



SMALL CELL CANCER OF THE LUNG:
AN INITIAL EVALUATION OF THE YALE TREATMENT PROTOCOL

David Jonathan Birnkrant

1985

YALE



MEDICAL LIBRARY

Permission for photocopying or microfilming of "Small
Cell Cancer of the Lung: An Initial
(title of thesis)
Evaluation of the Yale Treatment Protocol"

for the purpose of individual scholarly consultation or refer-
ence is hereby granted by the author. This permission is not
to be interpreted as affecting publication of this work, or
otherwise placing it in the public domain, and the author re-
serves all rights of ownership guaranteed under common law
protection of unpublished manuscripts.

David Birnkant


(Signature of author)

DAVID J. BIRNKANT

(Printed name)

3/7/85

(Date)



Digitized by the Internet Archive
in 2017 with funding from
Arcadia Fund

<https://archive.org/details/smallcellcancero00birn>

SMALL CELL CANCER OF THE LUNG:
AN INITIAL EVALUATION OF THE YALE TREATMENT PROTOCOL

A Thesis Submitted to the Yale University
School of Medicine in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Medicine

by

David Jonathan Birnkrant

1985

ABSTRACT

SMALL CELL CANCER OF THE LUNG:

AN INITIAL EVALUATION OF THE YALE TREATMENT PROTOCOL

David Jonathan Birnkrant

1985

A review of small cell cancer of the lung (SCCL) is presented, followed by initial results from the Yale University treatment protocol for SCCL.

The review includes selected topics on the epidemiology, etiology, cytogenetics, cytomorphology, cells of origin, cell products, clinical diagnosis, staging, prognosis, and treatment of SCCL. The tumor emerges as one of diverse clinical behavior and cellular character; it remains poorly understood. Despite intermediate or slow doubling time, dissemination of the tumor--microscopic or gross--is the rule at diagnosis. Modest success has been achieved in treatment, allowing a small group of patients to go on to long-term survival (4 or 5 years), but most patients relapse after initial response to therapy and second-line therapy is rarely effective. Special attention is paid to treatment design, including the role of prophylactic cranial irradiation (PCI), adjuvant radiation therapy, and the concept of local tumor control.

Results from the Yale University treatment protocol are presented. Thirty-nine evaluable patients were prospectively randomized to therapy with cyclophosphamide, Adriamycin, and vincristine (CAV) every 21 days or CAV alternating with Etoposide

(VP-16-213). All limited disease (LD) patients underwent thoracic irradiation; complete responders received PCI. Eighty percent of LD patients achieved complete response as did 12% of extensive disease (ED) patients. Projected median survival ranged from 198 days for ED non-responders to 560 days for LD complete responders. It is too early to report on long-term survival. Addition of Etoposide (E) afforded no significant survival advantage over the CAV regimen. Etoposide added no significant additional toxicity; in fact, the percentage of patients experiencing infections requiring hospitalization was lower in the CAV/E group (6% vs. 33%). This may be the result of a smaller proportion of patients on CAV/E experiencing leukopenia (44% vs. 76%).

ACKNOWLEDGEMENTS

Dr. Carol Portlock was the perfect thesis advisor ($p < .0001$). Her scholarship was complemented by a commitment to scientific open-mindedness--which is to say: She came to the rescue when I was up to my elbows in it, but never imposed her point of view. Thus I had the happy experience of learning through discovery. Her gracious good humor was infectious and her tolerance of my eccentric work habits wonderful. Thanks to her, this thesis was transformed from a requirement for graduation into a rewarding scientific project.

Dr. Diana Fischer was my Virgil through the inferno of statistics. Because she never discussed this study except in the broader context of statistical concepts, I've gained a sense of the fundamentals of experimental design. Dr. Fischer shared her time, knowledge, and enthusiasm with a generosity for which I am very grateful.

Mrs. Terry O'Connor did the most extraordinary things with a computer and she did them better and faster than I had thought possible. No deadline was so pressing as to disturb her reassuring calm. I am lucky to have enjoyed the benefit of her expertise and good-naturedness.

Mrs. Rosemary Slattery was always ready with all manner of encouraging words and warm smiles. When things got rough, she would regale me with her classic answer to my desperate "Rosemary, will Dr. Portlock be around next week?": "Well, I've worked with her for eight years, and she hasn't taken a vacation yet...."

A large "thank you" to the physicians who made me welcome in their offices, made it possible for me to review patients charts, and made time to answer my questions: Drs. Fischer and Wiggans; Dr. M.E. Katz; Drs. Levy, Farber, Bobrow, and Lundberg; Dr. J.E. Brown; Dr. G.T. Kenneally; and Dr. I.S. Lowenthal.

Dr. J. Bernard Gee read this thesis for the Department of Internal Medicine. His criticisms and comments were uniformly helpful. At his suggestion, I was in contact with...

Dr. Raymond Yesner, who very kindly took the time to meet with me on an "emergency" basis. Dr. Yesner's summary of the conclusions reached at the September, 1984 meeting of the pathology panel of the International Association for the Study of Lung Cancer made it possible for me to include mention of an exciting new approach to the histological classification of small cell lung cancer in this paper.

Thank you, Mrs. Fran DeGrenier, for typing strange words at strange hours and meeting every deadline.

Finally, if a dedication were appropriate for so modest a piece of work, it would be to my parents, with love.

TABLE OF CONTENTS

PART I: THE BASICS	1
Introduction	1
Epidemiology and Etiology	2
Cytogenetics, Cytomorphology, Cells of Origin and Cell Products	5
Clinical Diagnosis	16
Staging and Prognosis	21
PART II: TREATMENT	30
Overview	30
Treatment of Limited-Stage Disease and Treatment- Related Toxicities	36
Extensive-Stage Disease and Experimental Therapies	45
Closing Comments	49
PART III: THE STUDY	53
Methods	53
Patients and Results	57
Discussion	67
REFERENCES	71
TABLES	
Table 1: Age Standardized Percentage Distribution of SCCL by Cigarette Smoking Habit	85
Table 2: Distribution of Excess (Presumably Radiation- Induced) Bronchogenic Cancers by Radiation Exposure Group	86
Table 3: Symptoms of SCCL	87
Table 4: Percent Distribution of Metastases at Presentation and at Autopsy in Two Studies	88
Table 5: Recommendations for Restaging	89
Table 6: Prognostic Factors in SCCL	90

Table 7:	Treatment Results in SCCL: Selected Studies	91
Table 8:	Long-Term Survival (<u>></u> 5 years) in SCCL	92
Table 9:	Treatment Protocol for Limited Disease	93
Table 10:	Treatment Protocol for Extensive Disease	94
Table 11:	Patient Characteristics by Treatment Arm	95
Table 12:	Metastatic Sites at Diagnosis in Extensive Disease (ED) Patients by Treatment Arm	96
Table 13:	Sites of Relapse	97
Table 14:	Treatment Results: Response and Time to Relapse	98
Table 15:	Survival	99

FIGURES

Figure 1:	Time to Relapse for Responders (CR + PR) by Disease Extent	100
Figure 2:	Time to Relapse for Extensive Disease Patients by Response Group	101
Figure 3:	Time to Relapse for Limited Disease Patients by Treatment Group	102
Figure 4:	Time to Relapse for Extensive Disease Patients by Treatment Group	103
Figure 5:	Overall Survival	104
Figure 6:	Survival for Responders (CR + PR) by Disease Extent	105
Figure 7:	Survival for Extensive Disease Patients by Response Group	106
Figure 8:	Survival for Limited Disease Patients by Treatment Group	107
Figure 9:	Survival for Extensive Disease Patients by Treatment Group	108

List of Abbreviations

A	= Adriamycin (doxorubicin)
ACTH	= adrenocorticotrophic hormone
ADH	= antidiuretic hormone
APUD	= Amine Precursor Uptake and Decarboxylation
BN	= bombesin
C	= cyclophosphamide
CBC	= complete blood count
CEA	= carcinoembryonic antigen
CK-BB	= BB isoenzyme of creatine kinase
CNS	= central nervous system
CR	= complete response
CT	= computerized tomography
DDC	= dopa decarboxylase
DNA	= deoxyribonucleic acid
E	= Etoposide (VP-16-213)
ECOG	= Eastern Cooperative Oncology Group
ED	= extensive-stage disease
EKG	= electrocardiogram
HCG	= human chorionic gonadotropin
INH	= isoniazid
LD	= limited-stage disease
LDH	= lactic dehydrogenase
LI	= labeling index
M	= methotrexate
MoAb	= monoclonal antibody
NCI	= National Cancer Institute
NR	= non-response
NSE	= neuron specific enolase
P	= cis-platin
PCI	= prophylactic cranial irradiation
PPD	= purified protein derivative
PR	= partial response
PS	= performance status
PTH	= parathyroid hormone
RT	= radiation therapy
SIADH	= syndrome of inappropriate secretion of antidiuretic hormone
SVC	= superior vena cava
TNM	= tumor-nodes-metastases
V	= vincristine
VA	= Veterans Administration
WHO	= World Health Organization

SMALL CELL CANCER OF THE LUNG:
AN INITIAL EVALUATION OF THE YALE TREATMENT PROTOCOL
PART ONE: THE BASICS

Introduction

Small cell cancer of the lung (SCCL) is a disease whose significant incidence and poor prognosis make it of major concern. This is especially true in a society like ours, with its increasing emphasis on preventive medicine and the containment of health care costs. The etiologic factors in the disease--tobacco smoking, ionizing radiation, asbestos and chemicals--make SCCL somewhat preventable. Treatment for SCCL is often initially effective, but relapse is the rule and the disease then proves resistant to second-line therapies. In light of the relatively poor results achieved with today's state-of-the-art therapy, it would be wise to direct concerted efforts toward prevention of SCCL.¹ Unfortunately, the medical profession has made no successful attempt to wrest responsibility for such a goal from businessmen and politicians. As long as tobacco remains an important, heavily subsidized cash crop and images from Madison Avenue dictate our behavior, the individual medical practitioner--haranguing his patients about smoking--will remain at best a nagger, at worst a bore.

This paper will emphasize the diversity in data on SCCL. Even the most basic aspects of the disease are poorly understood and the lack of an effective treatment strategy reflects that ignorance. The

first part of the paper takes the form of a review; the second part presents initial data from the Yale University treatment protocol for SCCL.

Epidemiology and Etiology

Lung cancer death rates have been increasing at a spectacular rate when compared to that of other cancers.² After World War II, lung cancer death rates for men began rising at a faster rate than straightline projections would have predicted. The rate curve for women has followed suit for the last twenty years.^{1,2} Projections for 1984 show that lung cancer will be the most common cause of cancer deaths for men and the second most common cause of cancer deaths for women.²

Weiss has reviewed numerous studies on the incidence of SCCL.³ He reports W.E. Morton's unpublished data on SCCL rates in Portland, Oregon for the period 1968-1972. The disease was more frequent in men than women. Mean annual rates per 100,000 population were 13 for males, 4 for females. In contrast, Annegers et al.⁴ reported a rate of 6/100,000 among males in rural Olmstead County, Minnesota for the period 1965-1974. This lower rate is consistent with the notion that SCCL is less common in rural areas.³

The median age at diagnosis in most series is about 60 years.⁵ The Philadelphia Pulmonary Research Project studied the natural history of lung cancer in men 45 years of age and older, each of whom was followed for ten years.⁶ Unpublished data from the study, quoted

by Weiss,³ show the highest incidence of disease among men 55-64 years of age. The study reported the highest rate of lung cancers in general, irrespective of subtype, in the 60- to 64-year-old age group. In contrast, Annegers et al.⁴ found their highest incidence rate among men 75 years or older for the period 1965-1974.

SCCL is generally quoted as accounting for 20-25% of all lung cancers.⁷ When the data are examined, however, the frequency of small cell as a percentage of all typed cancers varies widely. In Weiss's review,³ SCCL accounts for 13.7% - 39.6% of all typed lung cancers among men and 9.4% - 31.3% of lung cancers among women, depending on the study consulted. Perhaps these ranges represent differences in histological interpretation, or differences in incidence related to the population observed (the highest relative incidence figures come from a study done in Iceland⁸). Kyriakos and Webber,⁹ reporting on lung cancer in young adults, have found a rate of 13% SCCL among patients of all ages with lung cancer at Barnes Hospital, St. Louis. Their review of the literature revealed that SCCL accounted for 2-38% of lung cancers in several large series. Interestingly, these authors found a slightly higher relative incidence of SCCL (24%) among younger patients (45 years of age or less). Kennedy¹⁰ found a remarkably high proportion of small cell tumors (65%) in his series of 40 lung cancers occurring in patients under the age of 40 in England. In contrast, Putnam¹¹ at Walter Reed Army Medical Center found 17% small cell tumors among 24 patients with lung cancer under the age of 40.

The male:female ratio of SCCL is generally thought to be higher than for other types of lung cancer, with a ratio of 3 males:1 female reported by Morton.³

Etiological factors in SCCL include exposure to tobacco smoking, ionizing radiation, asbestos, chemicals, metals, and possibly air pollution. Pathogenesis of the disease is not well understood; the tumors are usually central in location and are presumed to arise, like squamous cell carcinoma, through chronic irritation, mucosal denudement, and absorption of carcinogens.¹² The cells of origin of the tumor are of great interest and will be discussed later on.

There is probably a dose-response relationship between cigarette consumption and the development of SCCL. The Philadelphia Pulmonary Neoplasm Research Project's data supported this notion.¹³ Auerbach et al.¹⁴ found that small cell as a percentage of all lung cancers rose from 14.5% for ex-smokers progressively to 31.1% for those patients smoking more than two packs a day. (See Table 1.) This rise was not seen in other histological subtypes. Of note is the possibility that cessation of smoking is associated with longer survival in SCCL, even when patients stop at the time of diagnosis.¹⁵

The link between exposure to ionizing radiation and SCCL is a strong one. Archer et al.¹⁶ compared rates of lung cancer and its subtypes among uranium miners to the rates expected for a matched group without radiation exposure. The authors expected to find 14.06 respiratory cancers in their study group. Instead, 107 cases were recorded among the miners, 66 of which were SCCL (62%). In the

matched control group, SCCL should have accounted for 14.05% of the lung cancers. There was, in addition, a dose-response relationship found for SCCL with increasing radiation exposure. These data appear in Table 2. Unlike smoking, then, radiation exposure may produce a predominance of small cell cancers in the lung. Agreement on this point is not universal, however.³

Asbestos and chemicals have been implicated in the etiology of lung cancers in general. Although data on subtypes is limited, SCCL appears to be associated with exposure to these agents. The role of smoking in the carcinogenicity of asbestos is still not clear; is asbestos a carcinogen or a synergistic agent which promotes cancer in smokers? The chemicals for which there is evidence of carcinogenicity in humans include: "polycyclic aromatic hydrocarbons, certain metals or their compounds, and certain simple organic chemicals."³ The list of possible carcinogens grows longer every day, but the strict scientific criteria needed to show causality make such proof a task that is pain-staking, if not impossible.

Cytogenetics, Cytomorphology, Cells of Origin, and Cell Products

The basis of understanding the small cell tumor lies in an understanding of its component cells. One approach to these cells is through cytogenetic studies. Do the chromosomes of the tumor have identifiable characteristics?

