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Tumor heterogeneity in lung cancer based on light microscopic features

A retrospective study of a consecutive series of 200 patients, treated surgically

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Summary. In order to study the problem of morphological tumor heterogeneity in lung cancer, 200 consecutive patients who had undergone surgery for a malignant lung tumor, were evaluated retrospectively with regard to morphological type. The tumor was classified morphologically in 187 patients, and 163 (87%) had a morphologically homogeneous tumor, based on light microscopic features and using the criteria recommended by the World Health Organization. The remaining 24 patients (13%) had a tumor with morphologic features of more than one cell type.

It is concluded that morphological heterogeneity is a considerable problem in the classification of malignant lung tumors. This heterogeneity has been regarded as evidence of an endodermal origin of all major types of lung cancer. Future prospective studies will have to determine whether it has any therapeutic significance.

Key words: Lung cancer – Tumor heterogeneity – Histopathological classification

Introduction

The considerable therapeutic progress obtained with chemotherapy for patients with small cell lung cancer in particular, great interest has been focused on the histopathological classification of malignant lung tumors within the last decade.

The World Health Organization (WHO) published the first international classification of malignant lung tumors in 1967 (Kreyberg 1967) and the first revision of this classification has recently been published (WHO 1981).

Subsequent to the therapeutic interest, increased biological research activity with biochemical markers, experimental models, i.e. in vitro growth

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and nude mice studies, and flow cytometric DNA analyses, has been noticed within the last years (Gazdar et al. 1981), and several publications have demonstrated the morphological heterogeneity of lung cancer (Churg et al. 1980; Hashimoto et al. 1979; McDowell et al. 1978; McDowell and Trump 1981). However, most of the studies are selective and often include only a small number of patients.

The present study was undertaken in order to elucidate the problem of heterogeneity in a large consecutive series of surgical patients.

Material and methods

The study is a retrospective review of a consecutive series of patients, who underwent surgery for a malignant lung tumor in two Danish University Hospitals. In order to obtain unselected material the time was chosen from a period where patients with all types of lung cancer, including those with small cell carcinoma, underwent surgery.

All patients who were recorded to have had a lung cancer removed by surgery in the files of the pathology departments in the designated period of time were included in the study. The histological material was resectioned and stained routinely with Haematoxylin-Eosin and Kreyberg's staining for mucin and keratin. The Grimelius silver staining was performed in some patients suspected of having a carcinoid. The slides were reviewed by the pathology panel, and the tumors were classified according to both the current WHO classification of malignant tumors and to a classification based on morphological phenotypes.

The morphological criteria used for the classification of the major types were as follows:

Squamous cell carcinoma. Tumors with the presence of intra- or extracellular keratin and/or significant intercellular bridges.

Small cell carcinoma. Small, hyperchromatic cells with sparse cytoplasm and characteristic nuclei with fine distributed chromatin ("salt and pepper") without prominent nucleoli.

Adenocarcinoma. Cells with prominent nucleoli and with demonstrable intracellular or intercellular mucin. This cell type also includes tumors with a characteristic papillary or acinar growth pattern but without demonstrable mucin.

Large cell carcinoma. Cells larger than small cells with more cytoplasm, more vesicular nuclei with a prominent nucleolus. No demonstrable features of squamous cell carcinoma (keratin or intercellular bridges) or adenocarcinoma (mucin).

Results

Altogether 200 patients were included in the study, one hundred consecutive patients from January 1, 1965 at the Bispebjerg Hospital, and 100 consecutive patients from January 1, 1960 at the Gentofte Hospital.

Histological material from 13 patients was not suitable for evaluation, which leaves 187 patients for morphological classification. The histological classification according to WHO is shown in Table 1. Squamous cell carcinoma was diagnosed in 75 patients (40%), small cell carcinoma in 41 patients (22%), large cell carcinoma in 32 patients (17%), adenocarcinoma in 28 patients (15%), and 11 patients (6%) had other types of lung cancer.

