HCC: predicting recurrence
Peter Ghali, MD, FRCP, MSc (epid)
Toronto, February 2014

Disclosures
- None relevant to this talk other than off-label use of sirolimus

Outline
- Traditional predictors
- Biomarkers
- Genomic signatures
- Modification of risk (immune suppression)

Recurrence after what? Locoregional therapy vs resection vs transplant
- Tumour factors – size, number, and vascular invasion - but what about biomarkers?
- Predisposing Disease factors – may be modifiable, but what does that mean for recurrence? (ex: HBV)
- Host factors – largely neglected in transplant, less so in non-transplant. (The carcinogenic bed concept)
- “Iatrogenic factors” – ex: immune suppression, does it really matter?

Liver transplant: Beyond Milan?
- Milan remains the gold standard; size and number by imaging, but what about vascular invasion?
- Exceeding tumour size or number comes with a cost, but most models are based on these factors
- Snapshot approach, but tumour behaviour in theory is approximated by “falling off the list”
- Yet tumours are favoured in modern allocation systems
Refining our assessment of tumour biology

- Desirable to have easily measured variables (blood preferable over liver tissue)
- Histology: differentiation and expression of markers
- Can we improve prediction in the era of cancer biomarkers?
Alpha-fetoprotein

- The most widely used (misused?) biomarker
- Illustrates the difficulties with biomarkers
  - Variable expression by different tumours
  - Heterogeneity between individuals harbouring tumours
  - Difficult to establish a “normal”
  - Used dynamically, would likely be more useful (patient is own control)

Alpha-fetoprotein slope predicts post transplant outcome


Combining tumor size/number with AFP improves recurrence prediction

- Transplant patients within or beyond Milan (n=435)
- AFP transformed to log₁₀ ng/ml

<table>
<thead>
<tr>
<th>Variables</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legend</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
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<tr>
<td>Number of tumours</td>
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<td>1.00</td>
<td>1.00-1.01</td>
<td>&lt; 0.001</td>
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<tr>
<td>Log, AFP, ng/ml</td>
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<td>0.00</td>
<td>0.00-1.00</td>
<td>&lt; 0.001</td>
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<tr>
<td>1-year survival</td>
<td>0.000</td>
<td>0.00</td>
<td>0.00-1.00</td>
<td>&lt; 0.001</td>
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Who are the low risk group patients?

- Low risk group (sens = 53%, spec = 81.6%)
  - A) Within Milan and AFP < 1000
  - B) 1-3 nodules, largest 3-6 cm, and AFP < 100
  - C) More than 4 nodules, largest < 3cm, AFP < 100

Outcomes:
- Recurrence - 8.8% vs 50.6%
- 5-year survival - 67.8% vs 47.5%

The model also works when reassessing tumour while waiting.

**Figure 1**


AFP-L3 vs AFP or DCP may predict recurrence, but few data

- Fucosylated fraction of AFP – AFP-L3 compared to AFP or Des-gamma-carboxy prothrombin (DCP)
- Japanese study; n=420 (within Milan), resected or RFA

Tamura et al. Dig Dis Sci 2013;58:2406-12

AFP-L3 vs AFP or DCP may predict recurrence

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Glypican-3 expression may predict recurrence but again few data

- Chinese study - resection samples, n=172
- GPC3 correlates with # and size of tumours
- Also correlates with disease-free survival
- Most useful in early stage disease, and is regardless of AFP

Fu et al. Surgery 2013;154:536-44

Glypican-3 expression in resected HCC may predict recurrence

**Figure 2**

Fu et al. Surgery 2013;154:536-44

Angiogenesis factors correlate with survival: perhaps recurrence?

- For advanced HCC (SHARP trial), angiogenesis biomarkers highly predictive
  - Ang2
  - VEGF
- Significance in curative intent patients / tumours not clear

Llovet, Clin Cancer Res. 2012;18(8):2290-300
Although increased neutrophil–lymphocyte ratio predicts recurrence, it does not seem to be by VEGF alone.

Did not correlate with VEGF or IL8, but did with IL17.


Can we measure circulating tumour cells?

- Recent study: epithelial cell adhesion molecule expressing (stem cell like) circulating tumour cells measured in patients undergoing resection
- Higher expression correlated with:
  - Higher AFP
  - More satellite lesions
  - Vascular invasion
  - Recurrence

Sun et al. Hepatology 2013:57:1458-68

Genomic signature may predict recurrence after resection

- N=287 resection patients from New York, Milan and Barcelona
- 22 gene signatures assessed
- Both tumour and adjacent liver
- G3 signature from tumour - strongest predictor of early recurrence. Poor survival signature from surrounding liver also predictive
- In this study progenitor cell signature had poor prognostic ability (EPCAM, hepatoblastoma-C2, CK-19)

Villanueva et al. Gastroenterology 2011;140:1501-12

Genomic signature may predict recurrence after resection

Villanueva et al. Gastroenterology 2011;140:1501-12
Chinese study looking at genomic signature for recurrence

- N=454, resection specimens, included a validation cohort
- Looked at gene expression both for progenitor/stem cells (ex: CK7, 19, ABCG2, EPCAM) and for angiogenesis (ex: VEGF)


Recurrence is earlier in HCC expressing mTOR regulatory protein (pRPS6)


mTOR inhibition or anti-CD25 induction may reduce recurrence risk

Toso et al. Hepatology 2007;51:1237-43

mTOR inhibition may reduce recurrence risk in transplants

Summary

- As HCC progresses, factors that influence recurrence may weigh differently.
- Size, number, vascular invasion remain key in a transplant setting.
- Pre-operatively, these are assessed radiologically, but surrogates for unidentified vascular invasion are desirable (ex: AFP).
- Other biomarkers may refine risk prediction, but none in isolation: assessment on multiple fronts (e.g., stem cells and angiogenesis markers) may prove more fruitful.
- Genomic signature of tumour / surrounding liver may aid risk prediction.
- While therapy may affect recurrence, wise stewardship (and more data) seems warranted.