Wurster-Hill and Maurer¹⁷ studied the chromosomes of patients' SCCL tumors using direct bone marrow preparations and trypsin-Giemsa banding. Chromosome number and structural aberrations (markers) were frequent and highly variable. Chromosome number (ploidy, DNA index) in untreated patients ranged from hypodiploid to polyploid with the latter most common (the chromosome count was typically in the 80's). A structural abnormality of chromosome #1 was found in 14 of the 18 patients with karyotypic abnormalities (total patients = 26). But very few markers were common to two or more patients and the consistency of given markers among the cells from one patient was usually poor. The presence of cells with different abnormalities of chromosome number in the same patient (e.g., diploid and polyploid) was discovered. Vindelov et al.¹⁸ found that ploidy in their SCCL tumor cells could be grouped into near-diploid, near-triploid, and near-tetraploid values. Each of five patients was found to have two clones with different chromosome number in a single metastasis (17% of the total patients). The authors view this as evidence that SCCL, at least for some patients, is not monoclonal. That is: new cell lines evolve from the original tumor. These cell lines may have characteristics (clinical, biochemical) that are entirely different from those of the original tumor. The heterogeneity of the SCCL tumor--a concept emphasized in this paper--may lie in the evolution of more than one cell line from the original tumor.

Whang-Peng et al.¹⁹ found two distinct stem lines in 2 of their 12 cell lines cultured from human small cell lung cancer tissue.

These authors describe a consistent, acquired chromosomal abnormality--a deletion in the short arm of chromosome #3--present both in SCCL cell lines and in fresh clinical specimens cultured for 2 days in a serum-free medium. Chromosome studies of other types of neoplasms have not shown a specific abnormality of chromosome #3. The data of Wurster-Hill and Maurer (abnormality of chromosome #1) do not fit easily into the scheme of Whang-Peng et al.; an explanation of the discrepancies awaits elucidation. Whang-Peng et al. appear to have found a specific, acquired somatic cell defect (deletion 3p, 14-23) associated with continued replication of SCCL tumor cells. If this holds true, the diagnosis and treatment of SCCL will be aided--especially if the function of the genes present in the region of chromosome #3 where the deletion was found can be understood.

Another approach to the cells of the tumor is to ask: where does SCCL arise from? That is, which cells in the lung first acquire the chromosomal abnormalities, due to exposure to carcinogens, which lead to the growth of a tumor?

Hattori et al.²⁰ studied 24 cases of oat-cell (small cell) carcinoma of the lung and four cases of bronchial carcinoid tumor both under the electron microscope and biochemically. They found that SCCL tumor cells were characterized by the presence of neurosecretory-type granules (NSGs) of 800-2000 Angstroms, almost identical to but somewhat smaller than the NSGs found in 4 samples of bronchial carcinoid tumor. NSGs were not found in 139 samples of other types of lung tumors studied. Serum serotonin level was elevated in 13 of 20

small cell cases and the degree of elevation seemed to correlate with the number of NSGs present in the tumor cells. Serotonin level in tumor tissue was elevated in 7 of 12 cases of SCCL but in only 1 of 4 cases of bronchial carcinoid tumor. In 5 of 7 cases of SCCL, both serotonin and ACTH were elevated in tumor tissue samples. Other types of lung cancer, which lacked NSGs, showed no elevation of serotonin activity with the exception of one case of squamous cell carcinoma (and one case of pleurisy due to collagen vascular disease). The authors noted that the NSGs they found in bronchial carcinoid and SCCL were identical to those which had been previously described by Bensch et al.²¹ in the Kulchitsky-type cells in bronchial mucus glands. Hattori et al. thus concluded that "oat-cell carcinoma is a special type of lung tumor producing neurosecretory-type granules and a highly malignant variant of bronchial carcinoid tumor which is originated from neurosecretory-type cell (Kulchitsky-type cell) found in bronchial glands."²⁰ This is a remarkable statement, for the authors have found an association between electron microscopic characteristics of the tumor (NSGs) and tumor products (serotonin, ACTH) known to have clinical significance as ectopic hormone products of SCCL tumors.²² Moreover, the ultrastructure of the tumor cells has provided a clue to cell origin: the Kulchitsky-type cells of bronchial glands. The latter can produce serotonin from tryptophan and 5-hydroxy-tryptophan, which means they fit into Pearse's conception of an APUD (Amine Precursor Uptake and Decarboxylation) cell.²³ APUD origin would, in turn, imply a way of attacking the embryological lineage of SCCL's

cells of origin and relate SCCL to other cells of APUD origin in the body. In fact, the above associations reach beyond our ability to apply them. Indeed, Hattori et al.²⁴ examined the cytomorphology of SCCL tumors in relation to response to therapy in an article published five years after the one already discussed. Surprisingly, although almost all SCCL tumor cells were found to contain NSGs, the cells from tumors which did not respond to combination chemotherapy showed few or no NSGs. Some of the tissue specimens used in the study were obtained from autopsy material, and it is possible that chemotherapy affected the cell structure. Alternatively, a cell line without NSGs could have arisen from the original tumor. Still, the lack of NSGs in the non-responder group shakes the foundation of attempts to characterize SCCL at an ultrastructural level in a way that is consistent with the presumed cells of origin.

Tischler²⁵ notes that the APUD concept has been elucidated and revised since its initial introduction. APUD cells are now known to occur in two distributions in the lung: as scattered Kulchitsky-like cells and as organized groups of cells called neuroepithelial bodies. Both occur in close proximity to nerve endings. The secretory products and physiological role of APUD cells in the lung are obscure. While the APUD concept may explain the source of some of the hormones SCCL tumors produce, cytogenetic abnormalities--"derepression of the genome"--might also account for production of ectopic hormones.²⁶

Still, APUD has been used as a window to the study of SCCL's ectopic hormones. A wide variety of such hormones have been identified and include ACTH, ADH, calcitonin, glucagon, HCG, serotonin, PTH, and estradiol.^{18,22,27} The frequency of ectopic hormone production by small cell tumors is not known; it is clear, however, that clinically apparent syndromes that can be traced to these hormones are much rarer than production of the hormones themselves. Thus, while more than 50% of patients may have abnormally high levels of hormones such as ACTH, ADH and calcitonin, clinical syndromes such as SIADH or Cushing's syndrome appear to occur in less than 10% of patients.²⁸ Richardson et al. point out that the identity of these tumor-produced "ectopic hormones" is not really known; they may or may not be identical to "normal" hormones and radioimmunoassays of these substances may be neither truly sensitive nor specific.²⁸

Despite these caveats, Science marches on. Baylin and Gazdar²⁹ have measured biochemical indices in SCCL with established relationships to APUD cells outside the lung. These include L-dopa decarboxylase (central to the APUD concept--it converts precursor amino acids into their corresponding amines); and calcitonin (produced by the APUD tumor medullary thyroid carcinoma). They also measured histaminase and beta-endorphin, neither of which is specific to APUD cell activity; still, both substances are thought to be involved in hormone production by cancers. The authors found that the biochemical parameters studied were not specific to SCCL and that there was great heterogeneity of findings between different patients with SCCL, among

different lesion sites (primary vs. metastatic) in the same patient with SCCL, and even within individual SCCL lesions. These data are viewed as a reflection of heterogeneous cell populations all of which are grouped together under the clinical term "small cell lung cancer." The authors noted that quantitatively, however, their endocrine parameters tended to group more with SCCL than with other lung tumors.

An attempt has been made to find tumor products which will prove to be specific markers of SCCL, whose concentrations are proportional to tumor burden, and which are present in enough patients to make measurement worthwhile. Three such newly described products are bombesin, the BB isoenzyme of creatine kinase (CK-BB), and neuron-specific enolase (NSE). I will describe a study of NSE as an example.

Carney et al.³⁰ studied serum NSE levels at diagnosis in 94 patients with SCCL. The levels were repeated during and after therapy. Sixty-nine percent of all patients had a serum NSE level more than 3 S.D. above control, including 87% of the patients with extensive-stage disease (ED). Mean serum NSE was significantly higher in patients with ED than in those with limited-stage disease. In 20 of 21 patients, all of whom had elevated NSE levels at diagnosis, serum NSE fell significantly as the patients responded to chemotherapy. In the one patient whose level remained unchanged, no response to therapy was achieved and the disease progressed. The NSE level dropped into the normal range for all patients achieving a

complete response.

Serial NSE measurements showed a good correlation between clinical condition and the level of the marker. For example, in 9 patients with raised NSE levels on diagnosis the levels fell to near normal range with therapy then rose again when the patients relapsed. NSE has been identified in all cell lines of SCCL tested; it has not been found in substantial amounts outside central and peripheral nervous system tissue, findings consonant with the fact that APUD cells and neurons tend to express much of the same genetic information—they are "neuro-endocrine programmed."²⁵ NSE thus has the potential to be a useful marker for SCCL; immunohistochemical staining of lung tissue for NSE might someday help in making pathological diagnoses.

A recent cytomorphological finding deserves mention. SCCL cells from biopsies and derived cell lines were shown to contain neurofilament-type intermediate filaments.³¹ Since the expression of these filaments is tissue type specific and thought to be unchanged after malignant transformation, another line of approach to the APUD origin and diagnosis of SCCL may have been uncovered.

Despite the uncertainties described, a picture begins to emerge of the cells that make up SCCL tumors. At a cytogenetic level, they are characterized by variable numbers of chromosomes (ploidy) and a specific acquired deletion of the short arm of chromosome #3--3p (14-23). The cells contain neurosecretory granules and appear to be of APUD origin. Although SCCL cells express a variety of biochemical

products, including certain hormones which account for clinical syndromes associated with the disease, truly useful biochemical markers for SCCL, which combine sensitivity and specificity, may include neuron-specific enolase (NSE); bombesin (BN); and the BB isoenzyme of creatine kinase (CK-BB). Finally, the idea that SCCL is a collection of multiple cell lines, both in individual tumors and between patients, is supported by the variety of tumor products and their levels expressed by cells from single tumor sites; by cells taken from primary vs. metastatic sites; and by cells from tumors found in different patients. The notion of multiple cell lines is further supported by the variable number of chromosomes (ploidy) found by Vindelov et al.¹⁸ in some tumor samples from a single metastatic site and by Hattori et al.'s²⁴ finding of decreased or absent neurosecretory granules in the cells of tumors unresponsive to chemotherapy. The characteristics of SCCL have been further elucidated by recent studies which build on the picture above.

Tumor cell chromosome number was recently examined in relation to treatment response by a group at M.D. Anderson Hospital.³² They found a DNA index of 0.70 to 2.09 (1.0=diploid) among 126 pre-treatment specimens. Six percent of the cases had bi-clonal stem lines. Hypodiploid tumors had decreased percent S-phase cells (reflecting lesser proliferative activity). These tumors showed slower drug response, but the response was more prolonged with resultant better survival when compared to hyperdiploid tetraploid tumors characterized by high % S-phase cells. Percent survival at more than 60 weeks could

be stratified by DNA index in a significant way, raising the possibility that chromosome number and proliferative activity analysis may one day be used as prognostic criteria. The presence of more than one cell line in some tumors was again confirmed.

The use of monoclonal antibodies (MoAbs) may prove to be a useful method whereby antigenic expression--and thus, indirectly, the tumor genome--can be studied. Implications for future treatment design are numerous and include the attachment of anti-tumor drugs to MoAbs, creating a highly specific tumoricidal agent.

Groups at the NCI have published numerous abstracts in the last two years reporting on studies in which MoAbs have been applied. Considerable antigenic heterogeneity has been found within individual SCCL tumors, between tumor lines, and, to a more limited degree, between clonally related lines.³³ SCCL is thus proving to be heterogeneous in a way that challenges our understanding of cellular behavior at the level of molecular genetics. Relative homogeneity has been found in cell lines from different metastatic sites in the same patient. This homogeneity was especially evident when numerous characteristics of the cells were examined simultaneously: the biomarkers dopa decarboxylase (DDC) and bombesin (BN), DNA index, and three forms of antigenic expression (using MoAbs).³⁴ Still, the heterogeneity of antigen expression in tumor tissue and the poor specificity of "tumor" antigens--i.e., their diverse distribution in normal tissue--may cause considerable difficulty in the clinical application of MoAbs.³⁵

A finding which may prove to be specific is that of HLA-A,B,C, and beta-2 microglobulin deficiencies on the cell surfaces of human SCCL lines, detected by MoAbs. Thusfar, non-SCCL lines have been strongly positive for these structural markers.^{36,37}

Two exceptionally interesting reports from the NCI^{38,39} have appeared recently which illustrate our ability to study SCCL at a cellular level through the use of biochemical markers, continuous cell lines, and measurements of radiosensitivity and tumorigenicity. The authors report two major subgroups of SCCL: a classic form, which expresses DDC, BN, NSE and CK-BB; and a variant form, which has a faster doubling time and shorter latent period to tumor induction in nude mice than the classic form. The variant form is radioresistant, nor does it produce DDC or BN in appreciable quantities. It has metabolic features which distinguish it from the classic form: despite the presence of CK-BB, the product whose formation that enzyme catalyzes (phosphocreatine) is not present in classic cell lines. Phosphocreatine isn't present in non-SCCL lines, but is present in the variant cell lines.

The possibility that there are two major subgroups of SCCL--one clinically aggressive, resistant to treatment, and lacking the characteristic APUD enzyme (DDC)--is reminiscent of the findings of Hattori et al.²⁴ Recall that those authors reported on the lack of neurosecretory granules (NSGs) in a group of tumors resistant to chemotherapy. Are Hattori's resistant tumors composed of cells from the NCI's variant subgroup? The absence of DDC in a tumor one would

expect to be clinically aggressive (the SCCL variant) is like the absence of NSGs in tumors proven to be therapy-resistant: basic APUD characteristics are lacking. The usefulness of APUD characteristics in understanding SCCL is not clear. The APUD origin of some cell lines becomes questionable. Perhaps tumor cells lacking NSGs and cell lines with characteristics of the variant subgroup are highly aggressive subpopulations of cells which have evolved from the original, more indolent APUD-derived tumor. The concept of classic and variant cell lines and the presence of more than one cell line in a tumor also brings to mind the report from M.D. Anderson³² which stratified tumor aggressivity by chromosome ploidy and proliferative activity.

Cytogenetic study of the classic and variant cell lines-- evaluating chromosome number and seeking the deletion in chromosome #3 associated with SCCL¹⁹--as well as cytomorphological study, with a special interest in neurosecretory granules, may prove fruitful. Clearly, researchers are only beginning to explore the cellular basis of SCCL's clinical behaviors.

Clinical Diagnosis

Cohen and Matthews,¹² Matthews and Hirsch⁴⁰ and Matthews⁴¹ have reviewed the radiographic, clinical, and pathological presentations of SCCL.

On X-ray, SCCL usually appears as a central mass. Because the tumor metastasizes early, hilar node involvement is common, with or

without mediastinal widening on presentation (64%).¹² Post-obstructive pneumonitis, atelectasis, and pleural effusion (due to lymphatic blockage) may be present. Less commonly, a peripheral tumor mass is seen on presentation (19%). Very rarely, the patient presents with a central tumor mass and no obvious nodes (3%). The lesion must be distinguished from epidermoid (squamous cell) carcinoma, which also presents as a central lesion. But epidermoid lesions are rarely associated with mediastinal adenopathy or widening as evident as that in SCCL. Moreover, SCCL tumors demonstrate central cavitation less frequently than squamous cell lesions.