Using a phenotypic classification 163 patients (87%) had a morphologically homogeneous tumor (Table 2), while 24 patients (13%) had a tumor demonstrating features of more than one cell type, as can be seen in Table 3. Eleven of these patients had features of small cell/large cell carcinoma, and 7 patients showed features of squamous cell/adenocarcinoma. Four of

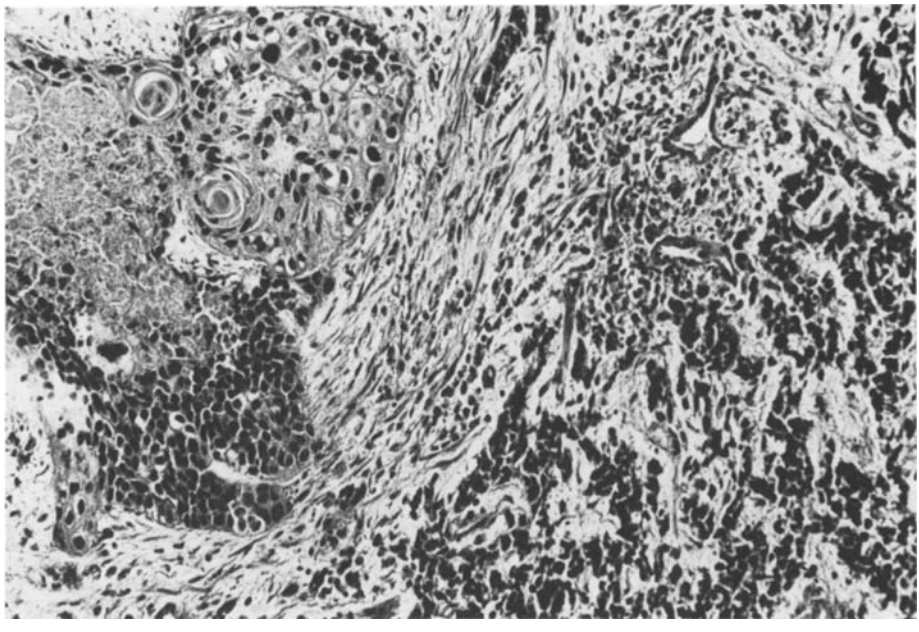

