Biology Predicts Outcomes in Patients Undergoing Resection for Colorectal Liver Metastases

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Association Between Outcome and RAS Mutation?

RAS Mutant
Dead of Disease
After 17 months

RAS Wild Type
Alive No Recurrence
After 60 months
Evaluation and Prognosis of CLM in 2016?

1. *RAS* mut Pattern of Disease and Prognosis
2. Resection Margins in the *RAS* era
3. *RAS* mut and Ablation of Metastases
4. *Pik3CA* mut and *APC* mut Cooperation
5. Embryonic Origin of Primary
1. RAS mut Prognosis and Pattern of Disease
Liver Metastases Mutational Status in 193 Patients Curatively Resected After Preoperative Chemotx+

<table>
<thead>
<tr>
<th>Mutational status</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study cohort</td>
<td>193 (100)</td>
</tr>
<tr>
<td>(K or N)RAS *</td>
<td>34 (17.6)</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>13 (6.7)</td>
</tr>
<tr>
<td>BRAF</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Single rare mutations (CTNNB1 (1), AKT1 (1))</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

+ 1\textsuperscript{st} Line  2-8 months FOLFOX or FOLFIRI with Bevacizumab

* Includes 27 with KRAS and 7 with NRAS

Vauthey JN Ann Surg 2013
Recurrence-free and Overall Survival after Hepatectomy for CLM According to RAS Mutational Status (n=193)

RAS Wild-Type: 3 yrs OS 33.5%
P= 0.001

RAS mutation: 3 yrs OS 13.5%
P= 0.002

RAS Wild-Type: 3 yrs OS 81%

RAS mutation: 3 yrs OS 52.2%

Vauthey JN Ann Surg 2013
Pattern of Recurrence After Curative Resection of CLM according to RAS mutational status (n=193)

**RAS Wild Type:**
- 3 yrs Lung RFS 59.3%
- 3 yrs Liver RFS 50.2%

**RAS Mutant:**
- 3 yrs Lung RFS 34.6%
- 3 yrs Liver RFS 43.8%

P < 0.001

P = 0.181

Vauthey JN Ann Surg 2013
KRAS Mutations Is Associated With Overall Survival in Meta-Analysis of 1181 Patients Undergoing Resection of CLM*

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>n</th>
<th>KRAS mutation (%)</th>
<th>HR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petrowsky et al.</td>
<td>2001</td>
<td>41</td>
<td>15.0</td>
<td>1.39 (0.45, 4.27)</td>
<td>4.62</td>
</tr>
<tr>
<td>Nash et al.</td>
<td>2010</td>
<td>188*</td>
<td>27.0</td>
<td>2.40 (1.40, 4.00)</td>
<td>21.15</td>
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<tr>
<td>Stremitzer et al.</td>
<td>2012</td>
<td>60</td>
<td>25.0</td>
<td>3.51 (1.30, 9.45)</td>
<td>5.92</td>
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<tr>
<td>Huang et al.</td>
<td>2013</td>
<td>228</td>
<td>36.7</td>
<td>2.38 (1.29, 4.37)</td>
<td>15.73</td>
</tr>
<tr>
<td>Umeda et al.</td>
<td>2013</td>
<td>100</td>
<td>27.0</td>
<td>2.38 (1.02, 5.40)</td>
<td>8.37</td>
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<tr>
<td>Vauthey et al.</td>
<td>2013</td>
<td>193</td>
<td>17.6</td>
<td>2.30 (1.10, 4.50)</td>
<td>11.74</td>
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<tr>
<td>Karagkounis et al.</td>
<td>2013</td>
<td>202</td>
<td>29.0</td>
<td>1.99 (1.21, 3.26)</td>
<td>23.73</td>
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<tr>
<td>Kemeny et al.</td>
<td>2014</td>
<td>169</td>
<td>30.2</td>
<td>2.00 (0.87, 4.46)</td>
<td>8.73</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>1181</td>
<td>27.6</td>
<td>2.24 (1.76, 2.85)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

(I^2-squared = 0.0%, p = 0.965)

KRAS mutations associated with better OS 1

KRAS mutations associated with worse OS

*Only 4 patients received Anti-EGFR Tx

Concordance of KRAS in Primary Tumor and CLM (>90%)

Tie J et al,  
Clin Can Res 2011

Cejas et al,  
PlosONE 2009

KRAS Mutational Concordance

Vakiani EJ. Clin Oncol 2012
2. Resection Margins in RAS Era
Surgical Margins and Overall Survival
Resection after Modern Chemotherapy, n=378

R0 Resection (n=326);
5-year survival rate, 55%

R1 Resection (n=52);
5-year survival rate, 26%

p=0.017

Andreou A Ann Surg 2013
Borderline Resectable Colorectal Metastasis

Before and After FOLFOX-6 Chemotherapy
Surgical Margins and Survival
Resection and Major or Complete Pathologic Response (n=217)

R1 Resection (n=23); 5-year survival rate, 67%
R0 Resection (n=194); 5-year survival rate, 63%

p=0.59

Andreou A Ann Surg 2013
Predictors of **Poor** Response to Chemotherapy After Resection Following FOLFOX or FOLFIRI with bevacizumab (n=184)