While the pathogenesis of SCCL and epidermoid cancer is probably similar, there are numerous differences in gross pathology. Epidermoid tumors are often bulky, polypoid, obstructive intraluminal growths, with a friable consistency, with or without central cavitation and liquefaction necrosis. SCCL, in contrast, tends to form submucosal plaques that spread to involve central structures: the trachea, mainstem bronchi, and the bronchial, hilar, and mediastinal lymph nodes. If the superior vena cava is invaded, it can be thrombosed, causing SVC syndrome. (SVC syndrome may also arise secondary to compression.) SCCL tumors have a glossy grey-white cut surface that is frequently hemorrhagic and necrotic--but central cavitation is rare.

Pathological classification of SCCL is based on light microscopy. In 1977, the World Health Organization revised their classification system based on a decade of study. The subtypes now

used include lymphocyte-like or oat cell (#21); intermediate forms (fusiform, polygonal, "other"--#22); and combined (oat cell with a definite component of squamous cell or adenocarcinoma).

The nuclear detail of small cell--its fine or coarse stippled pattern of nuclear chromatin and small, indistinct nucleoli--is highly characteristic. Cytoplasm is usually scanty or may appear to be absent. Cells are arranged in a loosely cohesive but clustered pattern, forming cords, sheets, or pseudorosettes (cuffing around blood vessels).

There are numerous problems that arise in diagnosing SCCL, as reviewed by Matthews and Hirsch.⁴⁰ These include inadequacy of biopsy material (biopsy samples that are too small, bronchial washings or sputa of equivocal cytology); crushing of tissues, resulting in overinterpretation of malignancy; and improper tissue processing, with resultant artifacts. The authors contributed to two interobserver studies designed to identify problems and assess reliability in SCCL diagnosis.^{42,43} They found unanimity or "near unanimity" (7 of 8 pathologists) in the diagnosis of SCCL in over 90% of the tumors studied. The consistency of subtyping of SCCL tumors according to the 1977 WHO criteria was assessed in one of the studies. Unanimity among 3 pathologists was achieved in only 54% of the cases. This is a remarkable figure, for it raises doubts about all studies designed to characterize SCCL subtypes (e.g., the response of different subtypes to therapy--a topic to be discussed later).

The great majority of patients with SCCL are symptomatic at presentation. Cough is a common symptom, referable to the primary tumor. Chest pain, dyspnea, symptoms of pneumonitis (due to obstruction or compression), wheeze and hemoptysis may occur. (See Table 3.)^{12,44} Mediastinal extension of the tumor results in hoarseness or SVC syndrome, the former secondary to involvement of the recurrent laryngeal nerve (usually on the left, where its course is longer). SVC syndrome tends to be associated with right lung tumors, since the superior vena cava passes through the chest on the right.

Early, widespread metastases are the hallmark of SCCL and contribute to its symptomatology. Livingston et al.,⁴⁵ in their series of 375 patients, found liver to be the metastatic site most often involved in extensive-disease patients, followed closely by bone; then, bone marrow, brain, skin/soft tissue/nodes, and pleural effusion. (See Table 4.)⁴⁵ Thirty-seven percent of these patients had involvement of more than one metastatic site, in contrast to 49% in a study of 106 patients at the NCI.⁴⁶ The significant metastatic sites, in terms of symptomatology, are bone and brain, causing pain and neurological complaints, respectively. Although cardiac involvement is rarely mentioned in clinical series, 20-25% of SCCL patients have been reported to have cardiac metastases at autopsy.^{12,14} (See Table 4.) Such involvement can result in signs and symptoms of heart failure, EKG changes, even tamponade. Adriamycin, commonly used in treatment protocols for SCCL, has cardiotoxic side effects; thus, ejection fractions are routinely computed at the start

of therapy. Still, one wonders what implications subclinical cardiac involvement might have with respect to treatment complications.

The existence of clinical syndromes related to ectopic hormone production by SCCL tumors has already been mentioned. All are rare. SIADH, reported in 5-10% of most series, seems to occur most frequently in association with SCCL when the cause of SIADH is neoplastic.²² CNS manifestations predominate in symptomatic patients and may include seizures, disorders of consciousness, and extrapyramidal signs. The patient is unable to excrete a maximally dilute urine when presented with a water load and such testing can uncover many subclinical cases. Fluid restriction helps correct the hyponatremia, but chemotherapy is the definitive approach.

Ectopic ACTH production is clinically significant in 3-7% of patients with SCCL.²² Numerous tumors thought to be of APUD origin make the hormone. Symptomatic patients rarely present with the classic features of Cushing's syndrome--instead, weight loss, severe weakness, glucose intolerance, edema and/or hypertension are more likely presentations of their hypercortisolism. The metabolic complications of symptomatic ACTH overproduction can be severe and management is difficult, although Greco et al.²² report early evidence that combination chemotherapy can be effective.

Paraneoplastic syndromes other than ectopic hormone production have been found to be associated with SCCL. Possible etiologies of these syndromes include viral agents, autoimmune phenomena, and humoral substances elaborated by the tumor.⁵

Eaton-Lambert syndrome is associated with SCCL more often than with other diseases.²² It is an unusual clinical entity, characterized by the dichotomous findings of proximal muscle weakness with difficulty walking coupled with facilitation of muscular potentials on repeated stimulation. Thus, the patient's grip may become stronger and stronger during testing. The syndrome tends to occur among male patients over 40 years of age and seems to respond to cytotoxic therapy. Should chemotherapy fail, guanidine may be effective by causing increased release of anticholinesterases.²² The electromyogram is diagnostic.

A final syndrome requiring mention is paraneoplastic encephalopathy.²² This is thought to be the cause of death in two patients in the present study. Clinically, the syndrome may involve the cerebrum, brainstem, optic nerves, and cerebellum. Pathologic lesions are generally found in all these regions, although involvement of one area may dominate the clinical picture. Dementia is the most common manifestation of cerebral involvement. Radiologic studies are normal; the CSF may show an elevated protein level; the EEG is often slow and diffuse.

Staging and Prognosis

There is a TNM (tumor-nodes-metastases) staging system for SCCL but its use, until recently, had fallen out of favor. The TNM system is surgically-oriented and poor therapeutic results have been achieved using surgery alone. TNM was viewed as prognostically useless. More

recently, however, interest in surgery as an adjuvant therapy (part of a multimodal therapeutic approach) has been revived and the TNM system may yet take its place as a standard method of staging. (See the section on treatment.) Still, the system of the Veterans Administration Lung Cancer Study Group remains the one employed in almost all current studies. It divides patients into limited-stage (LD) and extensive-stage (ED) disease groups. LD is defined as tumor confined to one hemithorax with or without mediastinal lymphadenopathy, with or without ipsilateral supraclavicular node involvement. The tumor must fit within a single radiation therapy portal. Tumor beyond these confines is defined as extensive disease.⁴⁷

In general, two-thirds of all patients present with ED; one-third with LD.^{5,48,49} Ihde and Hansen⁴⁸ have pointed out that, with very thorough diagnostic work-ups, more patients with metastatic disease not easily detectable are placed in the ED group. When this is done, survival data for the individual ED and LD groups may appear improved, since a group of relatively "healthy" ED patients is created by removing a group of relatively "sick" LD patients. Overall survival (ED + LD) does not change. The truth of this observation must be supplemented by the observation that, despite the sophistication of the technology available to the physician determined to uncover the most retiring metastasis, test results are often equivocal. It is not clear whether or not to include certain patients in the ED group and they may be given the "benefit of the doubt"--identified as patients

with limited disease so that they might enter the LD treatment group. When this happens, the survival of the ED group presumably goes up and that of the LD group goes down. Again, overall survival remains unchanged.

Involvement of certain metastatic sites has been found to have prognostic significance. More fundamentally, extent of disease has strong prognostic implications. Staging procedures in SCCL must be designed with these facts in mind. Diagnostic modalities must be selected for their combination of sensitivity and specificity.

Chest X-ray remains the basic method by which intrathoracic disease is evaluated. However, fiberoptic bronchoscopy is a very useful tool--it allows diagnosis by biopsy or bronchial washings and can detect small lesions. The bronchoscope is used routinely at some centers to document complete response to therapy.

CT scans of the chest are less widely used, although they provide a better sense of tumor volume. Some note that the CT scan's sensitivity is not matched by its specificity in detecting malignant pulmonary nodules when compared to conventional linear tomography.⁵⁰ Others point to the relative inaccuracy of CT scans in diagnosing disease in the middle mediastinum when compared to staging mediastinoscopy or thoracotomy.⁵¹ Still, CT provides useful information not obtained with conventional radiography.^{51,52}

Both mediastinoscopy and CT of the chest may take on a more important role in initial staging in the future. The reason for this is the resurgence of interest in TNM staging to evaluate adjuvant

surgery for early control of intrathoracic tumor mass. Surgery aside, data is accumulating that would indicate a survival advantage for patients with smaller presenting tumors in the chest. A group in England⁵³ found a higher incidence of complete response and a survival advantage for patients with intrathoracic tumors whose total cross-sectional area was less than 30 cm² on CT. A Toronto group⁵⁴ reported a significant survival advantage for limited disease patients without superior mediastinal node involvement as diagnosed by mediastinoscopy or roentgenographic appearance--i.e., patients with so-called "very limited" disease, which is potentially resectable. These two studies illustrate the potential use of CT and/or mediastinoscopy in evaluation of chest tumor extent. Such information could be useful for treatment and/or prognosis.

Bone and bone marrow are common sites of metastatic spread. It seems important to perform both bone marrow biopsy and aspiration⁵⁵ as well as bone scan⁵⁶ if extent of disease is to be assessed, for the procedures complement each other to some extent. The prognostic significance of these sites of involvement is unclear, however.⁵⁷ Two recent studies found bone marrow involvement to be a negative prognostic factor;^{58,59} a third report found no prognostic significance.⁵⁵ A study from the Finsen Institute⁶⁰ identified a group with an especially poor prognosis: patients with bone marrow metastases and thrombocytopenia. In any case, bone scan and bone marrow biopsy and aspiration remain standard procedures in staging SCCL. Ihde and Hansen⁴⁸ have reported worsening of the bone scan

during overall disease remission in a minority of patients.

Liver metastases appear to be a negative prognostic factor. Groups at the NCI^{46,61} and Toronto⁵⁹ have found liver involvement to bode ill and the level of interest in accurate diagnosis of liver metastases supports the wide acceptance of this notion.

A variety of techniques may be used to evaluate the liver, including liver function tests, radionuclide scanning, CT, peritoneoscopy with biopsy, percutaneous biopsy, and ultrasonography with fine needle aspiration. Liver-spleen radionuclide scan remains the mainstay of current staging. Although this modality has been maligned, it remains a reliable, available, relatively inexpensive, non-invasive diagnostic tool in SCCL.⁶² At the NCI, peritoneoscopy with liver biopsy was found to be the most sensitive diagnostic method, but an algorithm combining radionuclide scan with liver function tests was highly accurate while remaining non-invasive.⁶¹ A recent study from the Finsen Institute⁶³ reported ultrasonography with fine needle aspiration to be more accurate than peritoneoscopy. The ultrasound technique was also "less invasive"--but the number of patients studied was small.

Whether or not prophylactic irradiation should be employed to avoid CNS metastases in patients with SCCL is a controversial topic. Less controversial is the prognostic significance of CNS involvement and how to diagnose it.

Brain metastases are present in approximately 10% of patients with SCCL at diagnosis and in 30-65% of patients at autopsy.⁴⁸ As

therapy improves and patients with SCCL live longer, they accumulate greater risk for developing this complication.

Both the NCI⁴⁶ and Toronto⁵⁹ groups found brain metastases to be a negative prognostic factor, but this result has not been invariable.⁵⁷ Diagnosis can be made by radionuclide scan or CT of the head. CT scans are thought to be superior,⁵⁷ uncovering lesions before they become symptomatic and allowing accurate staging.⁶⁴

A current set of recommendations for restaging of patients thought to have achieved clinical response is presented in Table 5.⁵⁷ The argument that restaging should be effected with as much care as initial staging is a good one since any metastasis large enough to be clinically detectable is of great significance. Perhaps someday biomarkers already described (e.g., bombesin, neuron-specific enolase) will become standard indicators of subtler disease.

What factors can be said to have prognostic significance in SCCL? Performance status--a numerical estimate of a patient's ability to go about his daily routine with or without symptoms--and stage of disease (limited vs. extensive), predominate in most studies of significant prognostic factors.^{48,59} In fact, the International Association for the Study of Lung Cancer feels it is no longer necessary to demonstrate the superior survival of patients with LD in current chemotherapy treatment reports.⁶⁵ Still, significantly improved survival for LD patients is not a universal finding.⁴⁶ Data already mentioned indicate that small intrathoracic tumor area and a finding of "very limited" (i.e., potentially resectable) disease may confer a

prognostic advantage.^{53,54} Patients who have failed a previous chemotherapeutic protocol invariably have a bad prognosis on second-line therapy.⁴⁸

The following are of less certain significance. Weight loss on presentation (0-10%) has been found to be associated with significantly decreased median survival,⁶⁶ as has multiple metastatic sites (one vs. two vs. three or more).⁴⁶ Age of 55 years of more has been associated with decreased response rates and shorter survival in patients not achieving complete response.⁶⁷

Numerous laboratory parameters may be useful as prognostic indicators; carcinoembryonic antigen (CEA) has been reported to be an independent prognostic factor,⁶⁸ as has LDH.^{59,69} The feasibility of using an objective prognostic index based on laboratory parameters at diagnosis to replace subjective performance status assessment is under study. At the NCI,⁷⁰ albumin and hemoglobin were found to be the most influential prognostic factors in survival.

The fact that, of the various metastatic sites, CNS and liver are the most likely to have prognostic significance has already been discussed.

Finally, the prognostic significance of the various subtypes of SCCL remains unclear. The VA Lung Group⁷¹ reported better survival for patients with lymphocyte-like (classic, oat-cell) vs. intermediate-type disease. This held true for patients within the extensive disease group, but not the limited disease group, when analyzed separately. In contrast, a large NCI study⁷² found no

clinically significant differences among the subtypes. A recent community hospital study indicates that lymphocyte-like SCCL may be associated with better 2 year survival.^{73a}

The pathology panel of the International Association for the Study of Lung Cancer is in the process of proposing a revision of the current WHO histological classification system for SCCL.^{73b} The "combined" subgroup would remain; however, "oat cell" and "intermediate" subtypes would be classified together in the new "classic small cell" subgroup. Another new subgroup would be created: "small cell-large cell," in which there is an admixture of classic small cells with large cells having open nuclei and prominent eosinophilic nucleoli.