Fig. 1. Tumor with small cell and squamous cell features. × 50

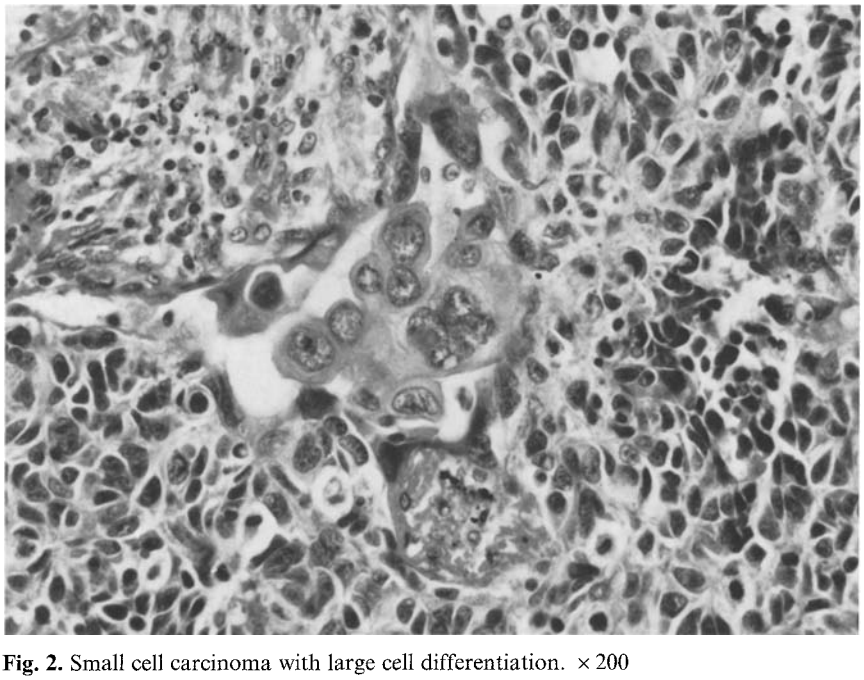

Fig. 2. Small cell carcinoma with large cell differentiation. × 200

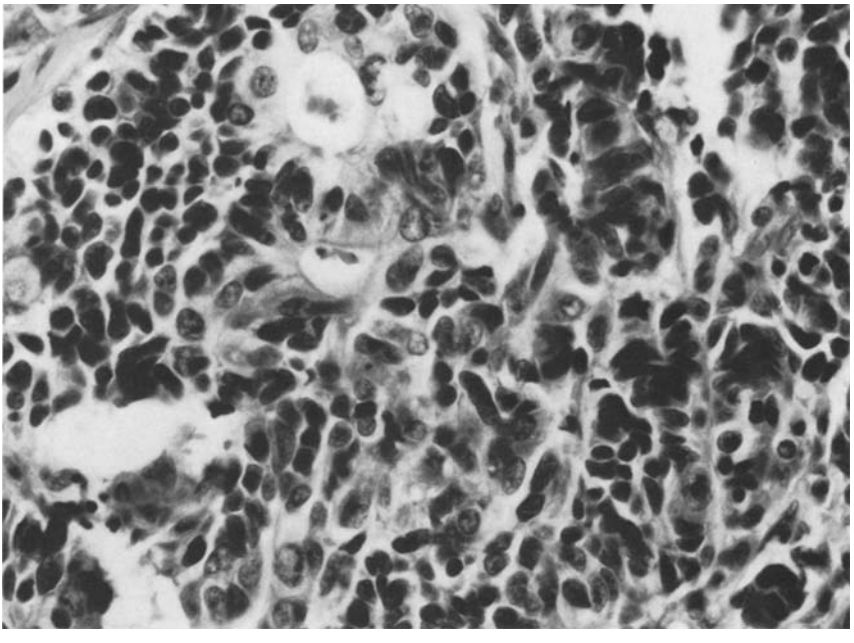

Fig. 3. Small cell carcinoma with tubular components. × 200

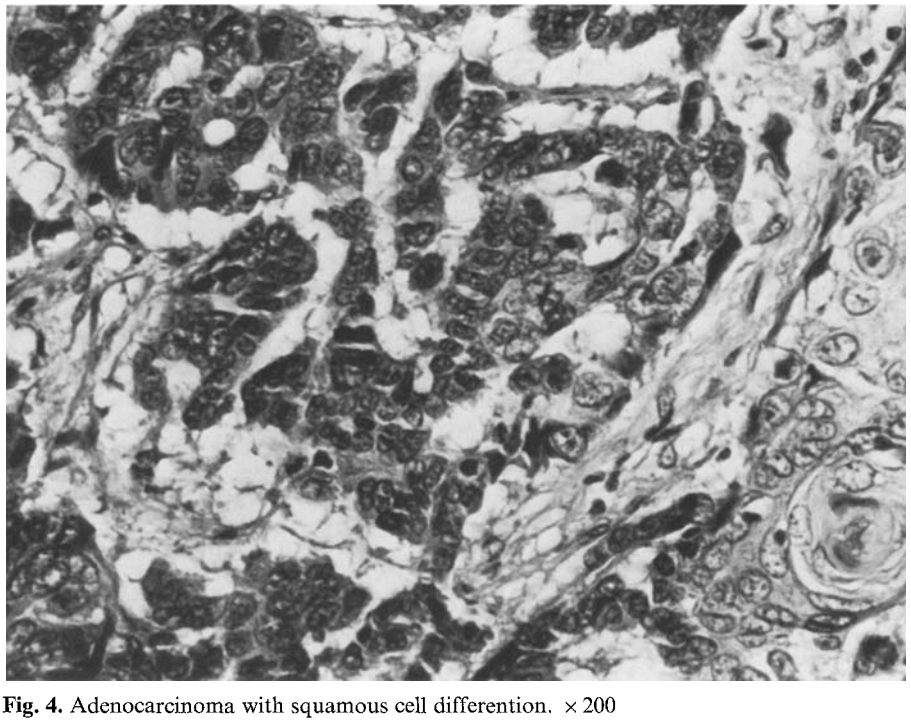

Fig. 4. Adenocarcinoma with squamous cell differention. × 200

Table 1. Histologic classification (WHO 1981)

