Perifissural nodules in metastatic renal cell carcinoma patients treated with vascular endothelial growth factor receptor (VEGFR) inhibitors

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Purpose

Perifissural nodules (PFN) are frequently seen in CT examinations performed for lung cancer screening. PFNs were defined by Ahn et al as well-circumscribed, smoothly margined nodules which lie within or adjacent to the pulmonary fissures.\(^1\) They are considered to represent benign perifissural lymph nodes and have been histopathologically confirmed as such in a few cases.\(^2,3\) However, malignant PFNs are known to exist. So far, few information about their frequency and imaging features is available.

Survival of patients with metastatic renal cell carcinoma (mRCC) has improved substantially with the introduction of vascular endothelial growth factor receptor (VEGFR) inhibitors like the tyrosine kinase inhibitors sunitinib, sorafenib, pazopanib and cediranib.\(^4,5,6,7,8\)

Pulmonary metastases of these patients present themselves not only as solid intraparenchymal nodules but may also exhibit unusual features. In our experience a considerable number of these pulmonary metastases from RCC fulfil the criteria used for the definition of PFN.

Purpose of this study was to determine the frequency of appearance of these perifissural nodules in mRCC patients and establish whether VEGFR inhibitor therapy may increase the frequency of such malignant PFNs. To our knowledge, this is the first study to describe these PFNs and the malignant progression of these nodules in mRCC patients.
Methods and Materials

Patient selection

We performed a retrospective chart and database analysis of 158 patients with mRCC treated in our hospital from February 2003 to 1 January 2010.

Twenty patients were not included because
(1) there were less than three CT scans available;
(2) the images were difficult to evaluate due to the very large number of pulmonary metastases, pleural fluid or carcinomatous lymphangitis.

The remaining 138 patients were included in this study. Treatment medication, initiation and duration of therapy and information about smoking were retrieved from the medical record. In these patients, CT scans were available at time intervals of approximately every 2-3 months.

Data Acquisition

Images were acquired with a 16-slice multidetector CT scanner. Scanning of the entire chest was performed in a caudocranial direction with 16x1.5mm collimation. Overlapping 3mm-thick sections were reconstructed from the data. Scans were acquired at 120 kV with adaptive dose modulation. Intravenous contrast material (Xenetix® 300, Guerbet, Paris, France) was injected if no contraindications were present.

Image analysis

A total of 1,770 chest CT scans were retrospectively reviewed by two observers using a lung window settings. All detectable PFNs were recorded in a database and, when present, the PFNs were followed in time and monitored for radiologic progression.
Results

Patient characteristics

A total of 138 patients were included in this study. The median patient age at diagnosis was 57.1 (range: 23.2-82.1). The male female ratio in the study group was 3:1.

Almost all patients (99%; 136/138) had undergone tumour nephrectomy. In 84% of cases (116/138) a clear cell subtype was present. The proportion of other subtypes is listed in Table 1.

Among the patients were 25 (18%) smokers, 46 (33%) former smokers and 54 (39%) non-smokers. Information on smoking history could not be obtained for 13 (9%) patients.

Seventy-seven patients (56%) were treated with VEGFR inhibitors for longer than six months. Twenty-three patients (17%) received medication for less than six months and 34 patients (25%) had not been treated with VEGFR inhibitors at all. Information about VEGFR inhibitor treatment was unknown for four patients (3%).

A total of 55 patients in our study population had been treated with cytokine-based therapies, predominantly interferon-# therapies in different regimes.

Presence of PFNs

During the total observation time, 42 patients (30%) were found to have one or more PFNs. In 36 of the 42 patients (86%) pulmonary metastases were already present when the PFNs were first detected. In two cases, the PFNs were calcified.

The group of patients with a PFNs on CT included 11 smokers (26 %), 14 former smokers (33%) and 16 non-smokers (38%). Information about smoking history was unknown for one patient.

Ten patients (24%) were treated with VEGFR inhibitors prior to the presence of the first PFN.

Thirty-two patients (76%) had PFNs without prior treatment with VEGFR inhibitors. The proportion of smokers for each group is listed in Table 2.
Among the 42 patients who developed PFNs, 20 patients were pre-treated with cytokine-based therapies. No evidence of a significant correlation between cytokine based therapies and the development of PFNs was found.

**Progression of PFNs**

In twelve of the 42 patients (29%) with PFNs there was clear radiologic progression of the nodules, suggesting a malignant PFN (Figure 1). The median time from diagnosis to progression of PFN was 11 months.

In eleven patients (92%) with progression of a PFN pulmonary metastases were already present at detection of the first PFN.

Five patients (42%) developed perifissural metastases during VEGFR inhibitor treatment and seven patients (58%) developed PFNs prior to VEGFR inhibitor therapy.

In two patients, cavitation in these lesions after initiation of VEGFR inhibitor therapy was seen (Figure 2).

The group of patients with radiologic progression of their PFNs consisted of smokers, former smokers and non-smokers. No significant differences between the proportion of smokers in the VEGFR inhibitor treated group and the proportion in the untreated group. Results are listed in Table 3.
Fig. 0: Malignant PFN due to mRCC. (a) Baseline CT demonstrates a PFN in the left major fissure. Five months (b) and seven months (c) later substantial progression of the nodule is seen.

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Fig. 0: Malignant PFN due to mRCC. A small solid nodule is seen adjacent to the right major fissure (a). The nodule grows within 6 months (b). After start of VEGF inhibitor treatment cavitation of the lesion develops three months after initiation of the therapy (c).
Table 1

Patient characteristics (n=138)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) at diagnosis [range (median)]</td>
<td>23-81 (57.1)</td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>104 (75)</td>
</tr>
<tr>
<td>Female</td>
<td>34 (25)</td>
</tr>
<tr>
<td>Histologic subtype [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>118 (86)</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Sarcomatoid carcinoma</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Chromophobe/papillary carcinoma</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Chromophobe/eosinophilic carcinoma</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Not otherwise specified (NOS) or unknown</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Smoking at diagnose [n (%)]</td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>25 (18)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>46 (33)</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>54 (39)</td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (9)</td>
</tr>
</tbody>
</table>

Fig. 0: Patient characteristics

Table 2

Presence of perifissural nodules on CT scan in 138 mRCC patients

<table>
<thead>
<tr>
<th>Presence of PFNs (n of cases)</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with PFNs prior to VEGFR inhibitor treatment</td>
<td>32 (76)</td>
</tr>
<tr>
<td>Smokers</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Patients with PFNs during VEGFR inhibitor treatment [n (%)]</td>
<td>10 (24)</td>
</tr>
<tr>
<td>Smokers</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Pulmonary metastases already present at detection of first PFN [n cases (%)]</td>
<td>36 (86)</td>
</tr>
<tr>
<td>Patients with PFNs treated with cytokine-based therapies</td>
<td>20 (48)</td>
</tr>
</tbody>
</table>

Fig. 0: Presence of perifissural nodules on CT scan in 138 mRCC patients
**Fig. 0:** Radiologic progression of perifissural nodules on CT scan in 42 mRCC patients with PFNs

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Conclusion

In conclusion, PFNs are frequently seen in mRCC patients. Malignant PFNs due to metastases occur in approximately 10% of patients with mRCC. A clear link between malignant progression of PFNs and smoking history nor between the progression and VEGFR inhibition therapy could not be found in this study.

While perifissural nodules in this patient group are mostly benign, one has to keep in mind that malignant PFNs exist in this group much more frequently than in a lung cancer screening population. In case of a suspicious PFN that might lead to therapeutic consequences, more rapid follow-up or biopsy needs to be considered.
References


Personal Information

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