Dr. Raymond Yesner has reported, in a personal communication,^{73b} that the new classification system is based on the belief that polygonal and fusiform cell types--currently grouped in the intermediate subtype--show no significant clinical, biological, or ultrastructural differences from classic oat cells. The VA Lung Group study,⁷¹ as reported earlier in this paper, found a survival advantage for oat cell over intermediate-type disease. It turns out that this group, unlike investigators who found no such survival advantage, included in the intermediate subtype only tumors with a mixture of classic small cells and large cells--not tumors of polygonal and fusiform cells, which they grouped with classic oat cell tumors. The proposed classification system is based on the belief that tumors of the small cell-large cell subgroup carry a graver prognosis than those

of the classic small cell subgroup.

Finally, the new small cell-large cell subgroup is thought to be identical to the in vitro "variant" cell line described earlier in this paper based on reports from the NCI.^{38,39} The variant cell line is relatively resistant to radiation and chemotherapy and has a large cell appearance, but produces some characteristic SCCL biomarkers. Similarly, the classic small cell subgroup is felt to have its in vitro equivalent in the NCI's "classic" subclass.

Table 6 presents a summary of prognostic factors.

PART TWO: TREATMENT

Overview

A better theoretical grasp of cancer in general now permits clinicians to treat SCCL with a modest degree of success. As the characteristics of the tumor become better understood, the limitations of current therapy become painfully clear. Will the treatment breakthrough come from the slow evolution of rational therapeutic design or through a fortuitous discovery? It is unlikely that stepwise investigation will cure SCCL in the near future; and, given the cost-conscious environment of present-day cancer research, the prospect of a serendipitous discovery is better thought of as a fantasy than a hope.

In order to treat SCCL and to evaluate properly its response to treatment, the growth characteristics of the tumor need to be known. Two basic approaches exist: measures of clinical doubling time made by estimating tumor volume changes on chest radiographs over time; and in vitro studies of tumor cells. Tritiated thymidine uptake by SCCL cells allows calculation of the labeling index (LI)--the fraction of labeled tumor cells among all cells counted. LI reflects the rate of cell production by the tumor--it measures the fraction of cells actively synthesizing DNA.

SCCL responds well--initially--to treatment with radiation therapy^{73c} (which acts on dividing cells) and to treatment with agents such as methotrexate (which is S-phase specific) and cyclophosphamide

(which is probably cycle-dependent).⁷⁴ Intuitively, one would therefore expect SCCL to be a rapidly dividing tumor--one with a high LI and short doubling time as measured in clinical studies.

Initial results were consistent with this view.⁷⁵ For a while, researchers took a value of about one month as the doubling time of small cell tumors. Based on this assumption, the period of risk--the amount of time for regrowth from a single cell to clinical recurrence--was thought to be about two years.⁷⁵

Two years became a magical interval, synonymous with long-term survival^{76,77} and, perhaps, cure. This view was consistent with clinical impression, doubling time data, and the finding that SCCL had a higher median LI than other solid tumors (except Burkitt's lymphoma).⁷⁸ Although it has since become clear that two year survival is of limited value, it remains, for many, an important criterion. A review article from 1982 states that "many patients who survive alive and disease-free for 2 years, remain disease-free."⁷⁹ The reference given, from 1979, was employed above.⁷⁷

In 1978, a group at the NCI⁸⁰ reported a median doubling time of 77 days (range: 25-160 days) among their 12 cases of SCCL. Most tumors were felt to have demonstrated relatively intermediate or long doubling times. Assuming that the range of 1×10^6 to 1×10^9 cells is clinically significant, the authors used the median doubling time of 77 days to project that therapy leaving a tumor burden of 1×10^6 cells would not present as a clinical relapse for at least two years;

therapy destroying all but one cell would produce an interval of risk lasting 4-5 years.

The above projections may not be entirely accurate. First, the range of tumor doubling times must be taken into account. Second, treatment may change the cell kinetic characteristics of SCCL tumors;⁷⁸ there is good evidence to support biochemical and histological changes in tumors after therapy.^{81,82} Still, 4 or 5 year survival is probably more accurately synonymous with long-term survival if cure is implied. Clinical evidence has accumulated to support this notion in the form of late relapses.

Such evidence has been available for a number of years. The NCI-International Association for the Study of Lung Cancer report⁸³ which appeared in 1980 studied patients who survived more than 2.5 years. Recurrent disease was noted in 21 of 96 patients: 8 patients died 30-33 months after diagnosis; one was alive, with disease, at 34 months; recurrence was detected in 10 other patients after 36-51 months; and two patients treated by surgery alone succumbed to recurrent disease at 8 and 9 years, respectively.

Recently, data from cooperative and single institutions have been gathered on late relapses. The NCI⁸⁴ reported that 8 of 28 patients who had been disease-free at 30 months relapsed with SCCL (median: 54 months from diagnosis; range: 31-74 months) after follow-up of 5-10 years. The group at M.D. Anderson Hospital reviewed patients surviving 3 years or more. Eleven of 43 such patients relapsed systemically. Seven of the 11 relapses were at more than 3

years.⁸⁵ Livingston,⁸⁶ reporting for the Southwest Oncology Group, looked at 17 patients who survived 5 years or more in a single study (13% of those entered). Five late deaths were due to recurrent tumor (onset: 33-73 months from treatment).

As early as 1978, Greco et al.⁸⁷ published a paper in which the notion that 2 year survival might not represent cure was clearly expressed. The existence of "late recurrences" was recognized.

Before discussing treatment modalities: What is the natural history of SCCL? The median length of survival of untreated patients with SCCL is generally quoted as 2-3 months, depending on extent of disease at presentation.⁵ One widely quoted study is that of the VA Lung Study Group,⁴⁷ in which 38 SCCL patients with limited disease achieved a median survival of 11.7 weeks and 108 patients with extensive disease achieved a median survival of 5.0 weeks on placebo.

In a cooperative VA study reported by Roswit et al.,⁸⁸ placebo-treated SCCL patients with limited disease had a median survival of more than 16 weeks.

Surgery was one of the first modalities used to treat SCCL. The results were not good. Even apparently resectable lesions were frequently found to have seeded distant sites; relapse was the rule. A study of pathology material from the tumors of 19 patients who died within 30 days of apparently successful surgical resection found persistent disease in 13 of 19 patients, 12 of whom had distant metastases.⁸⁹ Radiation therapy (RT) alone proved better than surgery in a British Medical Research Council trial.⁹⁰ The patients had

limited disease thought to be resectable and were fit enough for surgery or radical RT. At 10 year follow-up, the surgery group had a mean survival of 199 days, the RT group 300 days. Three patients in the RT group who survived five years remained alive and disease-free at 10 years. Four RT patients died between 2 and 5 years. The sole 5 year survivor in the surgery group in fact underwent no surgical treatment due to breathlessness and received RT instead.

In contrast, in a cooperative VA study already mentioned,⁸⁸ there was no significant increase in survival for a group with limited disease receiving 4-5,000 rads of RT compared to a placebo group. Median survival for the RT group was a bit over 16 weeks.

Selawry,⁷⁴ in a 1973 report, reviewed the response of SCCL to single agent chemotherapy. Small cell was found to be the most responsive to single agents of all lung cancer subtypes.

Therapeutic design moved quickly once the efficacy of chemotherapy had been shown. Radiation therapy was combined with chemotherapy, creating a multi-modal approach;⁹¹ multiple chemotherapeutic agents were employed.^{87,92} It became clear that patients who achieved complete response lived longer than those achieving partial response or no response (in complete responders, the disease had been made clinically undetectable); and partial responders seemed to live longer than non-responders.⁹³

Chemotherapy has become the backbone of therapeutic approaches to SCCL. Basic principles of chemotherapy design have been applied to the disease. Attempts have been made to: combine drugs which have

therapeutic efficacy as single agents; choose combinations of drugs with different modes of action; treat with apparently non-cross-resistant sequential combinations of drugs; find combinations of drugs with synergistic anti-tumor effects; and use drug dosages high enough to maximize dose-response advantages while minimizing the inherent trade-off of dose-related toxicity.

Disease extent is a major prognostic factor in SCCL and treatment results reflect this fact. It is wise to discuss therapy of limited disease and extensive disease separately. In general, limited disease treatment has changed little in the past five years and is dominated by controversies over the use of radiation therapy to the chest and prophylactic cranial irradiation as adjuvants to combination chemotherapy. An exception to this statement is the renewed interest in surgery as an adjuvant therapy in resectable lesions. The more creative approaches to therapy--new drugs, larger doses, non-cross-resistant sequential combinations--have been confined largely to treatment of extensive disease or patients who have relapsed. The reason for this is that current conservative therapeutic designs produce a predictable, although small, number of long-term survivors in the limited disease group; the extensive disease group has fewer responders and shorter survival.⁹³ Clinicians are reluctant to give up "acceptable" survival and known toxicity risks for experimental therapies.

Aisner et al.,⁶⁵ reporting for the International Association for the Study of Lung Cancer have summarized current expectations in

trials employing aggressive therapy against SCCL. Combination chemotherapy should produce complete response in more than 50% of patients with limited disease (LD) and more than 20% of patients with extensive disease (ED). With adequate staging, median survival of at least 14 months in LD and 7 months in ED may be expected. Finally, 15-20% of LD patients should achieve disease-free survival of 3 years or more although such survivors remain rare among ED patients.

Table 7 presents a summary of selected treatment protocols for SCCL. It is intended to show the evolution of therapy and variability of treatment results. It does not present highly experimental approaches of the kind usually reserved for extensive disease patients or patients who have relapsed from first-line therapy. Unless drawn from the same paper, the studies are not comparable.

Table 8 presents information on long-term survivors from studies using various treatment modalities.

Treatment of Limited-Stage Disease and Treatment-Related Toxicities

Two controversial aspects of therapy design are especially relevant to limited disease, since their goal is prophylaxis or rapid, effective local control: the use of prophylactic cranial irradiation (PCI); and intrathoracic irradiation for local tumor control, both as adjuvants to combination chemotherapy.

Neither non-randomized nor randomized trials of PCI have demonstrated any clear advantage in survival.^{99,103}

Baglan and Marks⁹⁹ thus argued that the nominal purpose of PCI was to prevent neurological signs and symptoms, since their review of the literature uncovered an incidence of brain metastases averaging 23% for patients not receiving PCI versus 5% for the PCI group. The authors were able to treat 64% of 39 patients with brain metastases (all but 4 of whom were symptomatic) successfully enough to eradicate symptoms for the rest of the patients' lives. The authors predicted that, based on their results treating symptomatic patients and on previous treatment results with PCI, of 100 prophylactically irradiated and 100 symptomatically irradiated patients, 77 extra patients would have to receive PCI so that 3 patients might be spared CNS symptoms. They considered the potential benefit of PCI to be insignificant.

Baglan and Marks's argument hinges on effective treatment of CNS metastases. Agreement on this point is not uniform;¹⁰¹ still, a recent NCI study indicated that brain metastases can be treated effectively enough so that such patients die of other causes in most cases.¹⁰²

A large retrospective NCI study¹⁰⁰ examined PCI with a special interest in: PCI timing; PCI's effect on long-term survival; and selection of any subgroups of patients for whom PCI would be most helpful. The results were of great interest: there was significant improvement in overall survival for the group receiving PCI. However, the group which received no PCI also had the least intensive chemotherapy. With that caveat in mind, the authors felt that PCI had

its greatest positive effect in the complete responders (with limited or extensive disease). Among patients achieving complete response who had received no PCI, 17% relapsed in a CNS site alone. Isolated CNS relapse was seen in no complete responders who had received PCI. Two and three year survival was improved in the PCI groups, but not significantly so. With respect to the timing of PCI: there were no CNS relapses in the first four months in any group and no striking treatment result differences between a group receiving PCI on day 1 of the protocol and a group receiving PCI at week 12 or 24, contingent on a complete or partial therapy response.

The NCI group thus suggested that PCI may be most effectively employed at 2-4 months, after documented complete response has been achieved. Patients achieving less than complete response could be treated symptomatically since the study found no apparent advantage using PCI in that group. A recent study from Toronto¹⁰³ found no increased survival but significantly decreased brain relapse at 2 years for complete responders receiving PCI (21% vs. 52%).

Data is accumulating to support selective use of PCI--the data is on toxicities associated with PCI. Numerous groups have reported neurological toxicities among long-term survivors which may be due to PCI or the combination of PCI and chemotherapy (nitrosureas, in particular).^{84,104,105} A group at Indiana University¹⁰⁶ found neurologic problems in 9 of 11 long-term disease free patients (>3 years) who had received PCI + nitrosureas, and in 6 of 8 patients who had received PCI and chemotherapy without nitrosureas. Onset of

neurological symptoms was usually 1-3 years after completion of therapy. Problems encountered included memory loss, dementia, confusion, ataxia, psychomotor retardation, dysphonia and optic atrophy. Two patients required institutionalization; 6 others have had great impairment of their daily lives. Only 4 of 18 patients have had no neurologic impairment after therapy. Recently, a prospective evaluation revealed an "extraordinary high frequency of CCT (computerized cranial tomography) abnormalities in patients with SCCL after treatment with chemotherapy and cranial irradiation...."¹⁰⁷

The role of PCI in the treatment of SCCL remains unclear. It appears that PCI may offer a relapse protection advantage in patients achieving a complete response that is worth the risk of possible long-term neurological side effects. Much may depend on the side effects clinicians are willing to tolerate to protect the subgroup of complete responders who, without PCI, would experience isolated CNS relapse. Neurological side effects need to be further studied so that especially toxic PCI-chemotherapy combinations can be avoided. More data are needed on survival, relapse, and toxicity through randomized trials of PCI in complete responders.

The controversy surrounding the use of radiation therapy to the chest to complement multi-agent chemotherapy is a complex one.

Multi-modal therapy, referring to combined radiation and chemotherapy, is of two main types: sequential and concurrent. In sequential therapy, there is a temporal pause between the two modalities; in concurrent therapy, they are given simultaneously.

Catane et al.,¹⁰⁸ found a trend favoring concurrent therapy over sequential therapy for increased two year survival. The difference was not statistically significant, however. The concurrent therapy group achieved better complete therapy response with local tumor control and, of patients achieving complete response, fewer patients receiving concurrent therapy relapsed in the radiation therapy portal.

The toxicity enhancement effects of concurrent therapy are critical in evaluation of protocol design. In Catane's study, 7 of 14 patients receiving maximal concurrent radiation and chemotherapy (9 weeks) died of treatment toxicity. Yet, 4 of the 7 treatment survivors achieved 2 year survival--the highest proportion of any group in the study. The authors concluded that 3 weeks of concurrent radiation therapy (RT) and chemotherapy (CT) produced the optimal combination of high 2 year survival and acceptable toxicity.

Cox et al.,¹⁰⁹ found that tumor control probability, assessed by serial chest radiographs, increased with increasing biological dose in patients treated with RT alone. But in RT + CT patients, local control was achieved at lower RT doses than would have been expected. RT was generally begun during the last week or immediately after completion of chemotherapy.

