88; CI: 0.68 - 1.14, p = 0.339

LV5FU + Oxaliplatin Periop CT
51.2%

Surgery only
47.8%

+7 months in median OS
+3.4%
At 5 years

Number of patients at risk:

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>N</td>
</tr>
<tr>
<td>114</td>
<td>182</td>
</tr>
<tr>
<td>107</td>
<td>182</td>
</tr>
<tr>
<td>138</td>
<td>94</td>
</tr>
<tr>
<td>145</td>
<td>107</td>
</tr>
<tr>
<td>94</td>
<td>72</td>
</tr>
<tr>
<td>107</td>
<td>72</td>
</tr>
<tr>
<td>72</td>
<td>6</td>
</tr>
<tr>
<td>37</td>
<td>46</td>
</tr>
</tbody>
</table>

Surgery
Pre&Postop CT

EORTC
European Organisation for Research and Treatment of Cancer
Cumulative incidence of deaths by cause

**All randomized patients**

**CRC deaths**
- HR = 0.81
- 95% CI (0.61, 1.08)
- P = 0.15

**Non CRC deaths**

CRC deaths = deaths from PD or from surgical complication
# Second line treatments

1) All patients

<table>
<thead>
<tr>
<th></th>
<th>Pre+Postop CT (N=182)</th>
<th>Surgery alone (N=182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>66 (36.3)</td>
<td>65 (35.7)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>93 (51.1)</td>
<td>117 (64.3)</td>
</tr>
</tbody>
</table>

2) Patients with cancer relapse

<table>
<thead>
<tr>
<th></th>
<th>Pre+Postop CT (N=123)</th>
<th>Surgery alone (N=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>66 (53.7)</td>
<td>65 (50.0)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>93 (75.6)</td>
<td>117 (90.0)</td>
</tr>
</tbody>
</table>
Conclusion

Peri-operative chemotherapy with FOLFOX4 improves PFS which was the primary endpoint.
This trial failed to demonstrate an improvement in OS, for which it was not powered.
• Trial was not powered to detect a 4% Increase in OS (Power 80% to detect HR=0.71)

• Observed HR is quite similar for PFS and for CRC deaths (HR=0.8). More deaths not related to cancer in CT arm

• Observed absolute increase in OS of 4% is similar to positive trials in CRC (ex.: Mosaic: + 4.2% OS at 6 years is significant because 1347 pts stage III were randomized)
  
  This can not be achieved in patients with resectable liver metastases because it is not possible to organize such large trials
• Demonstrating a treatment benefit was made more difficult by the high survival rates in the control arm, higher than anticipated, and even higher (median OS 73.3 mo.) than in the surgery + post-op 5FU arm of the pooled analysis (median OS 62.2 mo.)

Is post operative chemotherapy only an alternative?

-Trials of post-op chemo vs surgery (randomized AFTER surgery) evaluated a highly selected patient population

-In EORTC 40983 (randomized BEFORE surgery) 94% of patients received pre-op CT and only 63% received post-op CT

-No sufficient evidence to be standard treatment at the moment. Indicated for selected patients.
Ongoing and future trials

Two ways

Simplified treatment:

• Trials to compare peri-op and post-op chemo with sufficient power are very difficult to organize

More aggressive treatment to improve outcome:

• CRUK 06/031: phase III trial peri-operative FOLFOX ± cetuximab in KRAS WT

• EORTC 40091: BOS2 peri-operative FOLFOX ± bevacizumab or ± panitumumab
Acknowledgments

• Patients and Participating Centers
• EORTC Headquarters: M. Praet, M.A.Lentz, L. Collette
• Sanofi-Aventis: I.Tabah-Fisch, T.Pearce

EORTC GI Group, CR UK, ALMCAO, AGITG, FFCD, ACHBT and SFCD
Other Participating Investigators