Pulmonary carcinosarcoma: diagnostic problems and determinants of the prognosis

Abstract

Objective. Bronchopulmonary carcinosarcoma is a very rare tumor and the prognosis of patients with carcinosarcoma is assessed as unfavourable. The problems concerning diagnosis, therapy, and prognosis after resection treatment are discussed with reference to our seven cases and with consideration of the pertinent literature.

Methods. The retrospective data of seven patients with pulmonary carcinosarcoma were analysed. All were staged postoperatively according to the international TNM staging system. The diagnosis was verified by immunohistochemical investigation. The prognosis of the patients with carcinosarcoma was compared with the prognosis of patients with non-small cell carcinoma of the lung.

Results. Whether lung resection is the treatment of choice for these patients is of no relevance, because in most cases the preoperative diagnosis is incomplete, as only one component of the tumor, namely the epithelial one, is found in the biopsy specimen. The complete and correct diagnosis in five of the seven cases was not made before the resection had been performed and in the remaining two patients it was only made when tumor recurrence or metastases occurred. The prognosis of patients with carcinosarcoma of the lung is assessed to be comparable to that of patients with other pulmonary carcinoma: in this study survival times ranged from only 3 months (T2N3) to 4 years 6 months (T3N1). The causes of death of the patients with carcinosarcoma were local recurrence in four patients and metastases at distant sites in two. Two recurrent tumors as well as the metastases consisted only of the sarcoma component of the primary tumor histologically.

Conclusion. One may suggest that the prognosis of carcinosarcoma might be determined by the sarcoma component of the tumor. Therefore the generally accepted therapies of soft tissue sarcomas should be adopted for the follow-up treatment of patients with pulmonary carcinosarcoma.

Key words

Pulmonary carcinosarcoma • Diagnosis • Treatment • Prognosis

Introduction

The first reported case of carcinosarcoma in the lung is attributed to Kika in 1908, as noted by Herxheimer and Reinke in 1912 [11]. Kaik and colleagues (1973) reviewed 45 cases and Cohen-Salmon et al. (1985) reported on 50 cases in the lung [4, 15]. According to the WHO [23] carcinosarcomas are subdivided into two groups: the embryonic carcinosarcomas (pulmonary blastomas, embryomas) and other than embryonic carcinosarcomas. So far nearly 100 pulmonary blastomas and 80 cases of carcinosarcomas have been described in the literature. The carcinosarcoma is defined as a bidirectional tumor containing...
a mixture of carcinomatous and sarcomatous components [5].

There is agreement that the differentiation of carcinosarcoma is very difficult, and it is rarely diagnosed preoperatively [14, 21, 22]. The prognosis of patients with pulmonary carcinosarcoma is generally assessed as unfavorable [6, 13, 21], due to the marked tendency of the tumor to metastasize at distant sites and the high rate of local recurrence [13, 21]. In our institution we have experience of seven cases of pulmonary carcinosarcoma. The aim of this report is to report on the problems of the diagnosis of these tumors and to evaluate possible prognostic factors.

Patients and methods

Between 1975 and 1995, seven patients with pulmonary carcinosarcoma were treated surgically at our unit. The retrospective data from these patients were analyzed. All were staged postoperatively according to the international TNM staging system.

After the preoperative diagnosis "non-small cell carcinoma" by histological or cytological examination of specimens obtained by bronchoscopy or percutaneous needle biopsy, the following investigations were undertaken to confirm functional and anatomical operability: the patient's general condition was assessed by exercise electrocardiogram (E CG) and body plethysmography. In patients with cardiac history, radioisotopic imaging of the left ventricle and/or left heart catheterization were performed. Limited respiratory function led us to make perfusion and ventilation scans of the lung preoperatively. The resectability of the tumors was proven by radiographic and endoscopic methods including rigid bronchoscopy with biopsies of the carinas. To visualize the mediastinal N-status, pulmonary tomography was performed until 1984, from then on computed tomographic (CT) scans were available.

Mediastinoscopy was performed if signs of mediastinal lymph node enlargement in the N3 region were seen, because we considered N2 disease to be amenable to curative resection treatment. We began a study of multimodal treatment of N2 disease of non-small cell carcinomas in 1994, since then mediastinoscopy has become routine procedure if the CT scan reveals enlarged lymph nodes in the N2 region. Metastatic spread was ruled out with abdominal ultrasound, isotope bone scan, CT scanning of the brain, and CT scanning of the adrenal glands. Mediastinal lymph node dissection has been routinely included in the resection treatment of non-small cell carcinoma, before 1986 as a sampling dissection and since then as extensive dissection. All patients with involved mediastinal lymph nodes received postoperative percutaneous radiotherapy to the mediastinum.