The point is that RT and CT appear to act synergistically: they enhance each other's treatment effects but they also enhance toxicities. Acute toxicity enhancement effects include myocardial, pulmonary, skin and esophageal damage with Adriamycin;¹¹⁰ chronic

toxicities will be discussed shortly. However, delay of one week between modalities is thought to be protective.¹¹⁰

We enter the RT + CT vs. CT alone controversy with this perspective: the timing of combined modality treatment is important for toxicity and anti-tumor effects; RT seems to act synergistically with CT on tumor cells. To date, the critical parameters of RT-CT combination therapy--timing and dosage--have not been adequately studied.¹¹¹

The main argument for combined modality treatment is local tumor control. Byhardt and Cox¹¹² argue that failure of chemotherapy alone to prevent relapses in the chest is the reason to add adjuvant RT. Combined modality therapy reduces relapses in the radiation portal and, with this local tumor control, allows better long-term survival for limited disease patients.

Cohen¹¹³ notes that the true test of adjuvant RT is whether or not it increases the number of long-term survivors--i.e., patients living at least three years--in randomized trials comparing RT + CT to CT alone.

The use of adjuvant RT in extensive disease is not as controversial a topic. Most investigators seem to agree that survival is not increased by RT to the primary tumor. The data supporting this notion are relatively scanty,¹¹⁴ but meticulous local control apparently strikes most investigators as less essential when the tumor has already spread beyond one hemithorax. What can be said about local control and its relationship to long-term survival?

Peschel et al.,¹¹⁵ in a retrospective review of 12 patients achieving survival of more than 2 years, stressed the need for local tumor control--surgery or high dose (>4800 rads) lung irradiation--to avoid local relapse. Three of 5 patients who had received chemotherapy alone or low dose irradiation (<3500 rads) had late local relapses. Similarly, Matthews et al.⁸³ reported on the treatment received by patients in their long term (>2.5 year) survival registry. The two largest groups represented were patients who had received RT + CT and those who had received surgery alone. (The role of adjuvant surgery in current treatment protocols will be discussed later.)

Several controlled, randomized studies have compared CT + RT to CT alone. Hansen et al.¹¹⁶ reported shorter median survival in the RT + CT group compared to the CT group. In contrast, Bunn et al.¹¹⁷ and Perez et al.¹¹⁸ reported better median survival and complete response rate with thoracic irradiation. The Perez study also reported an initial, significant superiority in actuarial 3 year survival for the group receiving RT (20% vs. 5%). Toxicity was greater in the RT + CT group. There were 2 induction deaths in the RT + CT group vs. none in the CT group in Bunn's study. Mira et al.¹¹⁹ have added RT to CT at day 85 of their protocol and found that, in about 1/3 of responders who did not achieve complete response after initial CT, RT increased complete response rate and median survival.

Radiation therapy to the chest has a logical place in the care of patients with limited-stage disease. Local control is an extremely

useful concept in designing treatment protocols for long-term survival. Still, the trade-off is increased toxicity.

This is a good point to review treatment toxicities briefly, with a special interest in toxicities associated with combined modality therapy.^{120,121a} Most chemotherapy regimens used for treating SCCL produce some degree of myelosuppression. Addition of radiation affects the bone marrow and in a healthy adult, ribs, sternum, and scapula comprise 15-20% of functioning bone marrow.^{121b} With most standard CT protocols the duration of granulocytopenia is relatively short; febrile episodes are reported in about 30% of patients, documented infections in 5%, fatal infections in 2%. When adjuvant RT is added, infections have been reported to rise to 11.7%, fatal infections to 2.7%.¹²⁰ Infection can be documented in about 40% of febrile, neutropenic patients; 50% of these have bacteremia. A total of 60% of febrile, neutropenic patients are thought to be infected on the basis of cultures or clinical signs or symptoms.¹²⁰ Thus, antimicrobial therapy is empirically employed in all such patients.

Radiation therapy alone--but especially in combination with chemotherapy--contributes to two major acute toxicities: esophagitis and pneumonitis.

As has been mentioned, Adriamycin enhances radiation induced esophagitis. Chronic esophageal stricture is a hazard avoided through careful planning of the portals and timing of RT and of the dose and type of cytotoxic therapy.

CT adds to the problem of radiation pneumonitis; also, chronic pulmonary fibrosis has emerged as a major concern in long-term survivors after multi-modal therapy.¹⁰⁴

Cardiac toxicity is a potential complication of SCCL treatment. Pericarditis, aggravation of coronary artery disease, and cardiomyopathies especially associated with Adriamycin are all potential toxicities.

Peripheral neuropathy is a toxicity associated with vincristine. The long-term neurological sequelae of CT + RT have already been discussed in the context of prophylactic cranial irradiation.

Finally, second malignancies are arising as toxic complications. Four cases of acute leukemia--all arising 2-1/2 to 3 years after diagnosis of SCCL--have been reviewed by Abeloff et al.¹²⁰ All four patients had achieved complete responses; 3 of the 4 had received multi-modal CT + RT therapy.

Adjuvant surgery is a final topic to discuss in the treatment of limited-stage SCCL. Two studies have been mentioned which examined the characteristics of long-term survivors with SCCL;^{83,115} in each study, patients who had received surgery as initial or only treatment formed a significant subgroup.

The role of adjuvant surgery remains unclear. Comis et al.¹²² contributed a relatively early study, which they have recently updated.¹²³ TNM staging was used for the surgical procedure; the authors found that patients with superior mediastinal (N2) disease did not seem to benefit from adjuvant surgery. Foster et al.¹²⁴ found

that--due to extent of disease or such factors as poor medical condition and inadequate pulmonary function--only 10 of 37 eligible limited disease patients were surgical candidates. Friess et al.,¹²⁵ in a retrospective review, found that the 15 patients with limited disease who had entered one of their combined modality protocols after surgical resection had significantly better median and 2 year survival than patients without initial surgery. The best median survival was in patients with the smallest lesions (<5 cm) who had undergone surgery before starting the protocol.

Adjuvant surgery in SCCL may become an accepted treatment modality. Comis et al.¹²² have some good initial results, but the number of patients is very small. Basic questions remain. When is adjuvant surgery most effective? (I.e., should it be employed before or after initial chemotherapy?) Is adjuvant surgery only possible or efficacious in a relatively small number of patients? Finally: are the results of adjuvant surgery going to reflect better treatment or simply the better prognosis of a subgroup of patients with "very limited" stage disease?⁵⁴

Extensive-Stage Disease and Experimental Therapies

Comis,¹¹⁴ in his review of treatment for SCCL, considers infrequent long-term survival to be the distinguishing characteristic of extensive-stage disease. Intensive therapies (high dose, high toxicity; multiple, novel combinations; new drugs) have achieved better median survival. A glance at the registry of long-term

survivors⁸³ (>2.5 years) reported in 1980 reveals that, of 97 patients, only 8 presented with extensive-stage disease. Extent of disease is a powerful prognostic indicator and survival data reflect this fact.

Comis¹¹⁴ cites the following as the most prevalent new approaches to extensive disease: increasing the intensity of chemotherapy; using a sequence of drug combinations which are thought to be non-cross-resistant; and incorporating Etoposide (VP-16-213) into the initial combination of drugs.

Intensive chemotherapy seeks to take advantage of dose-response relationships and of the intuitive notion that if "effective" is good "intensive" is better. Aisner et al.⁶⁵ point to the paucity of data on dose schedule dependency. The determination of maximum doses proceeds slowly, on a drug-by-drug basis. Maximum acceptable toxicity appears to be the end-point. The results have not been encouraging and toxicity risks are considerable. Late intensive combined modality therapy with autologous bone marrow infusion¹²⁶ and high-dose therapy with protected environment-prophylactic antibiotic units to reduce infectious morbidity¹²⁷ have been reported to yield no long-term survival advantage over more conventional therapy. Neutropenia and infection are prominent risks. High dose regimens may be especially beneficial in patients achieving complete response;^{98,128} however, the generally low rate of complete response among extensive disease patients limits their potential application.

Another novel approach to therapy is the use of non-cross-resistant drug combinations in cycles. The results have not been exciting;^{114,129} still, the approach may hold some promise. Evans et al.¹³⁰ have pointed out that most alternating sequences of drugs do not appear to be truly non-cross-resistant. They cite a "truly" non-cross resistant sequence study in which response was improved.¹³¹ Still, "truly non-cross-resistant" seems to mean that potentially better response is achieved by achieving potentially better response--a suspiciously circular chain of reasoning.

New drug development is, of course, a major focus of continuing research. These drugs, for ethical reasons, are usually tested initially in patients for whom first-line chemotherapy has failed. Aisner et al.⁶⁵ note the hazards of this approach. It may be that aggressive initial therapy alters the nature of the tumor so that it becomes refractory to any subsequent treatment. (Evidence that therapy changes biochemical and histological characteristics of SCCL tumors has already been noted in this paper.^{81,82}) Aisner cites Etoposide and vindesine as examples. Etoposide is probably the most active single agent in untreated SCCL, with response rates averaging over 40%.¹³⁰ Yet, the drug has generally been found to produce insignificant response rates in patients refractory to standard therapy.¹³⁰ Perhaps the problem is not pre-treatment, but simply that tumors unresponsive to first-line therapy are refractory to most novel therapies as well.

In any case, Etoposide (VP-16-213) has proved to be a promising new agent in treating SCCL. It appears to show a dose-response relationship; a study of high-dose Etoposide achieved an 80% response rate in 10 patients with extensive disease.¹³² Etoposide is often used in current multi-agent chemotherapy combinations.

VM-26 (related to vincristine),¹³³ vindesine,^{134,135} and, "logically," vindesine + Etoposide¹³⁶ may have activity against SCCL. The latter seems a good example of combining two drugs to see if the combination proves to have some magical synergism. Sometimes synergism is found. When Etoposide alone was compared to Etoposide + cis-platin (EP) in patients refractory to cyclophosphamide-Adriamycin--vincristine (CAV) therapy¹³⁰, the EP group experienced a better response rate, higher median survival and increased thrombocytopenia all thought to reflect the synergistic action of Etoposide and cis-platin described in some animal tumor systems.¹³⁷ Since their patients had been refractory to CAV therapy, the authors suggested they may have found a truly non-cross-resistant sequence for further investigation (CAV-EP). The usefulness of EP as consolidation therapy after initial CAV or "combined alkylators" has been reported to show little promise.¹³⁸

Finally, mention should be made of two studies similar to the Yale treatment protocol for SCCL whose results appear in the next section of this paper. Zekan et al.¹³⁹ found that CAVE afforded significantly increased total treatment response over CAV (82% vs. 66%). Etoposide was said to have added little toxicity although

3/57 CAVE patients suffered treatment-related deaths vs. 1/59 CAV patients. Estimated median survival was not significantly different for the two treatment groups in limited disease or extensive disease.

Messeih et al.¹⁴⁰ reported a significantly increased overall response rate (65% vs. 50%), and complete response rate (44% vs. 18%) for their CAVE group and--strikingly--extensive disease patients achieved a complete response rate of 35% on CAVE versus 0% on CAV. Overall median survival for all responders and median survival for complete responders was not significantly different for the two treatment groups.

Closing Comments

Despite the tantalizing response of SCCL to initial radiation or chemotherapy, relapse is the rule. Long-term survival (best defined as longer than 4-5 years if any association with cure is to be implied) is rare. Extensive disease patients have an especially dismal prognosis but this may improve if more can achieve complete response to therapy. Still, the disease remains one in which many patients are treated to allow survival of a few. Severe treatment toxicities can be avoided with rational dosage, timing, and selection of therapeutic modalities. They should be avoided, for there is no evidence that toxic therapies are the best therapies, and when cure is rare treatment should be relatively palatable.

Limited-stage disease offers the most hope. Prophylactic cranial irradiation (PCI) appears to have enough chronic neurological

toxicities that its use is best limited to complete responders, two to four months after the start of therapy. Thus, PCI will be employed mostly in limited-stage disease. PCI may fall out of favor entirely if, for example, its chronic toxicities are found to outweigh its protection of the subgroup of patients who would otherwise suffer isolated CNS relapse. Nitrosureas appear to be especially associated with the chronic toxicity of PCI. Patients with less than complete responses can be treated for CNS metastases as they arise. Chest irradiation makes a great deal of sense in limited disease; there is enough clinical evidence and good theoretical speculation to support the notion that local control of intrathoracic disease is essential for long-term survival. Care must be taken to avoid acute toxicities that accompany multi-modal therapy; chronic pulmonary toxicity is a significant factor which requires further study.

The importance of local control makes adjuvant surgery a potentially useful treatment modality. The apparently superior survival of patients with small "very limited" tumors highlights the need for a biochemical marker or other method of early diagnosis before SCCL becomes clinically apparent. If high risk populations could be screened for the disease, survival in SCCL would certainly improve, even with the limitations of current therapy.

Our understanding of SCCL is poor. The variability of treatment results and the resistance of small cell tumors to second-line drugs are but two reflections of our ignorance in the clinical setting. The variability among pathologists in identifying tumor subtypes and the

lack of apparent prognostic significance of these subtypes make the current system of histological classification questionable.

Heterogeneity is the hallmark of SCCL: tumor cells are variable in chromosome number, proliferative activity, antigenic expression, clonal origin, cytomorphology and biochemical behavior (including expression of tumor products and biochemical markers). Tumor cells with few or no neurosecretory granules, low dopa decarboxylase and bombesin activity, high ploidy and active proliferative behavior have all been identified as belonging to a clinically more aggressive subclass. The "variant" subclass of tumor cells may be both radioresistant and more aggressive than the "classic" subclass. The origin of aggressive tumor cells is obscure since dopa decarboxylase and neurosecretory granules are distinguishing APUD characteristics. Perhaps they evolve from cells in the original tumor (i.e., the tumor formed by initial malignant transformation).

The reclassification of SCCL proposed by the pathology panel of the International Association for the Study of Lung Cancer is of great significance. It is thought that the NCI's "variant" subclass tumor cells are the in vitro equivalent of the proposed small cell-large cell subgroup, and that the NCI's "classic" cells are the in vitro equivalent of the proposed classic small cell subgroup. If, for the first time, a prognostically significant classification system has been found, whose subtypes can be reliably identified by different pathologists and studied with equivalent in vitro cell lines, then a major step will have been taken in the struggle to link basic science

research on cellular characteristics with clinical practice. Until then, information on the heterogeneity of SCCL tumor cells and the cellular characteristics of clinically aggressive tumors goes beyond our ability to use it: the information doesn't help in diagnosis, for our diagnostic tools detect only gross disease; it doesn't clarify our histological classification system, which is based on light microscopy; it doesn't assist us in prognosis, which is based on gross extent of disease and subjective evaluation of a patient's ability to carry out his daily tasks; and it probably won't help us design better therapy, since our therapeutic modalities are so very limited. But only work on cells will characterize the SCCL tumor. Our methods of diagnosis, classification, prognosis, and treatment will become more refined as understanding of the tumor cells expands. New modalities--hyperthermia, monoclonal antibodies, radiosensitizing drugs⁵--may prove useful by empirical trial. Today's dilemma is that a hit-or-miss approach to SCCL is bound to fail and the information we need for rational therapy is elusively basic.

PART THREE: THE STUDY

This paper presents the initial results of a Yale University treatment protocol for small cell cancer of the lung (SCCL). The data are part of a continuing study; methods, patients, results, and discussion are presented below.

Methods

During the period October, 1980 to April, 1983 all referred patients with histologically confirmed SCCL (by cytology or biopsy of metastatic sites) were entered in the study. Patients were accepted regardless of stage of disease, performance status, or life expectancy, provided they had at least one site of measureable or evaluable disease. Patients were ineligible for inclusion in the study if they had received prior treatment for their disease, with the exception of surgery, or if their left ventricular ejection fraction, by gated blood pool scan, was too low to permit treatment with Adriamycin (doxorubicin).

