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Review

Small Cell Anaplastic Carcinoma of the Lung

A Review of Growth Characteristics and Implications for Chemotherapy

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Summary. *Small cell anaplastic lung cancer is increasingly considered to be potentially curable. The opinion that this tumor is a rapidly proliferating one has not been substantiated by kinetic studies, and for this reason late relapse may occur in complete remitters. Differential rates of response/relapse in different tumor sites may be explained on the basis of heterogeneity in tumor kinetics.*

Introduction and Background

The purpose of this review is to update the growth characteristics of small cell anaplastic carcinoma of the lung (SCACL) and to correlate the data with certain clinical features of this disease. This tumor type comprises 19%–29% of all lung cancers in several large series [15, 28, 51]. The 1977 WHO classification further subtypes it into lymphocyte-like (oat cell), intermediate cell, and combined categories [14]. The most notable pathologic feature of clinical importance in SCACL is the widespread dissemination in a high proportion of autopsy cases. Even at presentation most patients have tumor spread beyond the chest [20]. There is a predilection for involvement of bone marrow, retroperitoneal organs, CNS, liver, and distant lung [27]. In adenocarcinoma and large cell carcinoma of the lung, dissemination beyond the chest is much less common than in SCACL, and this difference is even more marked in squamous cell carcinoma of the bronchus, in which the disease is confined to the thorax in almost 50% of autopsies [27].

Several studies have demonstrated a correlation between tumor growth rate and patient survival [22, 31, 45, 49]. Tumors which grow rapidly and do not respond to therapeutic intervention have the worst prognosis [41], although of course poor prognosis may often be the result of metastatic spread in the presence of a slowly growing primary tumor. The poor survival of SCACL following local therapies has been well documented [16, 33] and is comparable to the median survival of untreated histiocytic lymphoma. In an early Medical Research Council trial comparing surgery and radiotherapy in SCACL [16], there was an improvement in median survival of only a few weeks with radiation, but none with surgery. This is in spite of the sensitivity of this tumor to radiation. Such poor survival after local therapies could be taken as confirmation of the frequent dissemination of this disease, and would suggest that patients in whom no endeavor is made to control the disseminated disease will usually die within a few months.

In recent years the responsiveness of SCACL to chemotherapy has been will documented [5]. Intensive chemotherapy with certain combinations of agents has been reported to lead to response rates in excess of 95% and complete remission rates of up to 75% in selected patients. Survival beyond 2 years has been reported in 25%–50% of selected patients [10, 18]. This improvement in survival with chemotherapy has been so marked that recently several papers have discussed the prospects for cure in SCACL [1, 32, 37].

Dissemination, poor untreated survival, and therapeutic responsiveness, which are features of SCACL, are also characteristic of Burkitt's lymphoma, which is a malignancy with very rapid growth: the tumor volume doubles in a matter of hours [21]. In several chemotherapy studies more than half of Burkitt's lymphoma patients have been cured [52].

Within the last decade, Straus has popularized the concept that SCACL is a rapidly proliferating neoplasm [46, 47]. To many clinicians this explained the poor survival of untreated patients with the disease. Unfortunately, the small number of cases reported in these reviews and the imprecise nature of some of the data have resulted in a lack of appreciation of the true growth characteristics, as they have been examined to date. The following discussion of published data concerning the growth of SCACL is an attempt to correlate the kinetics with the clinical behavior of the disease.

Two commonly used means of examining the proliferative characteristics of human tumors are radiolabeled thymidine uptake studies [26] and doubling time studies [41]. Thymidine is utilized in DNA synthesis and DNA repair, but is virtually only taken up in S phase (DNA-synthetic phase). In the majority of human tumors, the growth fraction or the percentage of cells actively proliferating is small. Additionally, the proliferating cells are in various phases of the cell cycle [12]. Use of labeling indices is one method of assessing the proliferative potential of tumors [40]. This technique utilizes the fact that tritiated thymidine, which is an electron emitter, is incorporated into DNA in those cells in S phase.

Recent data show that the concentration of tritiated thymidine and emulsion exposure time are important variables [39, 42]. The specific activity that relates to the proportion of thymidine molecules labeled is important to a lesser extent. Threshold and background counts should also be considered. The influence of these variables on the labeling index should have been predicted on theoretical grounds, but this influence was not appreciated in early studies.