### Suboptimal Morphologic Radiologic Response (n=132)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-chemotherapy tumor size &gt; 3 cm</td>
<td>1.98 (1.02-3.87)</td>
</tr>
<tr>
<td><strong>RAS mutant</strong></td>
<td><strong>4.38 (1.45-13.4)</strong></td>
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</table>

### Minor Pathologic Response (n=84)

<table>
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<th>Predictor</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Pre-chemotherapy tumor size &gt; 3 cm</td>
<td>2.39 (1.25-4.59)</td>
</tr>
<tr>
<td><strong>RAS mutant</strong></td>
<td><strong>2.79 (1.29-6.04)</strong></td>
</tr>
</tbody>
</table>

Zimmitti G *Ann Surg Oncol* 2015
Margin and RAS Mutation

Resection of CLM with Known RAS status (2005-2013) 757

- Combined Resection with RFA: 77
- Non-curative Resection: 47

Curative Resection without RFA 633

- RAS Wild-Type 404
  - Positive Margin 5.4% (n=22)
- RAS Mutation 229
  - Positive Margin 11.4% (n=26)

$P=0.007$
CLM Patients Who Later Presented with Liver-First Recurrence (n=225)

$P = 0.476$

$P = 0.031$

- RAS Mutation (n = 86)
- RAS Wild-Type (n = 139)

Mean Tumor Diameter

Median Resection Margin

3. *RAS* mut and Ablation of Metastases
Rates of Local Recurrence Progression per Ablated CLM According to CLM Size

Even CLM size is <2 cm, Local Tumor Progression occur in 28% (11/39) in Patients with Mutant RAS.

Odisio et al, Br J Surg, Submitted
RAS Mutation and Local Recurrence in CLM Patients Undergoing Percutaneous Ablation (92 Patients, 137 CLM)

- **RAS wild local tumor progression** (8/86 lesions, 9.3%)
- **RAS mutant local tumor progression** (17/51 lesions, 33%)

*P* = 0.0004

4. **APC and PIK3CA Mutations Cooperation**
# 50-Gene Somatic Mutation Analysis Panel

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<tbody>
<tr>
<td>ABL1</td>
<td>CSF1R</td>
<td>FGFR2</td>
<td>IDH1</td>
<td>MLH1</td>
<td>PTPN11</td>
<td>TP53</td>
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<tr>
<td>AKT1</td>
<td>CTNNB1</td>
<td>FGFR3</td>
<td>IDH2</td>
<td>MPL</td>
<td>RB1</td>
<td>VHL</td>
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<tr>
<td>ALK</td>
<td>EGFR</td>
<td>FLT3</td>
<td>JAK2</td>
<td>NOTCH1</td>
<td>RET</td>
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<tr>
<td>APC</td>
<td>ERBB2</td>
<td>GNA11</td>
<td>JAK3</td>
<td>NPM1</td>
<td>SMAD4</td>
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<tr>
<td>ATM</td>
<td>ERBB4</td>
<td>GNAQ</td>
<td>KDR</td>
<td>NRAS</td>
<td>SMARCB1</td>
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<tr>
<td>BRAF</td>
<td>EZH2</td>
<td>GNAS</td>
<td>KIT</td>
<td>PDGFRA</td>
<td>SMO</td>
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<tr>
<td>CDH1</td>
<td>FBXW7</td>
<td>HNF1A</td>
<td>KRAS</td>
<td>PIK3CA</td>
<td>SRC</td>
<td></td>
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</tr>
<tr>
<td>CDKN2A</td>
<td>FGFR1</td>
<td>HRAS</td>
<td>MET</td>
<td>PTEN</td>
<td>STK11</td>
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</tbody>
</table>
APC and PIK3CA Mutations Cooperation
Survival after Resection of CLM (n=396)

Patients undergoing resection for CLM 2005-2015
1163

50-gene panel performed
518

- Use of anti-EGFR: 45
- Concomitant ablation: 28
- Previous liver treatment: 24
- Extrahepatic metastases: 13
- Incompletion of surgical strategy: 12

396

Both APC and PIK3CA mutant 45

Others 351

- APC wild, PIK3CA wild: 165
- APC wild, PIK3CA mutant: 38
- APC mutant, PIK3CA wild: 148
APC and PIK3CA Mutations Cooperation

Survival after Resection of CLM

Compared with Patients with Double Mutation of APC and PIK3CA, Patients with Wild-type APC and/or Wild-type PIK3CA had Better Survivals.
Survival in Validation Set is Also Worse in Patients with Double Mutation of **APC** and **PIK3CA**, Suggesting that Effect of Double Mutation of **APC** and **PIK3CA** is Independent of Treatment Strategy.
5. Embryonic Origin of Primary and RAS
Embryonic Origin Study Set after Resection (n=725)

CLM from Midgut are Associated with Worse Survival after Resection for Patients Treated with Preoperative Chemotherapy. This Effect is Independent of RAS Mutation Status.

Yamashita et al, Ann Surg, Submitted
Effect of Embryonic Origin on Prognosis is Independent of Effect of Preoperative Chemotherapy.

Conclusion

• RAS status may guide decisions regarding surgical resection and ablation

• Double Mutation Cooperation predicts worse prognosis in resectable and unresectable patients with colorectal metastases

• Double mutation cooperation has implication for future trial design and development of novel therapies in CLM