Pretreatment staging evaluation included history and physical examination with evaluation of performance status. Blood tests included CBC, platelet count, BUN, creatinine, bilirubin (total/direct), alkaline phosphatase, glucose, electrolytes, prothrombin time/partial thromboplastin time, cortisol, and studies for ectopic hormones as indicated.

Diagnostic procedures included bone marrow biopsy and aspirate; chest x-ray with tomography in all patients with limited-stage disease and others as indicated; liver-spleen scan and bone radionuclide scans; CT scan of the head; skin tests for SKSD, PPD, candida, mumps; electrocardiogram; and left ventricular ejection fraction gated blood pool scan.

Patients were defined as having limited-stage disease (LD) if the disease was confined to one hemithorax, with or without involvement of hilar, mediastinal and ipsilateral supraclavicular lymph nodes. Extensive-stage disease (ED) was defined as disease beyond these confines.

For treatment, patients were randomized prospectively to CAV (cyclophosphamide, Adriamycin, vincristine) or CAV/E (the above plus Etoposide (VP-16-213)). Drug dosages were: Adriamycin 40 mg/m^2 ; cyclophosphamide 1000 mg/m^2 IV; vincristine 1.4 mg/m^2 IV (not to exceed a total dose of 2 mg); Etoposide 125 mg/m^2 IV. CAV cycles were every 21 days. CAV/E cycles were every 42 days, with CAV given on day 1, Etoposide 125 mg/m^2 IV on each of days 21, 23, and 25, beginning again with CAV on day 42.

In limited disease, 3000 rads of radiation therapy (RT) to the primary tumor, mediastinum, and bilateral supraclavicular nodes as 300 rads per day, 5 treatments per week (10 treatments total) was given initially. Vincristine and cyclophosphamide in the doses above were given after staging, concurrent with the first phase of RT, followed by 4 cycles of CAV or 2 cycles of CAV/E. Adriamycin-containing

combination therapy thus began after completion of the first phase of RT and at least 21 days after initial cyclophosphamide and vincristine. An additional 2400 rads of RT to the primary sites, with concurrent cyclophosphamide and vincristine, were given as 8 treatments of 300 rads each, after the first 4 cycles of CAV or 2 cycles of CAV/E, before completing 6 more cycles of CAV or 3 more cycles of CAV/E.

In extensive disease, treatment was as above, except irradiation of the primary site was at the option of the responsible clinician.

After cycle 4 of CAV or cycle 2 of CAV/E, all complete responders with no known brain metastases received prophylactic whole brain irradiation as 3000 rads over 2 weeks at 300 rads per treatment, regardless of disease extent at presentation.

Treatment was continued to 10 cycles of CAV or 5 cycles of CAV/E.

See Tables 9 and 10 for summaries of the treatment protocols.

If, after 6-8 weeks of chemotherapy, there was disease progression, patients were considered off-study and treatment was individualized. Otherwise, patients were treated per protocol until clear-cut evidence of progression or relapse. Subsequent therapy was individualized.

At the conclusion of therapy, patients were restaged to document response.

Dose attenuations were guided by CBC prior to therapy.

Complete response was defined as total disappearance of all disease with biopsy confirmation (e.g., for bone marrow or liver)

lasting at least 30 days.

Partial response was defined as a 50% decrease in the product of 2 tumor diameters perpendicular to one another, without associated progression of any other lesions or the appearance of a new lesion. Regression had to last a minimum of 60 days.

Stable disease was defined as less than 50% regression of measureable lesions with the appearance of no new lesions and no deterioration of performance status.

Progression of disease was defined as the appearance of any new lesion or the increase in size of any measureable lesion by greater than 50%.

In this report, patients with stable disease and progressive disease are grouped together as "non-responders."

ECOG toxicity criteria were used as a basis for patient comparison.

Performance status was defined as follows: 0-asymptomatic; 1-fully ambulatory with symptoms; 2-bedridden less than 50% of the time; 3-bedridden 50% of the time or more; 4-100% bedridden.

Statistical analysis of time to relapse and survival was performed using Kaplan-Meier plots; comparisons were made using the generalized Wilcoxon (Breslow) test of statistics. All median values are from the Kaplan-Meier plots and therefore may be projections.

Patients and Results

Of the 47 patients entered into the study, 8 were inevaluable. Five of the 8 patients had extensive disease (ED). Of these 5: 2 patients never got Adriamycin due to inadequate pre-treatment cardiac function; 1 had intercurrent prostatic cancer; 1 chose to leave the care of a physician participating in the study after one visit, for unknown reasons; and 1 patient had a sudden cardiac death 48 hours after her only cycle of CAV therapy.

Three of the 8 inevaluable patients had limited disease (LD). Of these 3: 1 patient had not been on-study long enough to evaluate response--in addition, this patient's tumor was of mixed small cell/large cell histology; 1 had intercurrent prostate cancer; and 1 patient's chemotherapy was discontinued at the patient's request when symptoms of congestive heart failure developed after one dose each of cyclophosphamide and vincristine (the cycle contained no Adriamycin).

On-study time was defined as the date treatment started to the date last seen or date of death. The 39 evaluable patients had a median on-study time of 219 days (range 6-907 days).

Twenty-eight of 39 patients have relapsed. Eleven of 39 patients have not relapsed, one of whom died without apparent relapse (of infection or radiation pneumonitis, as will be described later); the other ten patients are still living and are disease-free. Sixteen of 39 patients are still alive, including 6 who have relapsed. The median follow-up for patients still alive is 219 days (two shortest

follow-ups: 70 and 97 days; two longest: 674 and 907 days).

Patient characteristics are presented in Table 11, subdivided by extent of disease and treatment arm. Fifteen of 39 patients (38%) had limited disease (LD). Twenty-four of 39 (62%) had extensive disease (ED). Two ED patients presented with superior vena cava syndrome; 1 ED patient had SIADH on presentation. One LD patient had significant non-neoplastic disease on presentation (diffuse scleroderma; she is the only patient whose initial performance status is unknown).

As expected, LD patients had better initial performance status than ED patients (LD--11 of 15 patients fully ambulatory (performance status 0 or 1); ED--11 of 24 patients fully ambulatory). The LD group was slightly younger than the ED group (median ages: LD-60 years; ED-63.5 years). The LD group contained a greater proportion of women (LD- 9 women:6 men; ED- 11 women:13 men).

Comparing treatment arm groups (Table 11): On the whole, the CAV group contained younger patients (median ages: CAV-59 years; CAV/E-66 years). LD-ED distribution was similar for both treatment groups: of 21 CAV patients, there were 8 LD (38%) and 13 ED (62%); of 18 CAV/E patients, there were 7 LD (39%), 11 ED (61%).

Fourteen of 21 CAV patients (67%) were fully ambulatory (performance status 0 or 1) versus 8 of 18 CAV/E patients (44%). Most of this difference can be accounted for by the fact that 8 of 13 patients (62%) in the ED-CAV group were fully ambulatory versus 3 of 11 patients (27%) in the ED-CAV/E group.

The CAV/E group contained a greater proportion of women (CAV/E- 10 women:8 men; CAV- 10 women:11 men).

Three patients had surgery before beginning the protocol: 2 LD, 1 ED. Patient characteristics are continued in Tables 12 and 13.

Eighteen of 24 ED patients presented with metastatic disease in more than one site. Sites of presenting metastases, by treatment arm, with the number and percentage of patients presenting with them are shown in Table 12. Six of 24 ED patients presented with metastatic disease involving single sites (see Table 12).

Sites of relapse among all 39 patients (ED + LD) with the number and percentage of patients relapsing at those sites are presented in Table 13. There were 10 relapses in sites of initial disease, excluding the chest (see Table 13).

Of the 5 brain relapses, 4 occurred in ED patients who had received no prophylactic cranial irradiation (PCI). Three of these 4 patients received no CT scan or radionuclide brain scan on diagnosis. One of the 5 brain relapses occurred in an LD patient with negative CT scan on diagnosis who relapsed 4 months after 3000 rads of PCI. The ED patient who experienced a choroidal relapse had no PCI.

Two LD patients deserve special mention. The first patient had a palpable subcutaneous nodule at diagnosis, refused biopsy, and later relapsed in the same site; the second had a radionuclide scan equivocal for liver involvement at diagnosis and later relapsed in liver, bone and bone marrow.

Nine patients had chest relapses. Five of the 9 had ED and received no thoracic irradiation. It is not known whether the remaining 4 patients (2 LD; 2 ED) relapsed within their radiation therapy portals.

Response to therapy, grouped by disease extent and treatment arm, is presented in Table 14. Objective responses (CR + PR) occurred in 28 of all 39 patients (72%); in 13 of 15 LD patients (87%); 15 of 24 ED patients (63%); 8 of 8 LD-CAV patients (100%); 5 of 7 LD-CAV/E patients (71%); 9 of 13 ED-CAV patients (69%); and 6 of 11 ED-CAV/E patients (55%).

The following sections present data from Kaplan-Meier curves for time to relapse and survival. Subgrouping was performed in analyzing the data by treatment group (e.g., LD-CAV responders vs. LD-CAV/E responders); such subgrouping is intended only to reflect the distribution of the data, since the small number of patients in these subgroups precludes in-depth analysis.

Time to relapse was defined as the date treatment began to the date of disease progression. The data are presented in Table 14 and Figures 1-4.

Median time to relapse was 361 days in responders (CR + PR) with LD; for ED responders, the median was 188 days. Analysis of these relapse curves showed a significantly longer time to relapse for the LD responders ($p=.0001$). (See Figure 1.) Time to relapse for ED non-responders (median: 71 days) was significantly shorter than for ED responders ($p=.006$). (See Figure 2.)

Time to relapse was studied by treatment group. For patients with LD, time to relapse on CAV (median: 334 days) versus time to relapse on CAV/E (median: 361 days) was not significant ($p=.55$). (See Figure 3.) In contrast, time to relapse for all ED patients on CAV (median: 193 days) compared to ED patients on CAV/E (median: 109 days) was barely significant ($p=.04$). (See Figure 4.) Further subgrouping revealed that time to relapse of ED responders (CR + PR) on CAV versus those on CAV/E was not significant ($p=.77$); but comparison of ED non-responders on CAV versus ED non-responders on CAV/E was significant ($p=.02$).

Survival data, the main criteria by which protocols are evaluated, are presented in Table 15 and Figures 5-9.

Median survival for all patients was 301 days. (See Figure 5.) Median survival for LD complete responders was 560 days.

Survival of LD responders (CR + PR) (median: 560 days) was compared to survival of ED responders (median: 230 days) and found to be significant ($p=.0007$). (See Figure 6.) Survival of ED responders versus ED non-responders (median: 198 days) was not significant ($p=.24$). (See Figure 7.)

Survival by treatment group was analyzed. When survival of LD patients on CAV (median: 560 days) was compared to LD patients on CAV/E (median: 424 days), no significant difference was found ($p=.24$). (See Figure 8.) Survival of ED patients on CAV (median: 230 days) versus ED patients on CAV/E (median: 186 days) was not significant ($p=.23$). (See Figure 9.)

A glance at the survival curve for all patients shows a plateau at about 6%. (See Figure 5.) The curve for LD complete responders plateaus at 35%. But 8 of the 12 patients in this group were still alive and those 8 had a median follow-up of only 305 days, while projected median survival was 560 days.

Thusfar, 4 patients have lived 1-1/2 years or more. Two are described in some detail below because they will be mentioned in the discussion of treatment results later on.

First, a male patient presented at 51 years of age with performance status 1 and extensive disease--bone involvement, pleural effusion of unknown cytology, a subcutaneous nodule in the left flank and a supra-clavicular node. After 4 cycles of therapy, his chest disease had not changed significantly; however, he experienced a choroidal relapse in the left eye, with detachment and uplifting of the retina. The patient received radiation therapy to the eye and additional cycles of CAV. His chest x-ray showed no significant improvement during 7 months of therapy--thus, he was a non-responder. However, he did not expire until 847 days after the start of therapy.

Second, a 60-year-old woman with limited disease and performance status 0 underwent a left lower lobectomy then received CAV therapy, achieving complete response. She was still alive at 907 days, without relapse.

Some toxicities were common but not severe enough to cause great concern: radiation esophagitis (never causing strictures or requiring hospitalization); nausea and vomiting (controllable); mucositis (never

precluding oral food consumption); alopecia. All were ECOG #2 (moderate toxicity) or better.

Myelosuppression significant enough to cause a drop in WBC count to <2000 (ECOG #3 or worse) was experienced by 24 of 39 patients (62%): 14 of 24 patients with ED (58%) and 10 of 15 with LD (67%); by treatment group: 16 of 21 CAV patients (76%); 8 of 18 CAV/E patients (44%).

Anemia severe enough to require transfusion (ECOG #3) was experienced by 9 of 39 patients overall (23%): 5 of 24 with ED (21%); 4 of 15 with LD (27%); 6 of 21 on CAV (29%); 3 of 18 on CAV/E (17%). Three patients require special mention: one extensive disease patient on CAV had a Hgb/Hct of 8.6/25.3 but no transfusion documented; one LD-CAV/E patient had Hgb/Hct of 10.1/25.5 but refused transfusion; one ED-CAV patient had chronic anemia status post Bilroth II surgery and his anemia was not evaluable as a toxicity.

No platelet counts <50,000 (ECOG #3 or worse) were documented and there were no episodes of bleeding.

Six patients were hospitalized 8 times for pneumonia; 3 episodes of concurrent sepsis were documented. Two patients were hospitalized three times for fever: one of these patients was hospitalized separately for pneumonia, and is included among such patients above; one patient was hospitalized twice with negative cultures but a left upper lobe cavitory lesion on chest x-ray and a positive PPD test. The latter patient was treated with INH and Rifampin.

One patient was hospitalized once with a lung abscess and failure to thrive.

One patient was hospitalized once for pancytopenia (WBC count of 300) but neither fever nor infection was documented.

Eight patients were thus considered to have been hospitalized at some time for infection (all those described above except the patient with pancytopenia only). Seven of these 8 patients had ED; the one LD patient was hospitalized twice, once for pneumonia without sepsis, once for fever only.

Thus, 7 of 24 ED patients (29%) experienced significant infection as did 1 of 15 LD patients (7%); 7 of 21 CAV patients (33%); and 1 of 18 CAV/E patients (6%). One patient not included above may have died of treatment-related infection, as discussed below.

Two patients, both with LD on CAV/E, experienced radiation pneumonitis, one requiring treatment with steroids. A third patient, with ED on CAV, who had superior vena cava syndrome and liver involvement at presentation, was hospitalized 12 days after her last chemotherapy cycle, 5 weeks after radiation therapy to the chest, with leukopenia, fever, chills, and bilateral pulmonary infiltrates. Cultures were negative, but she was begun on antibiotics. Her lung disease was thought to be consistent with radiation pneumonitis, but this was diagnosed by chest x-ray and clinical impression only. The patient progressed to "Adult Respiratory Distress Syndrome" after one week of hospitalization and expired two and one-half weeks after admission. This patient almost certainly died of treatment-related

toxicity. Infection is thought to be the most likely cause; radiation pneumonitis is a possibility. The patient died without documented relapse after a partial response to therapy.