The use of serial X-ray measurements of metastatic lung lesions for calculation of tumor doubling times is well established. In 1956 Collins et al. [11] demonstrated exponential growth and deduced that the majority of volume

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Table 1. SCACL labeling index data from the literature

Study	^{3}HTdR incorporation technique (in vivo/vitro)	Radioautography details a) Concentration ^{3}HTdR b) Specific activity c) Emulsion exposure time (EE) d) Threshold and (background count)	Sites sampled (number of cases)	Median LI (%)	Range LI (%)
Muggia and De Vita [35]	Intralesional injection (in vivo)	a) 50 μCi/0.1–0.2 ml[a] b) 1.9 Ci/mmole c) 2 weeks EE d) Not stated	Metastatic lesions (5 cases)	19	8–24
Muggia [34, 36], same data both studies	Intralesional injection (in vivo)	a) 50 μCi/0.1–0.2 ml[a] b) 1.9 Ci/mmole c) 2–4 weeks EE[a] d) Not stated	Metastatic lesions (12 cases)	16.7	7.2–23.8
Livingston et al. [26]	Minced tumor, Hypaque-ficoll separation (in vitro)	a) 5 μCi/ml b) 1.9 Ci/mmole c) 1 day EE d) > 8 grains = labeled (B/g < 5 grains)	Sites not stated (5 samples)	24	19–30
Hainau et al. [19]	Tissue slices (in vitro)	a) 20 μCi/10 ml b) 25 Ci/mmole c) 4 weeks EE d) > 5 grains = labeled (B/g < 3 grains)	9 primary tumors 5 metastatic lesions Total 14 (all sites)	9 11.4 11.2	– – 1.9–28

[a] Variable techniques used, as noted above

doublings occur in the preclinical phase. Approximately 30 doublings in tumor volume were considered necessary to produce a 1-cm nodule from a 10-μm cell, assuming that the lesions were spherical and that the stroma was negligible. Apart from measuring errors, imprecision may also be due to the interpretation of collapse or consolidation as tumor extension. It is further noted that doubling time measurements relate to overall volume and give no indication of cell turnover. Although two reports have shown some variability of tumor growth, there is general agreement (and overwhelming supporting data) that it is exponential during the period of clinical observation in humans [2, 4, 6, 7, 11, 17, 43, 45]. There is also a considerable amount of doubling time data showing that pulmonary metastases grow faster than the primary tumor. This has been established for breast cancer [23, 24, 38, 44] and colorectal cancer [50]. In the former, Kusama et al. (1972) demonstrated that the doubling time was slowest in the primary tumor, and progressively faster in pulmonary, lymph node, and local metastases [23]. Although there are no reports confirming a similar phenomenon in lung cancer, it is the author's experience that this is also the case in SCACL, on the basis of unpublished data.

Specific Data for Lung Cancer with Special Reference to SCACL

Labeling Index Data. Table 1 reviews the labeling index data for SCACL [19, 26, 34–36]. There are four sets of data shown. In these, not only are the methods of tritiated thymidine incorporation variable, but also the factors that are known to effect the labeling index, such as concentration of tritiated thymidine, specific activity, emulsion exposure time, and threshold/background counts. In three of the four studies [34–36], there are important intra-study variations in techniques, and some technical data are not reported. In all studies, median labeling indices range from 9% to 24%, and there is quite a wide range in labeling indices for the individual tumors. Although Muggia and co-workers [34, 36] compared labeling indices for the different lung cancer types because of the intra-study variations their data [34, 36] can no longer be used for such a comparison. A more recent report from Hainau et al. [19] compared the labeling indices of the different lung cancer types (Table 2). Apart from adenocarcinoma of the lung, the median labeling indices of the different lung cancer types are comparable. Note the wide range in labeling indices in individual cases.

Table 2. Labeling index data for the different lung cancer types [19]

Histologic type	Number of biopsies	LI range (%)	Median LI (%)
Squamous cell	30	0.6–26.2	7.5
Large cell	29	1.6–26.4	11.0
Adenocarcinoma	18	0.4–20.6	4.9
Small cell anaplastic	14	1.9–28.0	11.2

It is also noted from Table 1 that most of the studies have only examined labeling indices of metastatic disease. There is little published data on labeling indices of primary lung tumors, except that of Hainau et al.

Doubling Time Data. The median doubling time of 24 days (mean 33 days) for SCACL quoted by Straus was based on data from only five patients [46, 47].

