Vascular endothelial growth factor (VEGF) and its receptor expression in lung carcinoids: clinicopathological correlations

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LUNG CARCINOIDS

- Neuroendocrine epithelial malignancies
- <1% lung cancer, 0.1-1.5/100000 incidence
- <60 yrs, female, caucasian
- Family history of carcinoid tumor or MEN1 mutation
- Not related to tobacco smoking
- Rarely associated with DIPNECH
- Divided in two categories

**TYPICAL CARCINOIDS** 70-90%

**ATYPICAL CARCINOIDS** 10-30%
<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Typical carcinoid</th>
<th>Atypical carcinoid</th>
<th>Large cell neuroendocrine carcinoma</th>
<th>Small cell lung carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age</td>
<td>Sixth decade</td>
<td>Sixth decade</td>
<td>Seventh decade</td>
<td>Seventh decade</td>
</tr>
<tr>
<td>Sex predominance</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Smoking association</td>
<td>No</td>
<td>Variable*</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mitoses per 2 mm²</td>
<td>0–1</td>
<td>2–10</td>
<td>&gt; 10 (median of 70)</td>
<td>&gt; 10 (median of 80)</td>
</tr>
<tr>
<td>Necrosis</td>
<td>No</td>
<td>Focal, if any</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Neuroendocrine morphology</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ki-67 proliferation index</td>
<td>Up to 5%</td>
<td>Up to 20%</td>
<td>40–80%</td>
<td>50–100%</td>
</tr>
<tr>
<td>TTF1 expression</td>
<td>Mostly negative</td>
<td>Mostly negative</td>
<td>Positive 50%</td>
<td>Positive 85%</td>
</tr>
<tr>
<td>Synaptophysin / chromogranin</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive 80–90%</td>
<td>Positive 80–90%</td>
</tr>
<tr>
<td>CD56</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive 80–90%</td>
<td>Positive 80–90%</td>
</tr>
<tr>
<td>Combined with a non-small cell lung carcinoma component</td>
<td>No</td>
<td>No</td>
<td>Sometimes</td>
<td>Sometimes</td>
</tr>
</tbody>
</table>

KI-67 has value in distinguishing carcinoids from high-grade NET in small and crushed biopsies.
LOW/INTERMEDIATE GRADE TUMOR...

LYMPH NODE METASTATIZATION

- 15% OF TC
- 50% OF AC

RECURRENCES

- 5% OF TC with a median time to recurrence of 4 years
- 20% OF AC with a median time to recurrence of 1.8 years

Relevance of Lymph Node Micrometastases in Radically Resected Endobronchial Carcinoid Tumors
Tommaso Claudio Mineo, MD, Giannaca Goggione, MD, Davide Mineo, MD, Gianlaca Vanni, MD, and Vincenzo Ambrogi, MD

Incidence and Prognostic Significance of Carcinoid Lymph Node Metastases
Peter J. Kneuer, MD, Mohamed K. Kamel, MD, Brendon M. Stiles, MD, Benjamin E. Lee, MD, Mohamed Rahouma, MD, Sebron W. Harrison, MD, Nasser K. Altorki, MD, and Jeffrey L. Port, MD
Division of Thoracic Surgery, the Ohio State University Wexner Medical Center, Columbus, Ohio, and Department of Cardiothoracic Surgery, New York Presbyterian Hospital, Weill Cornell Medicine, New York, New York

DFS

OS
• Carcinoid tumors are highly vascularized tumors
• Different angiogenetic pathways are implied in carcinogenesis of NET

Carcinoid tumors and VEGF pathway:

DIAGNOSTIC TOOL?
PROGNOSTIC STRATIFICATION?
VEGF and its receptors were consistently expressed in tumorlets and in NE-cell hyperplasia.