One inevaluable patient had a possible treatment-related death. She was a 70-year-old woman who presented with performance status 4, SIADH and extensive disease. Her cardiac ejection fraction was 50%. She received one cycle of CAV therapy and had a sudden cardiac death 48 hours later.

Three other patient deaths should be described.

A patient with LD on CAV therapy who received prophylactic cranial irradiation (PCI) developed dementia, dizziness, and double vision. Her CNS symptoms progressed, and, in light of a lumbar puncture and CT scan negative for tumor, she was felt to have died of paraneoplastic encephalopathy. However, combined Adriamycin-radiation therapy toxicity cannot be ruled out.

One patient with ED, a non-responder to CAV therapy, experienced dementia with memory loss and confusion. The patient's CNS symptoms progressed and, in light of a CT scan and lumbar puncture negative for tumor, his death was felt to be consistent with paraneoplastic encephalopathy. The patient received no PCI. However, death due to toxicity of chemotherapy alone cannot be ruled out.

Finally, a 58-year-old man presented with significant liver involvement, bilateral lymphadenopathy, and performance status of 3. He was randomized to CAV/E therapy and died due to progression of his disease in the liver 6 days after his only therapy cycle, which

consisted of CAV. This patient is mentioned because his case will be noted in the discussion of treatment results later in the paper.

Three patients experienced significant cutaneous infections. Two patients--one LD on CAV/E, one ED on CAV--experienced *H. simplex* infections while being hospitalized for concurrent problems. An ED patient on CAV/E experienced an *H. Zoster* infection as an outpatient.

Three patients had rash reactions to chemotherapy: one to Adriamycin; one to Adriamycin and cyclophosphamide or cyclophosphamide alone; one unknown. Two patients required treatment with IV steroids.

Adriamycin had to be discontinued in 2 patients due to cardiotoxicity. None experienced heart failure (both toxicities ECOG #2). One inevaluable patient experienced heart failure after a single cycle of chemotherapy which did not contain Adriamycin. Chemotherapy was discontinued at the patient's request.

Vincristine neurotoxicity was significant enough to cause discontinuation of the drug in 4 patients (3 LD on CAV; 1 ED on CAV/E). One of these patients (ED) experienced "Etoposide accentuated vincristine neuropathy with foot drop" and both drugs were discontinued. The only other documented attenuation of Etoposide was one cycle of 3 doses for myelosuppression just before the patient relapsed. Vincristine dose attenuation of more than 50% was required in 4 patients (2 ED-CAV; 1 ED-CAV/E; 1 LD-CAV) for whom discontinuation of the drug was not necessary.

Finally, 7 patients required significant attenuations (>50%) in the dose of their chemotherapy (cyclophosphamide and/or Adriamycin) for myelosuppression alone: 3 ED-CAV; 1 ED-CAV/E; 2 LD-CAV/E; 1 LD-CAV.

Discussion

The International Association for the Study of Lung Cancer Workshop has published its treatment result expectations for SCCL.⁶⁵ Expectations include complete response of 50% in LD and 20% in ED; median survival of at least 14 months in LD and 7 months in ED; and 15-20% 3 year disease-free survival among LD patients. These expectations may be excessively optimistic (especially those for long-term survival--see Table 8), but at least they establish some standard for comparison. Table 7 presents treatment results from selected studies; direct comparisons are not possible between studies.

The response rates in the present series were generally good, with 80% of LD patients achieving complete response. Just 12% of ED patients achieved complete response, a low but acceptable number.

Projected median survival was very good, ranging from about 6.5 months for ED non-responders to more than 18 months for LD complete responders. As expected, both time to relapse and survival were significantly longer for LD responders (CR + PR) than for ED responders. The presence in the ED non-responder group of a patient who survived 847 days after a choroidal relapse must be kept in mind

when evaluating the projected survival data for this relatively small group (n=9). The unusual choroidal relapse appears to have had no significant negative influence on this patient's survival. The projected median survival of 560 days for LD complete responders must also be approached with some caution since the projection is based on data from 12 patients, 8 of whom were still living. The living patients had a median follow-up of just 305 days.

Of the 12 LD patients achieving complete response, one was alive and disease-free at 907 days (slightly less than 2.5 years). Interestingly, this patient had surgery prior to beginning the protocol, adding further anecdotal evidence to the efficacy of adjuvant surgery in achieving local control and the importance of local control in long-term survival. In fact, it is too soon to predict the number of long-term survivors from this study.

The two treatment groups were very similar in survival results. The CAV/E group had shorter projected median survival in both ED and LD, but no comparison with CAV survival curves was significant. Time to relapse was shorter for the ED-CAV/E group than the ED-CAV group and the comparison was barely significant ($p=.04$). Further subgrouping showed a significantly shorter time to relapse for the ED non-responders on CAV/E than those on CAV. Comparison of time to relapse for ED responders was not significantly different for the two treatment groups. There are numerous reasons for quicker time to relapse in ED non-responders on CAV/E. These include the fact that the ED-CAV/E group contained a substantially smaller proportion of

fully ambulatory patients than the ED-CAV group (62% vs. 27%). The ED non-responder CAV group contained that patient with the choroidal relapse who went on to relatively long survival while the ED-CAV/E non-responder group contained the patient who died of progressive disease in only 6 days. ED non-responders on CAV survived longer than ED non-responders on CAV/E but the groups are small and comparison didn't quite reach significance ($p=.053$). Interestingly, survival was better for the ED responders on CAV/E than those on CAV, but the comparison was not significant ($p=.41$).

Clearly, the addition of Etoposide to CAV produced no difference in treatment results worthy of mention. Two previous reports^{139,140} cited better response rates with the addition of Etoposide to CAV; still, the studies found no significant differences between the treatment groups in survival.

No unexpected toxicities arose in the study. Myelosuppression was no greater than that consonant with a good therapeutic response. Etoposide added no apparent additional toxicity to the CAV regimen. In fact, only 1 of the 18 CAV/E patients (6%) required hospitalization for infection versus 7 of the 21 CAV patients (33%). The 33% rate for CAV patients is higher than the 11.7% "standard" infection rate for combined modality protocols cited in one review of SCCL treatment complications.¹²⁰ The 6% rate with CAV/E is lower than the "standard" rate and unexpected. Leukopenia (WBC count <2000) was experienced by 16 of 21 CAV patients (76%) versus 8 of 18 CAV/E patients (44%). Perhaps this underlies the difference in

infection rates, unless Etoposide has some heretofore undiscovered antibiotic properties.

One treatment-related death was probably caused by infection (although radiation pneumonitis is possible), yielding a fatal infection rate of 1 in 39 patients (2.6%). This is reasonable for a combined modality study.¹²⁰ Sudden cardiac death occurred after a single cycle of cyclophosphamide and vincristine in a patient presenting with extensive disease, SIADH, poor performance status (bedridden) and a cardiac ejection fraction of 50%. This must be viewed as a possible treatment-related death although no Adriamycin was given.

In summary, the present study employed state-of-the-art design (prophylactic cranial irradiation after complete response, thoracic irradiation in limited disease, and use of Etoposide, an agent with significant activity against SCCL) and achieved early treatment results comparable to those in the current literature. It is too early to evaluate long-term survival.

Addition of Etoposide to CAV therapy yielded no improvement in initial treatment results, including survival. However, an unexpectedly low rate of infections requiring hospitalization was found in the CAV/E group, substantially lower than that in the CAV group,¹⁴¹ perhaps secondary to a lower rate of leukopenia with the use of Etoposide in half the treatment cycles.

REFERENCES

1. Stolley, P.D.: Lung cancer in women--five years later, situation worse. *N. Engl. J. Med.* 309:428-429, 1983.
2. Silverberg, E.: Cancer statistics, 1984. *CA* 34:7-15, 1984.
3. Weiss, W.: Small cell carcinoma of the lung: Epidemiology and etiology, in Greco, F.A., Oldham, R.K., Bunn, P.A., Jr. (eds.): *Small Cell Lung Cancer (Clinical Oncology Monographs)*. New York, Grune and Stratton, 1981, pp. 1-34.
4. Annegers, J.F., Carr, D.T., et al.: Incidence, trend, and outcome of bronchogenic carcinoma, in Olmsted County, Minnesota, 1935-1974. *Mayo Clin. Proc.* 53:432-436, 1978.
5. Hoffman, P.C., Albain, K.S., et al.; Current concepts in small cell carcinoma of the lung. *CA* 34:269-281, 1984.
6. Boucot, K.R., Weiss, W., et al.; The Philadelphia pulmonary neoplasm research project: Basic risk factors of lung cancer in older men. *American Journal of Epidemiology* 95:4-16, 1972.
7. Carney, D.N., Matthews, M.J., et al.: Influence of histologic subtype of small cell carcinoma of the lung on clinical presentation, response to therapy, and survival. *JNCI* 65:1225-1230, 1980.
8. Hallgrimsson, J.: Lung tumors in Iceland. *Acta. Path. Microbiol. Scand.* 81:813-823, 1973.
9. Kyriakos, M., Webber, B.: Cancer of the lung in young men. *Journal of Thoracic and Cardiovascular Surgery* 67:634-648, 1974.
10. Kennedy, A.: Lung cancer in young adults. *Brit. J. Dis. Chest* 66:147-154, 1972.
11. Putnam, J.S.: Lung carcinoma in young adults. *JAMA* 238:35-36, 1977.
12. Cohen, M.H., Matthews, M.J.: Small cell bronchogenic carcinoma: A distinct clinopathologic entity. *Seminars in Oncology* 5:234-243, 1978.
13. Weiss, W., Boucot, K.R., et al.: Risk of lung cancer according to histologic subtype and cigarette dosage. *JAMA* 222:799-801, 1972.

14. Auerbach, O., Garfinkel, L., Parks, V.: Histologic type of lung cancer in relation to smoking habits, year of diagnosis and sites of metastases. *Chest* 67:382-387, 1975.
15. Johnston-Early, A., Cohen, M.H., et al.: Smoking abstinence and small cell cancer survival. *JAMA* 244:2175-2179, 1980.
16. Archer, V.E., Saccomanno, G., Jones, J.H.: Frequency of different histologic types of bronchogenic carcinoma as related to radiation exposure. *Cancer* 34:2056-2060, 1974.
17. Wurster-Hill, D.H., Maurer, L.H.: Cytogenetic diagnosis of cancer: Abnormalities of chromosomes and polyploid levels in the bone marrow of patients with small cell anaplastic carcinoma of the lung. *J. Natl. Cancer Inst.* 61:1065-1075, 1978.
18. Vindelov, L.L., Hansen, H.H., et al.: Clonal heterogeneity of small-cell anaplastic carcinoma of the lung demonstrated by flow-cytometric DNA analysis. *Cancer Research* 40:4295-4300, 1980.
19. Whang-Peng, J., Kao-Shan, C.S., et al.: Specific chromosome defect associated with human small-cell lung cancer: Deletion 3p (14-23). *Science* 215:181-182, 1982.
20. Hattori, S., Matsuda, M., et al.: Oat-cell carcinoma of the lung. Clinical and morphological studies in relation to its histogenesis. *Cancer* 30:1014-1024, 1972.
21. Bensch, K.G., Gordon, G.B., Miller, L.R.: Studies on the bronchial counterpart of the Kulchitsky (argentaffin) cell and innervation of bronchial glands. *J. Ultrastruct. Res.* 12:668-686, 1965.
22. Greco, F.A., Hainsworth, J., et al.: Hormone production and paraneoplastic syndromes, in Greco F.A., Oldham, R.K., Bunn, P.A., Jr. (eds.): *Small Cell Lung Cancer (Clinical Oncology Monographs)*. New York, Grune and Stratton, 1981, pp. 177-223.
23. Gazdar, A.F., Carney, D.N., et al.: Establishment of continuous, clonable cultures of small-cell carcinoma of the lung which have amine precursor uptake and decarboxylation cell properties. *Cancer Research* 40:3502-3507, 1980.
24. Hattori, S., Matsuda, M., et al.: Small cell carcinoma of the lung: Clinical and cytomorphological studies in relation to its response to chemotherapy. *Gann* 68:321-331, 1977.

25. Tischler, A.S.: Small cell carcinoma of the lung: cellular origin and relationship to other neoplasms. *Seminars in Oncology* 5:244-252, 1978.
26. Frenster, J.H., Herstein, P.R.: Gene de-repression. *N. Engl. J. Med.* 288:1224-1229, 1973.
27. Sorenson, G.D., Pettengill, O.S., et al.: Hormone production by cultures of small-cell carcinoma of the lung. *Cancer* 47:1289-1296, 1981.
28. Richardson, R.L., Greco, F.A., et al.: Tumor products and potential markers in small cell lung cancer. *Seminars in Oncology* 5:253-262, 1978.
29. Baylin, S.B., Gazdar, A.F.: Endocrine biochemistry in the spectrum of human lung cancer: Implications for the cellular origin of small cell carcinoma, in Greco F.A., Oldham, R.K., Bunn, P.A., Jr. (eds.): *Small Cell Lung Cancer (Clinical Oncology Monographs)*. New York, Grune and Stratton, 1981, pp. 123-143.
30. Carney, D.N., Ihde, D.C., et al.: Serum neuron-specific enolase: A marker for disease extent and response to therapy of small-cell lung cancer. *Lancet* 1:583-585, 1982.
31. Bergh, J., Virtanen, I., et al.: Classification of human pulmonary neoplasms into small cell and non-small cell carcinomas based on their expression of intermediate filaments. *Proc. AACR* 25:161, 1984.
32. Johnson, T.S., Valdivieso, M., et al.: Flow cytometric ploidy and proliferative activity in human small cell lung carcinomas: Potential diagnostic and prognostic features. *Proc. AACR* 24:124, 1983.
33. Fargion, S., Carney, D.N., et al.: Antigenic heterogeneity in small cell lung cancer (SCLC) defined by 15 monoclonal antibodies (MA). *Proc. ASCO* 2:55, 1983.
34. Morstyn, G., Fargion, S., et al.: Homogeneity among small cell lung cancer (SCLC) cell lines (CL) from different metastatic sites (MS) in the same patient. *Proc. ASCO* 2:197, 1983.