In 1977, the present author took part in a radiographic doubling time study of SCACL [3]. Two methods of tumor measurement were assessed and a 'cut out' technique was found more reliable than caliper measurements. Lesions were traced onto transparent plastic, the areas measured and the

Table 3. Radiological appearance and tumor location in SCACL, 392 cases [8]

Radiologic finding	Percent of total
Central tumor with hilar nodes ± mediastinal widening	64
Peripheral tumor ± mediastinal widening	19
Only indirect changes: atectasis, pneumonia, effusion	8
Only nodes involved	6
Central tumor with no obvious nodes	3

Table 4. Doubling time according to histologic subtype, size and location of the tumor [3]. Differences not significant (Wilcoxon analysis)

	Number of patients	Doubling time (days)	
		Median	Range
Histologic subtype			
Lymphocyte-like	8	85	50–146
Intermediate cell	4	90	25–160
Size			
Large (> 80 cm^3)	7	75	50–126
Small (< 40 cm^3)	5	115	25–160
Location of lesion			
Central	7	75	50–126
Peripheral	5	95	25–160

Table 5. Doubling times of different lung cancer types

Number of cases	D.T. range (days)	D.T. mean (days)	D.T. median (days)	Reference
Small cell anaplastic				
5	17– 71	33	24	[46, 47]
21[a]	9–160	71	67	[3][a]
46	17–264	–	68	[48]
20	12–209	79	58	[25]
Adenocarcinoma				
43	17–590	183	–	[46, 47]
18	45–529	–	154	[47]
Squamous cell				
99	7–381	100	–	[46, 47]
103	24–341	–	91	[48]
Large cell				
33	48–112	92	–	[46, 47]
24	9–160	–	68	[48]

[a] Includes unpublished data from author

volumes calculated at different time points during the pretreatment period. In that study the main assumptions made were that the growth rate was constant and the lesions were spherical. Because of the data of Collins et al. and numerous other workers [2, 4, 6, 7, 11, 17, 30, 43, 45], the former assumption is valid. The latter assumption is less important with exponential growth. Apart from difficulties in obtaining X-rays, there were also technical difficulties because of the nature of the tumor. Table 3 shows the anatomical sites and associated radiological findings in small cell lung cancer [8]. Most tumors are central and may be associated with atelectasis, pneumonia, or effusions in some cases. The peripheral lesions are the most readily measured lesions, but only make up a fifth of cases. As might be expected, in the study described a much higher percentage of the lesions were peripheral, but there did not appear to be any significant difference in the doubling time according to site distribution of the primary (Table 4). Neither was there any association with size of the lesion, as further confirmation that smaller lesions are not more rapidly growing than larger lesions. Histologic subtype did not seem to be important. The doubling times of the 12 lesions showed considerable variation within a range of 25–160 days.

Table 5 reviews lung cancer doubling time data from the literature. Included are some unpublished data of the present author. The accumulated number of SCACL cases shown amounts to more than 80 cases. The median doubling time is about 70 days, within a range of 9–264 days, which is similar to that of squamous and large cell carcinoma. The long doubling times of most adenocarcinomas suggest a more slowly growing malignancy and are consistent with the labeling index data of Hainau et al. [19]. Note the wide ranges in doubling time values for all lung cancer types. The doubling time data are relevant only to the primary tumor, and at present published data giving doubling time values for metastatic lung cancer are lacking.

Conclusions

Let us briefly review what has been discussed, and attempt to draw conclusions.

1) The *labeling index data* suffer from variability of technique and inadequate study size. More correlations between primary tumor and metastases need to be made.

2) There are *few doubling time studies,* and these have not examined metastatic tumors.

3) Both *thymidine uptake and doubling time studies* suggest that adenocarcinoma of the lung is a more slowly proliferating neoplasm than SCACL and that with regard to kinetic data SCACL tumors are not too unlike squamous and large cell carcinomas. This similarity, however, may not apply to kinetic differences between primary and metastatic tumors, as this aspect requires further investigation.

4) The wide ranges seen in both labeling indices and doubling times suggest marked heterogeneity between individual tumors.

5) The *doubling time data for SCACL* suggest that the primary tumor is not as rapidly proliferating as was believed previously. At least for the primary site, the risk of relapse continues for much longer than 2 years in a patient who achieves complete remission. Four to five years may be more realistic, but because of the wide doubling time range, some of the more slowly proliferating tumors may result in relapse as late as 10 years. See Fig. 1 for diagrammatic representation.

It is possible that differences in growth rate exist between primary tumor and metastases, as in breast cancer. If so, the dissemination is an even more important factor in determining prognosis and certainly will be more important than the doubling time of the primary tumor in untreated patients.