VEGF is highly expressed in localized NE cell proliferations without potential of malignancy and might participate in local development of fibrosis.
AIM

Evaluation, of the VEGF pathway expression in a series of resected lung carcinoids

Correlation of the results with morphological and clinical parameters

Usefulness of the VEGF pathway:
more precise differentiation between typical and atypical carcinoids?
better prognostic stratification?
**Material and methods**

**STUDY POPULATION**
- 78 consecutive patients that underwent lung resection (2005 - 2011) for lung carcinoids at Thoracic Surgery division of Padua University

<table>
<thead>
<tr>
<th>Findings</th>
<th>Lung carcinoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hystotype</td>
<td></td>
</tr>
<tr>
<td>Typical carcinoids</td>
<td>61 (78%)</td>
</tr>
<tr>
<td>Atypical carcinoids</td>
<td>17 (22%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30</td>
</tr>
<tr>
<td>Female</td>
<td>48</td>
</tr>
<tr>
<td>Age</td>
<td>50 ± 16</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>40</td>
</tr>
<tr>
<td>Non smoker</td>
<td>38</td>
</tr>
<tr>
<td>Dimension (cm)</td>
<td>2,47 ± 2</td>
</tr>
<tr>
<td>N+</td>
<td></td>
</tr>
<tr>
<td>8 TC (13%)</td>
<td></td>
</tr>
<tr>
<td>7 AC (41%)</td>
<td></td>
</tr>
<tr>
<td>Follow up (months)</td>
<td>89 ± 33</td>
</tr>
<tr>
<td>Recurrence</td>
<td>8</td>
</tr>
<tr>
<td>Death</td>
<td>3 (AC)</td>
</tr>
</tbody>
</table>

**IMMUNOHISTOCHEMISTRY**
- VEGF and its receptors VEGFR1, VEGFR2 and VEGFR3 immunostaining on neoplastic tissue (1 slides/case)
- % of neoplastic cells with membranous/cytoplasmic positivity, blindly evaluated by two pathologists
- Preliminary statistical analyses
Results

**TUMOR SIZE**

- TC: [Box Plot]
- AC: [Box Plot]

- **p=0.03**

**KI-67**

- TC: [Box Plot]
- AC: [Box Plot]

- **p<0.0001**

**Pathological Observations**

- TC: [Image]
- AC: [Image]

- **Ki-67**

- TC: [Image]
- AC: [Image]
Results

**VEGF**

- **Group for 0**
- **Group for 1**

**Box Plot**

- **Grouping Variable(s):** Tipico_0 e Atipico_1


**VEGF R1**

- **Group for 0**
- **Group for 1**

**Box Plot**

- **Grouping Variable(s):** Tipico_0 e Atipico_1


**VEGF R2**

- **Group for 0**
- **Group for 1**

**Box Plot**

- **Grouping Variable(s):** Tipico_0 e Atipico_1


**VEGF R3**

- **Group for 0**
- **Group for 1**

**Box Plot**

- **Grouping Variable(s):** Tipico_0 e Atipico_1

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**VEGF**

- **TC**
- **AC**

**p=0.02**

**VEGFR1**

- **TC**
- **AC**

**p=0.01**

**VEGFR2**

- **TC**
- **AC**

**p<0.001**

**VEGFR3**

- **TC**
- **AC**

**p<0.001**
Results

VEGFR3

Box Plot
Grouping Variable(s): INVASIONE LINFO NO_0 SI_1

Row exclusion: Carcinoidi 09.04.2019.svd

p<0.005
p<0.0001
• VEGFR-3 is activated by its specific ligand, VEGF-C, which promotes cancer progression
• The VEGF-C/VEGFR-3 axis is expressed not only by lymphatic endothelial cells but also by a variety of human tumor cells
• Activation of the VEGF-C/VEGFR-3 axis in lymphatic endothelial cells can facilitate metastasis by increasing the formation of lymphatic vessels (lymphangiogenesis) within and around tumors
Study limits

- Retrospective study
- Sample size
- Follow-up time

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECURRENCES</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>DEATH</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Future perspectives

- Multivariate analysis with several clinical and pathological data are ongoing
- Increase the study population, especially AC
- Study of the vascular network (D2-40, CD31)
- Extension of the follow-up
Conclusion

• The VEGF pathway is more expressed in AC than in TC, in particular VEGFR3 is more expressed in metastatic carcinoids, independently from histotype

• The factors involved in angiogenesis could represent a tool for a better classification of carcinoids, stratifying for example the typical forms based on lymph node invasion

• High expression of the VEGF pathway, particularly VEGFR3, in atypical and typical metastatic carcinoids could be a substrate for mechanistic studies to validate its prognostic and predictive value

THANKS FOR ATTENTION