	No. pts.	%
Squamous cell carcinoma	75	40
Small cell carcinoma	41	22
Large cell carcinoma	32	17
Adenocarcinoma	28	15
Adenosquamous carcinoma	4	2
Carcinoid	3	2
"Other"	4	2
Total	187	100

Table 2. Morphologic phenotypes – homogeneous tumors

	No. pts.	%
Squamous cell carcinoma	72	38
Adenocarcinoma	28	15
Large cell	32	17
Small cell	24	13
Carcinoid	3	2
"Other"	4	2
Total	163	87

Table 3. Morphologic phenotypes – heterogeneous tumors

	No. pts.	%
Small cell/large cell	11	6
Small cell/adenocarcinoma	2	1
Small cell/squamous cell	4	2
Squamous cell/adenocarcinoma	7	4
Total	24	13

the last patients had a morphological picture of classical adenosquamous carcinoma while 3 patients had tumors with two distinct cell types. Four patients had small cell/squamous cell carcinoma, and 2 patients small cell/adenocarcinoma.

Discussion

Due to the different treatment modalities for patients with small cell and non-small cell lung cancer an exact histopathological classification is needed. Morphological heterogeneity of malignant lung tumors was described as early as 1926 by Barnard (1926) and later by others (Azzopardi 1959; Hirsch et al. 1982). In their morphological description of small cell lung cancer

tubular formations, rosettes, squamous nests, giant cells and even mucin production have been noted. However, until recently, very little attention has been paid to these features.

From a histogenetic point of view great interest has centered on the coexistence of small cell lung cancer together with other main types of lung cancer (Gazdar et al. 1981). Pearse (1969) originally postulated that all APUD cells had a neuroepithelial origin. There is clear evidence that small cell lung cancer shares certain APUD characteristics with regard to hormonal production, and thus, the small cell lung cancer should have a different origin from the rest of endodermally derived bronchial mucosa and also from the non-small cell tumors. However, the morphological heterogeneity of lung cancers has been regarded as an important piece of evidence that all the major types of lung cancer have a common endodermal origin (Gazdar et al. 1981). Based on bronchial biopsies a morphologically mixed feature of small cell and large cell carcinoma is reported in 6–14% of the small cell lung cancers (Matthews and Gazdar 1981; Hirsch et al. in press), while at autopsy after chemotherapy 28–38% of the patients with small cell lung cancer are reported to have features of other histological types of lung cancer or had only a "non-small" histology (Abeloff et al. 1979; Matthews 1979). Transformation from one cell type to another is also seen in experimental models, such as nude mice studies and in vitro growth in defined media (Gazdar et al. 1981).

From a clinical point of view the heterogeneity of the tumors might call into question the diagnostic reliability of small pretreatment surgical biopsies. For patients with small cell lung cancer different clones of cells, demonstrated by flow cytometric measurements of DNA, have been reported in about 30% of the patients (Vindeløv et al. 1980), and electron microscopic features of more than one cell type in malignant lung tumors have also been demonstrated (Churg et al. 1980, McDowell and Trump 1981). It is not clear whether tumor heterogeneity with different clones of cells with different sensitivity to chemotherapy could explain a fairly good chemotherapeutic respons in some patients with tumors histologically classified as non-small cell lung cancer (Hansen and Rørth 1982). However, future prospective studies including other diagnostic modalities (i.e. immunohistochemistry) will have to be undertaken in order to elucidate the problem of heterogeneity further. It is necessary to define more exact criteria for classifying malignant lung tumors in order to predict the optimal therapy for the various subgroups of patients.

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