CORRELATION BETWEEN DOUBLING TIME OF VOLUME OF HUMAN LUNG TUMORS AND LABELING INDEX

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UDC 616.24-006.092-073.916

The labeling index (incubation with thymidine-H^3) and the volume doubling time (repeated roentgenography) were compared for three human lung tumors: two squamous-cell carcinomas with different levels of differentiation, and one hamartoma. The minimal doubling time (178 days) was found for the squamous-cell carcinoma with a lower level of differentiation and with the highest labeling index (19.0%). The hamartoma (a benign lung tumor) had the longest doubling time (1250 days) and the smallest labeling index (3.8%).

KEY WORDS: volume doubling time of tumors; labeling index; squamous-cell carcinoma; hamartoma.

Direct determination of the doubling time of the volume of a tumor is possible only for a few superficial neoplasms, but roentgenograms can also be used for this purpose [2, 3]. By investigating the kinetics of cell populations by autoradiography, the duration of the mitotic cycle of the proliferating cell fraction can be determined and the volume doubling time of the tumor calculated [5-8].

The simplest and most convenient method at the present time is by autoradiographic investigation of human tumors in vitro, by means of which the fraction of DNA-synthesizing cells, a parameter of proliferative activity, can be determined (as the labeling index). In this connection it is very important to investigate correlation between the labeling index and the volume doubling time of a tumor. By establishing such correlation, it will be possible to estimate the volume doubling time of the tumor from the value of the labeling index. This would be particularly important in cases when direct determination of the doubling time is impossible.

In the investigation described below the labeling index determined in vitro was compared with the actual volume doubling time of human lung tumors.

EXPERIMENTAL METHOD

Three patients admitted for observation or operation to the Thoracic Department, Institute of Experimental and Clinical Oncology, Academy of Medical Sciences of the USSR, were chosen for the investigation. Two of the patients had a carcinoma and the other a hamartoma of the lung.

Roentgenological investigation of the tumors was repeated three to five times (in the course of 10 months for carcinoma and 6 years for hamartoma), with different intervals between the examinations.

The mean diameter of the tumor was measured on the roentgenograms as half the sum of two mutually perpendicular diameters, one of which was maximal. The volume of the tumor was calculated on the as-

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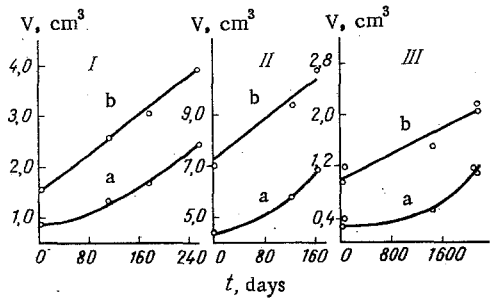

Fig. 1. Kinetic growth curves of lung tumors between normal (a) and semilogarithmic coordinates (b): I) squamous-cell carcinoma of the lung with keratinization (average level of differentiation); II) squamous-cell carcinoma of the lung with keratinization (high level of differentiation); III) hamartoma of the lung.

sumption that it was spherical. Kinetic curves were plotted on normal and semilogarithmic scales from these data and used to calculate the volume doubling time of the tumor by the method of least squares [2].

A piece from the periphery of the tumor was excized for autoradiographic investigation immediately after its removal. The tissue was cut into pieces measuring 2-3 mm and incubated in medium [1] containing thymidine-H^3 (1 μCi/ml medium) for 1 h at 37°C. Subsequent treatment of the material was by the usual method. The index of labeled nuclei for the whole population of tumor cells was determined in the autoradiographs.

EXPERIMENTAL RESULTS

Kinetic growth curves of the tumors between normal and semilogarithmic coordinates are shown in Fig. 1. The linear character of the semilogarithmic curves shows that growth of these tumors can be described by an exponential function of the form:

$$V = V_0 \cdot 2^{t/\tau},$$

where V_0 is the volume of the tumor at the first observation and τ the volume doubling time of the tumor. The volume doubling time of these tumors was 178 days (case 1), 278 days (case 2), and 1250 days (case 3).

Histological investigation of the tissue from both cases of lung cancer revealed a squamous-cell carcinoma with keratinization (Fig. 2a, b), but in the second case the features were more clearly defined. The stroma in this tumor was well developed. In the first case the tumor had a lower level of differentiation. Besides areas of squamous-cell carcinoma with keratinization and of solid structure, there was an area situated actually among the connective tissue in which the cells were larger and elongated (Fig. 2d).