If the postoperative histological examination revealed carcinomatous and sarcomatous components in the tumor, immunohistochemical examination was performed with a monoclonal cytokeratin antibody linking to most of the known cytokeratins (AE-1 and AE-2) 1 and anti-vimentin (monoclonal mouse antibody) 2.

Results

Five of the seven patients with pulmonary carcinosarcoma were men and two were women. The age range was 35–67 years. Table 1 shows age, sex and tumor location of the individual patients in the patient population.

The preoperative bronchoscopy revealed endobronchial non-small cell carcinoma in three patients only. In two cases it could be seen in the left main bronchus (T3 tumor) and in one case in the segmental bronchus 2 of the right lung (T3 tumor because of infiltration of the parietal pleura, in case 1). The four other tumors had an even more peripheral location. Two of these patients underwent diagnostic thoracotomy with the diagnosis "tumor of unknown dignity". The diagnosis "non-small cell carcinoma" was made in the other two patients by bronchial lavage and percutaneous puncture, respectively.

In the seven cases we report on the mesenchymal component of the carcinosarcoma was never diagnosed preoperatively. The correct diagnosis carcinosarcoma was obtained by histological examination in five cases postoperatively. In two of the seven cases the complete diagnosis was made following local recurrence of the tumor or metastases at distant sites, causing re-evaluation of the resected lung tissue (cases 5 and 6). Table 2 shows the epithelial and mesenchymal components of our series of carcinosarcomas.

On CT scan two patients were suspected of having mediastinal lymph node metastases in the N2 region, and one in the N3 region. We performed a mediastinoscopy in the patient with suspected N3 disease. Because of bleeding due to an injury of the brachiocephalic trunk, a median sternotomy had to be performed for hemostasis, and resection of the right lower lobe and mediastinal lymph node dissec-

**Table 1 Age, sex, and tumor location of the patients with carcinosarcoma of the lung**

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age</th>
<th>Sex</th>
<th>Tumor location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>Male</td>
<td>Right upper lobe</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>Male</td>
<td>Right upper lobe</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>Male</td>
<td>Left upper lobe</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>Female</td>
<td>Right lower lobe</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>Male</td>
<td>Left main bronchus</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>Female</td>
<td>Right lower lobe</td>
</tr>
<tr>
<td>7</td>
<td>67</td>
<td>Male</td>
<td>Left main bronchus</td>
</tr>
</tbody>
</table>

**Table 2 Epithelial and mesenchymal components of pulmonary carcinosarcomas**

<table>
<thead>
<tr>
<th>Cases</th>
<th>Epithelial components</th>
<th>Mesenchymal components</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adeno- and small cell carcinoma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>2</td>
<td>Squamous cell carcinoma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>3</td>
<td>Adeno- and squamous cell carcinoma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>4</td>
<td>Adenocarcinoma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>5</td>
<td>Squamous cell carcinoma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>6</td>
<td>Squamous cell carcinoma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>7</td>
<td>Squamous cell carcinoma</td>
<td>Myo-chondrosarcoma</td>
</tr>
</tbody>
</table>

1 Hybritech, San Diego, Calif., USA  
2 Boehringer, Mannheim, Germany
Table 3 Tumor stages, survival times, and causes of death of patients with pulmonary carcinosarcoma

<table>
<thead>
<tr>
<th>Cases</th>
<th>Tumor stage</th>
<th>Survival times (months)</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T3N0</td>
<td>8 (died)</td>
<td>Local recurrence (no histological examination)</td>
</tr>
<tr>
<td>2</td>
<td>T3N0</td>
<td>26 (died)</td>
<td>Local recurrence (no histological examination)</td>
</tr>
<tr>
<td>3</td>
<td>T2N2</td>
<td>11 (died)</td>
<td>Metastases (sarcoma component only)</td>
</tr>
<tr>
<td>4</td>
<td>T2N3</td>
<td>3 (died)</td>
<td>Metastases (sarcoma component only)</td>
</tr>
<tr>
<td>5</td>
<td>T3N1</td>
<td>54 (died)</td>
<td>Local recurrence (spindle cell component only)</td>
</tr>
<tr>
<td>6</td>
<td>T2N0</td>
<td>11 (died)</td>
<td>Local recurrence (spindle cell component only)</td>
</tr>
<tr>
<td>7</td>
<td>T3N2</td>
<td>21 (alive)</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis

Carcinosarcoma is defined to be a biphasic malignant tumor. From the first description of a carcinosarcoma by Kika in 1908 to the early 1980s, diagnosis was only made by conventional light microscopy and staining until Huszar and colleagues (1984) introduced immunohistological staining and immunofluorescent microscopy [12]. Carcinomatous and sarcomatous tumor formation can thus be readily distinguished from each other by cytokeratin and vimentin antibodies. The differences in the reaction of carcinosarcomas to these tumor markers is the basis for the most recent definition of carcinosarcomas. According to this definition, carcinosarcoma of the lung is a tumor comprising both malignant epithelial and malignant mesenchymal components in which features of epithelial differentiation may not be demonstrable immunohistochemically in the spindle cell component. Otherwise, these tumors are to be classified as carcinomas with spindle-cell differentiation [21].

