Vessels Encapsulating Tumor Clusters a Powerful Predictor of Aggressive Hepatocellular Carcinoma

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Introducing VETC

→ How does HCC metastasize?

• Is Epithelial Mesenchymal Transition (EMT) involved?

(Fang et al. HEPATOLOGY 2015;62:452-465)
A Novel Vascular Pattern Promotes Metastasis of Hepatocellular Carcinoma in an Epithelial–Mesenchymal Transition–Independent Manner

Jian-Hong Fang,¹* Hui-Chao Zhou,²* Chong Zhang,¹ Li-Ru Shang,¹ Lei Zhang,² Jing Xu,³ Limin Zheng,¹ Yunfei Yuan,³ Rong-Ping Guo,³ Wei-Hua Jia,⁴ Jing-Ping Yun,⁵ Min-Shan Chen,³ Yaojun Zhang,³ and Shi-Mei Zhuang¹,²

(Hepatology 2015;62:452-465)
Vessels Encapsulating Tumor Clusters (VETC)

Tumor cluster in cancer nest was entirely encapsulated by endothelium in HCC tissue with VETC pattern.

Tumor embolus in adjacent non-tumor liver was entirely encapsulated by endothelium.

(Fang et al. HEPATOLOGY 2015;62:452-465)
(Fang et al. *Hepatology* 2015;62:452-465)
How is VETC compared to established prognosticators?

AIM
Retrospective multicentric clinical-pathological study

METHODS
Methods – Patients and samples

• 541 HCCs (541 patients) treated by surgical resection
  • Humanitas Research Hospital, Rozzano, Italy
  • Severance Hospital, Seoul, Korea
  • Kurume University Hospital, Kurume, Japan

• 2006 → 2012
• Follow-up > 2 years
• Only R0
Methods – Variables ≈ 30 Prognosticators

- Clinical variables
- Macroscopic and Microscopic features
- Cytological features
- Tumoral variants
- Molecular phenotypes
Vessels Encapsulating Tumor Clusters (VETC) Is a Powerful Predictor of Aggressive Hepatocellular Carcinoma

Salvatore Lorenzo Renne,1,4 Ha Young Woo,2,4 Sarah Allegra,3 Noemi Rudini,1 Hirohisa Yano,3 Matteo Donadoni,4,5 Luca Viganò,4,5 Jun Akiba,6 Hye Sun Lee,7 Hyungjin Rhee,6 Young Nyun Park,3 Massimo Roncalli,1,5 and Luca Di Tommaso,1,5

Relevant Findings for Pathologists

RESULTS
How to assess VETC?

- CD34

- evaluated in 5% unit

→ Ranged from 0% to 100% of tumor surface
Is VETC assessment reproducible?

• *Whole Sectioned Slides VS TMA in 96 matched cases* → Good Correlation (Coefficient [95% CI]: 0.64 [0.50-0.73])

• *Among 4 reviewers* → Good Agreement (Fleiss’ Kappa value [95% CI]: 0.89 [0.78-0.99])
When a Tumor is VETC+?

- Multivariable regression analysis, evaluated in 5% unit
  → meaningful prognostic factor.

- K-adaptive partitioning algorithm
  → 55% as the optimal cutoff to predict prognosis.
  ≈ More than half

- Using this cutoff VETC+ 18.9% of cases
Where is VETC-HCC?
### Table 3. Impact of Clinical and Pathological Features on Early Recurrence, DFS, and OS (n = 532)

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Early Recurrence (n = 532)</th>
<th>DFS (n = 532)</th>
<th>OS (n = 532)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate Analysis</td>
<td>Multivariate Analysis</td>
<td>Univariate Analysis</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>1.44 (1.04-1.95)</td>
<td>0.018</td>
<td>1.47 (1.02-2.12)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>1.33 (1.33-2.6)</td>
<td>0.036</td>
<td>1.31 (0.91-1.73)</td>
</tr>
<tr>
<td>High-risk infection</td>
<td>0.75 (0.53-1.2)</td>
<td>0.223</td>
<td>0.17 (0.81-1.6)</td>
</tr>
<tr>
<td>Serum HIV viral load</td>
<td>1.36 (1.09-1.68)</td>
<td>0.299</td>
<td>1.35 (0.92-1.40)</td>
</tr>
<tr>
<td>Pre-operative treatment</td>
<td>0.36 (0.21-0.63)</td>
<td>&lt;0.001</td>
<td>0.32 (0.29-0.40)</td>
</tr>
</tbody>
</table>

**General Microscopic**
- **Tumor size <5 cm**
  - HR: 0.63 (0.39-1.03)  0.067
  - HR: 1.94 (1.22-2.17)  0.001
- **Multicentric**
  - HR: 2.16 (1.37-63)  0.001
- **Lymph node**
  - HR: 0.28 (0.15-0.47)  <0.001
  - HR: 0.33 (0.24-0.48)  <0.001
- **Overall metastasis**
  - HR: 0.49 (0.30-0.79)  0.002
  - HR: 0.97 (0.51-0.85)  <0.001
- **Tumor-specific metastasis**
  - HR: 1.35 (0.71-1.29)  0.716
  - HR: 0.89 (0.50-0.92)  0.001