Shackney et al., in a recent review of doubling time data for solid tumors, discuss the relapse patterns for rapidly growing and slowly growing tumors [41]. For rapidly growing tumors the fractional cell kill is greater than for slowly growing

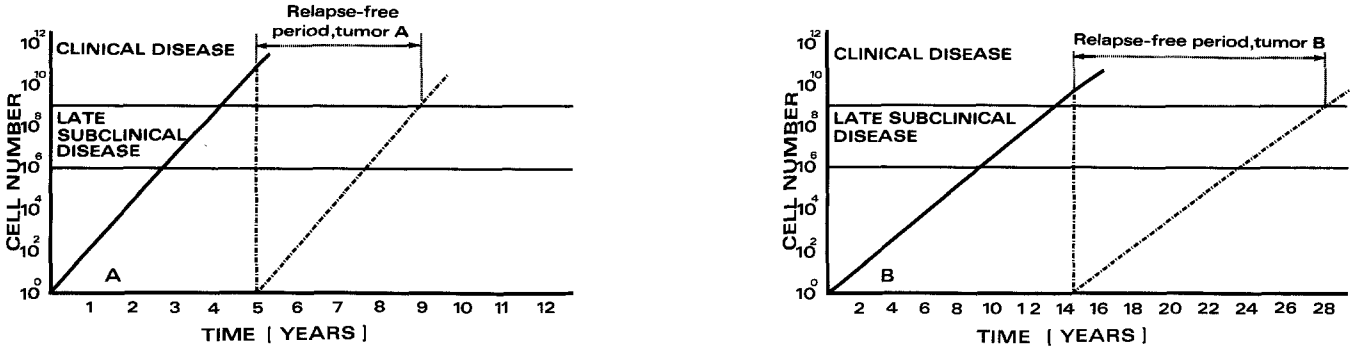

Fig. 1. Effect of D.T. on time to relapse; schematic representation of two tumors, with doubling times of 70 days (A) and 210 days (B). Shown are the relapse-free periods assuming reduction in tumor burden to one cell before regrowth

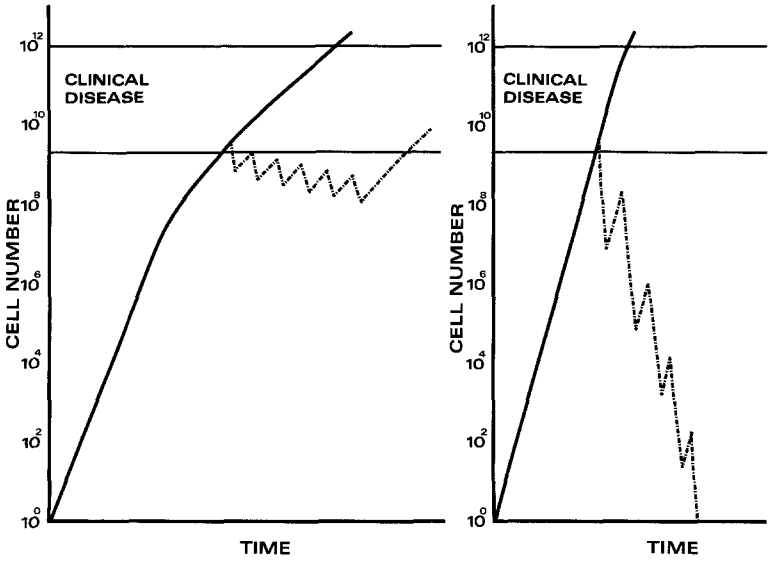

Fig. 2. Different doubling times of primary tumor and metastasis; schematic diagram showing a slow-growing primary tumor on the *left.* With chemotherapy tumor volume is reduced below clinical detection, but reappearance occurs later in the course. In the more rapidly growing metastasis on the *right,* the log cell kill is greater, resulting in eradication

tumors, and complete ablation is therefore more likely for these tumors. They will usually relapse early unless ablation is achieved. For slowly growing tumors, the fractional cell kill is less, and a complete remission merely represents subclinical disease. Relapse is inevitable.

Figure 2 is a schematic representation showing such a situation. A slowly growing primary tumor is compared with a more rapidly growing metastatic tumor. In the rapidly growing metastasis complete ablation is achieved, but at a comparable level of detection (10^{11} cells) the primary tumor is reduced merely to a subclinical level. If in SCACL some metastases do grow more rapidly than the primary, differential responses and rates of relapse might be expected. Such patterns have been reported in SCACL [5, 9], with relapse most often occurring at the primary site [9, 13, 29]. However, the exact relationship of these differences to the growth characteristics remains unknown. Nevertheless, it is probable that the poor prognosis is largely related to the metastatic potential of the disease, and the optimism about the treatment of SCACL expressed by the Vanderbilt group [37] and others may be premature in the light of late relapses in other malignancies. Researchers should be guarded about the long-term outlook of patients in complete remission.

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