Histology

The most common epithelial component of the carcinosarcoma is the squamous cell carcinoma (69%); adenocarcinoma is present in 20% and undifferentiated large cell carcinoma in 11% [3]. Thus far a small cell carcinoma com-
ponent has been only described in one case, by Tsubota and colleagues [22]. We also found such an epithelial compo-
nent in one tumor (Table 2). The most frequent stromal component is the spindle cell component, classically re-
ferred to as fibrosarcoma [1, 5]. At times, osteosarcoma, chondrosarcoma, leiomyosarcoma [19], and rhabdomyo-
sarcoma [18] may be found.

The histogenesis of carcinosarcomas remains unclear. Attempts have been made in the past to explain the his-
togenesis and several theories have been proposed. Dail (1994) concludes that a cell, once it becomes tumorous,
can dip into its heritage pool of totipotentiality and can differen-
tiate into diverse cell lines even within a single tu-
mor. Therefore the theories of histogenesis are no longer
necessary once one accepts this totipotentiality [5].

Treatment and prognosis

Whether resection treatment is the treatment of choice for pulmonary carcinosarcoma does not need to be discussed,
because in most cases the preoperative diagnosis is incom-
plete and only one component of the tumor, mostly the
epithelial one, is known. The prognosis of patients with
carcinosarcoma of the lung is assessed as unfavorable only
on the grounds of the small number of cases described
[6, 13, 21]. Davis et al. [6] reported a median survival time
of 12 months in 15 patients after potentially curative re-
section treatment, whereas the median survival time of five
patients reported by Ishida et al. [13] was only 9 months.
Reviewing the literature [1, 3, 4, 6] one can find great dif-
ferences in survival times. Most of the data do not define
the tumor stage, and therefore conclusions on the progno-
sis are difficult to achieve.

In order to compare the prognosis of the carcinosar-
coma with other malignant pulmonary tumors, the median
survival times and 5-year survival rates of patients with
adenocarcinoma and squamous cell carcinoma of the same
TNM-stages as the patients with carcinosarcoma are shown
in Table 4. Only the same tumor stages, that are comparable
with the tumor stages of the carcinosarcomas, are presented.
Because of the small number of cases of carcinosarcomas a
statistical analysis could not be performed, however, it
seems that the prognosis of these different tumors is sim-
ilar. The causes of death of patients with carcinosarcoma
were tumor recurrence of metastases at distant sites. Two
recurrent tumors could not be examined histologically, the
remaining two recurrent tumors, as well as the metastases,
consisted only of the sarcomatous component of the pri-
mary tumor. One might suggest that the prognosis in car-
cinosarcoma of the lung is determined by the malignant
mesenchymal component of the tumor. In general patients
with soft tissue sarcoma have a poor prognosis due to the
tendency of these tumors to recur locally and metastasize
hematogenously early in the course of the disease. This
specific behavior is independent of the pathological des-
ignation and tissue of the origin and independent of the an-
atomical site of the lesion [16]. The most important deter-
minant of biological behavior and the ultimate outcome is
the histological grade [16]. Nowadays the therapy of soft
tissue sarcoma is multimodal. Surgical resection treatment
is the most important part of therapy.

In addition, radiation is well established and effective
in the treatment of patients with soft tissue sarcomas. Even
if the sarcoma is resected incompletely and the resection
margins show residual tumor on microscopy, the rate of lo-
cal recurrence can be reduced to about 15% by local radi-
ation therapy [2]. Thus the combination of resection treat-
ment and external radiation is thought to be the standard
therapy of G II and G III soft tissue sarcoma at present.
Chemotherapeutic agents, e.g. doxorubicin, Adriamycin,
ifosfamide and dacarbazine, are known to be effective in
the treatment of soft tissue sarcomas as well [17]. If dis-
tant metastases of soft tissue sarcomas occur, a combina-
tion chemotherapy is indicated. The overall response rate
after systemic treatment of advanced tumors is estimated
to be 40%. The appropriate place for adjuvant chemother-
apy in the management of soft tissue sarcomas has not yet
been clearly defined [9], patients with G III diseases may
profit from chemotherapy, however.

In conclusion, the prognosis of the patients with pulmo-
ary carcinosarcomas seems to depend on the sarcoma
component of the tumor. For this reason, generally accepted
modes of therapy for soft tissue sarcomas should be adopted
in the treatment of patients with pulmonary carcinosarcoma.
References