**Histopathological Findings**
- **Pleomorphic cells**
  - HR: 1.23 (0.77-1.81)  0.298
- **Accurate changes**
  - HR: 0.65 (0.47-0.87)  0.003
  - HR: 0.68 (0.52-1.67)  0.138
- **Medullatic bodies**
  - HR: 1.47 (0.41-1.30)  0.019
  - HR: 1.47 (0.41-1.30)  0.020

**Tumor Viments**
- **Lymphphere kinase-like**
  - HR: 0.32 (0.14-0.27)  0.001
- **PAK**
  - HR: 0.32 (0.14-0.70)  0.003
- **Skeletin**
  - HR: 2.60 (0.14-6.0)  0.002
- **Stathophilin**
  - HR: 1.30 (0.62-0.85)  0.016
- **Vonichon-1**
  - HR: 1.30 (0.63-0.85)  0.348

**Molecular Phenotypes**
- **p53**
  - HR: 0.63 (0.32-1.27)  0.299
- **DendrRho**
  - HR: 1.34 (0.69-1.77)  0.770

**Presented at:**
- **EUROPEAN CONGRESS OF PATHOLOGY ’19**
- **#ECP2019Nice**

**Presented by:** SALVATORE L. RENNE MD
# VETC And Other Significant* Prognosticators

<table>
<thead>
<tr>
<th>Variable (Multivariable Analysis)</th>
<th>DFS HR (95% CI) P Value</th>
<th>OS HR (95% CI) P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size &gt;5 cm</td>
<td>1.77 (1.27-2.45) 0.001*</td>
<td>1.57 (0.90-2.73) 0.094</td>
</tr>
<tr>
<td>Multiplicity</td>
<td>2.01 (1.46-2.76) &lt;0.001*</td>
<td>2.12 (1.30-3.46) &lt;0.001*</td>
</tr>
<tr>
<td>Macrovascular invasion</td>
<td>1.84 (1.17-2.90) 0.008*</td>
<td>4.19 (2.45-7.16) &lt;0.001*</td>
</tr>
<tr>
<td>Microvascular invasion</td>
<td>1.34 (1.01-1.78) 0.045*</td>
<td>2.19 (1.31-3.66) 0.003*</td>
</tr>
<tr>
<td>Sarcomatoid Variant</td>
<td>8.72 (1.17-64.76) 0.034*</td>
<td>24.99 (3.05-204.63) 0.003*</td>
</tr>
<tr>
<td>VETC</td>
<td>1.66 (1.21-2.27) 0.002*</td>
<td>2.26 (1.37-3.72) 0.001*</td>
</tr>
</tbody>
</table>
How do VETC-HCCs Behave?

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VETC and Etiology

**HEPATOLOGY 1996, 23(2), 205-209**

**JCP 1979, 32, 590-600**

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**HEPATOLOGY 1996, 23(2), 205-209**

**JCP 1979, 32, 590-600**

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VETC and Size

Tumors of the Liver and Intrahepatic Bile Ducts

AFIP Edmondson 1959

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VETC and Vascular Invasion

Macro/microvascular invasion (n=289)

No macro/microvascular invasion (n=243)

AFIP Edmondson 1959
Vascular Invasion and Herniation by Hepatocellular Carcinoma in Cirrhosis

A Wolf in Sheep's Clothing?

Alberto Quaglia, MD, PhD, MRCPath; Nazanin Eissami, MD; Rosalind Sim, FIBMS; John Diford, FIBMS;
A. P. Dhillon, MD, FRCP, FRCPath

Arch Pathol Lab Med. 2005 May;129(5):639-44.
Vessels That Encapsulate Tumor Clusters (VETC) Pattern Is a Predictor of Sorafenib Benefit in Patients with Hepatocellular Carcinoma

Jian-Hong Fang,1,2 Li Xu, Xi Li-Ru, Shang,1 Chu-Zhi Pan,1 Jin Ding,1 Yun-Qiang Tang,1 Hui Liu,4 Chao-Xing Liu,1 Jie-Lin Zheng,1 Yao-Jun Zhang,2 Zhong-Guo Zhou,3 Jing Xu,3 Limin Zheng,3 Min-Shan Chen,2 and Shi-Mei Zhuang 1,4

VETC ∝ Sorafenib Response
So What?

• 18.9% of cases 1 in 5 → Frequent phenotype
• Easy to assess and reproducible between small and large samples (see biopsies)
• VETC ∝ Bad prognosis

Could these results redeem the pathologist in the pre-operative setting?
Financial support:
This study was supported by the National Research Foundation of Korea (NRF) funded by the Korean Government (MSIP) (No. NRF-2017R1A2B4005871, NRF-2017M3A9B6061512, NRF- 2016M3A9D5A01952416). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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- Co-authors and physicians involved

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