The autoradiographic investigation revealed some correlation between the labeling index and the degree of differentiation of the tumor tissue. The fraction of DNA-synthesizing cells (19.0%) was highest in tumor 1, where areas of squamous-cell carcinoma with different levels of differentiation were found, parenchyma was predominant, and the cells were large and exhibited considerable polymorphism (Fig. 2d). The mean labeling index in tumor 2 was 11.3%. Cells in areas of keratinization and solid structure were labeled (Fig. 2c).

Hamartoma of the lung is a benign tumor which arises through dysembryogenesis. The autoradiographic investigation showed that the labeled cells in the hamartoma were single. In the very rare small nodules consisting of pale, large cells, the labeling index reached 10% (Fig. 2d). On the average the labeling index of the hamartoma of the lung was 3.8%. The doubling time, according to calculations, was 1250 days.

Comparison of the results for the value of the labeling index determined in vitro, the level of tissue differentiation, and the volume doubling time of the tumor indicates correlation between these parameters. Tumor 1, with the highest rate of growth, also had the highest labeling index and a lower level of differentiation. The hamartoma of the lung grew slowly and this was reflected in the longest doubling time and a low labeling index.

Hirai and co-workers [4] investigated one case of squamous-cell carcinoma of the lung by the same method. The volume doubling time of the tumor in this patient was 50 days and the labeling index 23%, in agreement with the present results. With respect to the volume doubling time of the tumor, the two cases of lung cancer in the present series can be classed as tumors with a low rate of growth, and their mean labeling index also was low.

Malaise and co-workers [5] describe the results of their own investigations and data in the literature on correlation between the rate of growth, labeling index, and histological type of human solid tumors. They found that the doubling time depends on the labeling index: the greater the doubling time, the lower the labeling index.

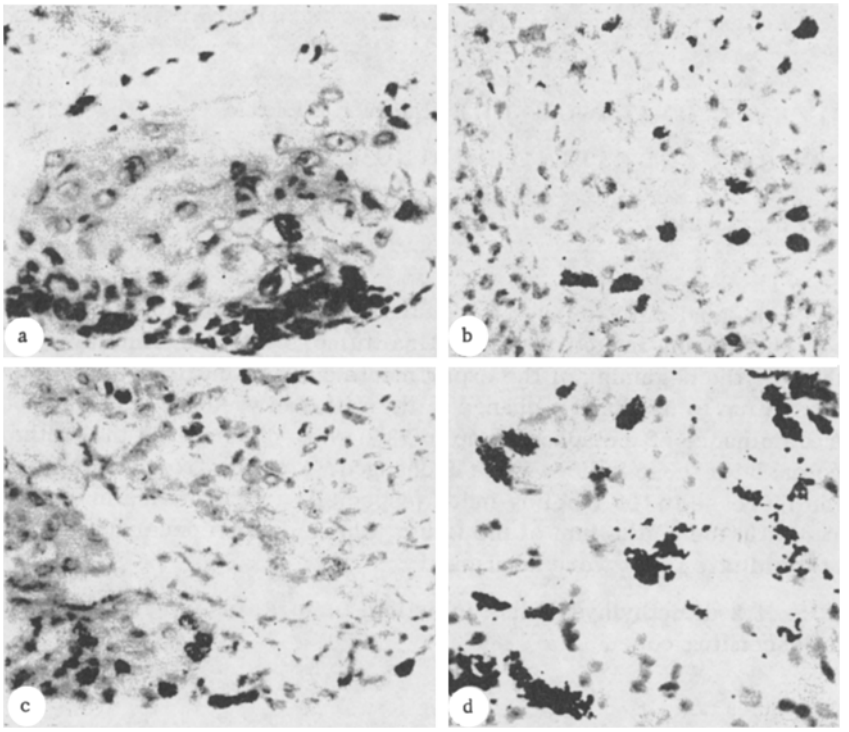

Fig. 2. Labeled cells in human lung tumors: a) squamous-cell carcinoma with keratinization (260×); b) area of solid structure (130×); c) area with low level of differentiation (200×); d) hamartoma: group of labeled cells and dust infiltration (200×).

Consequently, a definite correlation can be assumed between the labeling index determined in vitro and the volume doubling time of the tumor. To establish stricter correlations capable of quantitative description, much more factual evidence must be gathered.

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