35. Mulshine, J., Rosen, S., et al.: Immunohistochemical expression of human small cell lung cancer (SCLC) epitopes in malignant and normal tissue by a panel of rodent monoclonal antibodies. Proc. AACR 24:221, 1983.
36. Doyle, A., Cuttitta, F.: Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) lines differ markedly in the expression of HLA-frame and B-2 microglobulin (B₂-M) antigens. Proc. ASCO 2:12, 1983.
37. Doyle, A., Gazdar, A., et al.: The deficit in HLA expression in small cell lung cancer (SCLC) resides at the transcriptional level and is revised by interferon. Proc. ASCO 3:52, 1984.
38. Carney, D.N., Gazdar, A.F., et al.: Two distinct classes of tumor cells cultured from patients (pts) with small cell lung cancer (SCLC). Proc. ASCO 3:218, 1984.
39. Knop, R.H., Carney, D.N., et al.: Differentiation of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) human tumor cell lines (CL) using phosphocreatine (Pcr) signals as detected by ³¹P nuclear magnetic resonance (NMR) spectroscopy. Proc. AACR 25:25, 1984.
40. Matthews, M.J., Hirsch, F.R.: Problems in the diagnosis of small cell carcinoma of the lung, in Greco, F.A., Oldham, R.K., Bunn, P.A., Jr. (eds.): Small Cell Lung Cancer (Clinical Oncology Monographs). New York, Grune and Stratton, 1981, pp. 35-50.
41. Matthews, M.J.: Morphology of lung cancer. Seminars in Oncology 1:175-182, 1974.
42. Hirsch, F., Matthews, M., Yesner, R.: Problems in the histopathologic classification of small cell carcinoma of the lung. An interobservational examination. Abst. Int. Assoc. Study Lung Cancer, Copenhagen, 1980, p. 77.
43. Janis, M, Matthews, M.J., Bonfiglio, T., et al.: Consistency in the diagnosis of small cell carcinoma of the lung. Abst. Int. Assoc. Study Lung Cancer, Copenhagen, 1980, p. 79.
44. Friesenhahn, G.M., Clark, G.M., et al.: Clinical presentation of 689 patients with carcinoma of the lung. Proc. AACR 24:143, 1983.

45. Livingston, R.B., Trauth, C.J., Greenstreet, R.L.: Small cell carcinoma: Clinical manifestations and behavior with treatment, in Greco, F.A., Oldham, R.K., Bunn, P.A., Jr. (eds.): Small Cell Lung Cancer (Clinical Oncology Monographs). New York, Grune and Stratton, 1981, pp. 285-300.
46. Ihde, D.C., Makuch, R.W., et al.: Prognostic implications of stage of disease and sites of metastases in patients with small cell carcinoma of the lung treated with intensive combination chemotherapy. *Am. Rev. Respir. Dis.* 123:500-507, 1981.
47. Zelen, M.: Keynote address on biostatistics and data retrieval. *Cancer Chemotherapy Reports, Part 3*, 4:31-42, 1973.
48. Ihde, D.C., Hansen, H.H.: Staging procedures and prognostic factors in small cell carcinoma of the lung in, Greco, F.A., Oldham, R.K., Bunn, P.A., Jr. (eds.): Small Cell Lung Cancer (Clinical Oncology Monographs). New York, Grune and Stratton, 1981, pp. 261-283.
49. Livingston, R.B., Moore, T.N., et al.: Small-cell carcinoma of the lung: combined chemotherapy and radiation. *Annals of Internal Medicine* 88:194-199, 1978.
50. Chang, A.E., Schaner, E.G., et al.: Evaluation of computed tomography in the detection of pulmonary metastases. *Cancer* 43:913-916, 1979.
51. Underwood, G.H., Hooper, R.G., et al.: Computed tomographic scanning of the thorax in the staging of bronchogenic carcinoma. *N. Engl. J. Med.* 300:777-778, 1979.
52. McCrea, E.S., Fuks, J.Z., et al.: Computed tomography of the chest in staging and follow-up of small cell lung cancer (SCLC). *Proc. ASCO* 2:195, 1983.
53. Harper, P.G., Souhami, R.L., et al.: Tumor size, response rate, and prognosis in small cell carcinoma of the bronchus treated by combination chemotherapy. *Cancer Treatment Reports* 66:463-470, 1982.
54. Shepherd, F.A., Ginsberg, R., et al.: "Very limited" small cell lung cancer (SCLC)—results of non-surgical treatment. *Proc. ASCO* 3:223, 1984.
55. Compling, B., Quirt, I., et al.: Bone marrow involvement in small cell lung cancer (SCLC). *Proc. ASCO* 2:195, 1983.

56. Byrne, R., Levitan, N., et al.: The value of the radionuclide bone scan and bone marrow biopsy in staging small cell lung cancer (SCLC). Proc. ASCO 2:189, 1983.
57. Osterlind, K., Ihde, D.C., et al.: Staging and prognostic factors in small cell carcinoma of the lung. Cancer Treatment Reports 67:3-9, 1983.
58. Kramer, B.S., Wozniak, A.J., Ross, W.E.: A retrospective study of the value of staging procedures in patients (Pts) with small cell undifferentiated cancer of lung (SCCL). Proc. ASCO 1:2, 1982.
59. Feld, R., Deboer, G., Evans, W.K.: Prognostic factors in patients with small cell carcinoma of the lung (SCCL). Proc. AACR 24:145, 1983.
60. Hirsch, F.R., Hansen, H.H.: Bone marrow involvement in small cell anaplastic carcinoma of the lung. Cancer 46:206-211, 1980.
61. Mulshine, J.L., Makuch, R.W., et al.: Diagnosis and significance of liver metastases in small cell carcinoma of the lung. Journal of Clinical Oncology 2:733-741, 1984.
62. Mulshine, J., Matthews, J., et al.: Staging evaluation of the liver in small cell cancer of the lung (SCCL). Proc. ASCO 1:140, 1982.
63. Hansen, S.W., Jensen, F., et al.: Staging procedures of the liver in small cell bronchogenic carcinoma (SCC). A prospective comparative trial of peritoneoscopy with liver biopsy versus ultrasonography with fine needle aspiration. Proc. ASCO 2:5, 1983.
64. Levitan, N., Byrne, R., et al.: Computerized cranial tomography (CCT) in small cell lung cancer. Proc. ASCO 2:189, 1983.
65. Aisner, J., Alberto, P., et al.: Role of chemotherapy in small cell lung cancer: A consensus report of the international association for the study of lung cancer workshop. Cancer Treatment Reports 67:37-43, 1983.
66. Dewys, W.D., Begg, C., et al.: Prognostic effect of weight loss prior to chemotherapy in cancer patients. American Journal of Medicine 69:491-497, 1980.

67. Poplin, E., Whitacre, M., et al.: Small cell carcinoma of the lung (SCCL): Influence of age on treatment outcome. Proc. ASCO 3:223, 1984.
68. Sculier, J.P., Feld, R., et al.: CEA: A useful prognostic marker for small cell lung cancer (SCLC). Proc. AACR 25:158, 1984.
69. Koretz, M.M., Carter, S.K.: Laboratory parameters as alternative to performance status in predicting survival in oat cell carcinoma. Proc. ASCO 1:154, 1982.
70. Cohen, M.H., Makuch, R., et al.: Laboratory parameters as an alternative to performance status in prognostic stratification of patients with small cell lung cancer. Cancer Treatment Reports 65:187-195, 1981.
71. Davis, S., Stanley, K.E., et al.: Small cell carcinoma of the lung: Survival according to histologic subtype. Cancer 47:1863-1866, 1981.
72. Carney, D.N., Matthews, M.J., et al.: Influence of histologic subtype of small cell carcinoma of the lung on clinical presentation, response to therapy, and survival. J. Natl. Cancer Inst. 65:1225-1230, 1980.
- 73a. DeFusco, P., Cole, S., et al.: The effect of survival of histopathologic subtypes of small cell lung cancer (SCLC): A community hospital experience. Proc. ASCO 3:216, 1984.
- 73b. Yesner, R. Personal communication.
- 73c. Byhardt, R.W., Cox, J.D.: Is chest radiotherapy necessary in any or all patients with small cell carcinoma of the lung? Yes. Cancer Treatment Reports 67:209-221, 1983.
74. Selawry, O.S.: Monochemotherapy of bronchogenic carcinoma with special reference to cell type. Cancer Chemotherapy Reports, Part 3, 4:177-188, 1973.
75. Shackney, S.E., Straus, M.J., Bunn, P.A., Jr.: The growth characteristics of small cell carcinoma of the lung, in Greco, F.A., Oldham, R.K., Bunn, P.A., Jr. (eds.): Small Cell Lung Cancer (Clinical Oncology Monographs). New York, Grune and Stratton, 1981, pp. 225-234.

76. Cox, J.D., Byhardt, R.W., et al.: Dose-time relationships and the local control of small cell carcinoma of the lung. *Radiology* 128:205-207, 1978.
77. Ginsberg, S.J., Comis, R.L., et al.: Long-term survivorship in small-cell anaplastic lung carcinoma. *Cancer Treatment Reports* 63:1347-1349, 1979.
78. Muggia, F.M., Krezoski, S.K., Hansen, H.H.: Cell kinetic studies in patients with small cell carcinoma of the lung. *Cancer* 34:1683-1690, 1974.
79. Comis, R.L.: Small cell carcinoma of the lung. *Cancer Treatment Reviews* 9:237-258, 1982.
80. Brigham, B.A., Bunn, P.A., Jr., et al.: Growth rates of small cell bronchogenic carcinomas. *Cancer* 42:2880-2886, 1978.
81. Abeloff, M.D., Eggleston, J.C., et al.: Changes in morphologic and biochemical characteristics of small cell carcinoma of the lung. *American Journal of Medicine* 66:757-764, 1979.
82. Matthews, M.J., Ihde, D.C., et al.: Effects of chemotherapy on the histology of small cell carcinoma of the lung (SCCL)--a postmortem study of 54 cases. *Proc. AACR-ASCO* 20:397, 1978.
83. Matthews, M.J., Rozenzweig, M., et al.: Long-term survivors with small cell carcinoma of the lung. *Europ. J. Cancer* 16:527-531, 1980.
84. Johnson, B.E., Ihde, D.C., et al.: Five to ten year follow-up of small cell lung cancer (SCLC) patients disease free at 30 months: Chronic toxicities and late relapses. *Proc. ASCO* 3:218, 1984.
85. Kalter, S., Farha, P., et al.: Long term survivors with small-cell lung cancer (SCLC): The M.D. Anderson (MDA) experience from 1972-1980. *Proc. ASCO* 3:229, 1984.
86. Livingston, R.B.: Long-term survivors with small-cell lung cancer (SCLC): A southwest oncology group (SWOG) study. *Proc. ASCO* 2:187, 1983.

87. Greco, F.A., Einhorn, L.H., et al.: Small cell lung cancer: Progress and perspectives. *Seminars in Oncology* 5:323-335, 1978.
88. Roswit, B., Patno, M.E., et al.: The survival of patients with inoperable lung cancer: A large-scale randomized study of radiation therapy versus placebo. *Radiology* 90:688-697, 1968.
89. Matthews, M.J., Kanhouwa, S., et al.: Frequency of residual and metastatic tumor in patients undergoing curative surgical resection for lung cancer. *Cancer Chemotherapy Reports, Part 3*, 4:63-67, 1973.
90. Fox, W., Scadding, J.G.: Medical research council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. *Lancet* 2:63-65, 1973.
91. Medical Research Council Lung Cancer Working Party: Radiotherapy alone or with chemotherapy in the treatment of small-cell carcinoma of the lung. *Br. J. Cancer* 40:1-10, 1979.
92. Greco, F.A., Oldham, R.K.: Clinical management of patients with small cell lung cancer in, Greco, F.A., Oldham, R.K., Bunn, P.A., Jr. (eds.): *Small Cell Lung Cancer (Clinical Oncology Monographs)*. New York, Grune and Stratton, 1981, pp. 353-379.
93. Bunn, P.A., Cohen, M.H., et al.: Advances in small cell bronchogenic carcinoma. *Cancer Treatment Reports* 61:333-342, 1977.
94. Livingston, R.B., Moore, T.N., et al.: Small cell carcinoma of the lung: Combined chemotherapy and radiation: A Southwest Oncology Group Study. *Ann. Intern. Med.* 88:194-199, 1978.
95. Papac, R., Bien R., et al.: Combined modality treatment of small cell lung cancer (SCLC) with cyclophosphamide (CYT), VP-16, methotrexate (MTX) and high dose radiation. *Proc. ASCO* 3:216, 1984.
96. Goodman, G.E., Miller, T.P., et al.: Treatment of small cell lung cancer with VP-16, vincristine, doxorubicin (Adriamycin), cyclophosphamide (EVAC), and high-dose chest radiotherapy. *Journal of Clinical Oncology* 1:483-488, 1983.

97. Zekan, P., Jackson, D., et al.: Cyclophosphamide, Adriamycin and vincristine (CAV) versus VP-16-213 + CAV (VCAV) in the treatment of small cell carcinoma of the lung (SCC). Proc. ASCO 2:193, 1983.
98. Livingston, R.B., Mira, J.G., et al.: Combined modality treatment of extensive small cell lung cancer: A Southwest Oncology Group study. Journal of Clinical Oncology 2:585-590, 1984.
99. Baglan, R.J., Marks, J.E.: Comparison of symptomatic and prophylactic irradiation of brain metastases from oat cell carcinoma of the lung. Cancer 47:41-45, 1981.
100. Rosen, S.T., Makuch, R.W., et al.: Role of prophylactic cranial irradiation in prevention of central nervous system metastases in small cell lung cancer. Potential benefit restricted to patients with complete response. American Journal of Medicine 74:615-624, 1983.
101. Cox, J.D., Komaki, R., et al.: Results of whole-brain irradiation for metastases from small cell carcinoma of the lung. Cancer Treat. Rep. 64:957-961, 1980.
102. Crane, J., Lichter, A, et al.: Therapeutic cranial radiotherapy (RT) for brain metastases in small cell lung cancer (SCLC). Proc. AACR 24:145, 1983.
103. Sculier, J.P., Feld, R., et al.: Neurological complications in patients (Pts) with small cell lung cancer (SCLC). Proc. ASCO 3:222, 1984.
104. Ellison, N., Bernath, A., et al.: Disturbing problems of success: Clinical status of long-term survivors of small cell lung cancer (SCLC). Proc. ASCO 1:149, 1982.
105. Scher, H., Hilaris, B., Wittes, R.: Long term follow-up of combined modality therapy in small cell carcinoma of the lung. Proc. ASCO 2:199, 1983.
106. Looper, J.D., Einhorn, L.H., et al.: Severe neurologic problems following successful therapy for small cell lung cancer (SCLC). Proc. ASCO 3:231, 1984.

107. Craig, J., Jackson, D., et al.: Prospective evaluation of changes in computerized cranial tomography (CCT) in patients with small cell carcinoma (SCLC) treated with chemotherapy and cranial irradiation. *Proc. ASCO* 3:224, 1984.
108. Catane, R., Lichter, A., et al.: Small cell lung cancer: Analysis of treatment factors contributing to prolonged survival. *Cancer* 48:1936-1943, 1981.
109. Cox, J.D., Byhardt, R.W., et al.: Dose-time relationships and the local control of small cell carcinoma of the lung. *Radiology* 128:205-207, 1978.
110. Son, Y.H., Kapp, D.S.: Esophago-pulmonary toxicity from concomitant use of Adriamycin and irradiation. *Connecticut Medicine* 45:755-759, 1983.
111. Bleeher, N.M., Bunn, P.A., et al.: Role of radiation therapy in small cell anaplastic carcinoma of the lung. *Cancer Treatment Reports* 67:11-19, 1983.
112. Byhardt, R.W., and Cox, J.D.: Is chest radiotherapy necessary in any or all patients with small cell carcinoma of the lung? Yes. *Cancer Treatment Reports* 67:209-215, 1983.
113. Cohen, M.H.: Is thoracic radiation necessary for patients with limited-stage small cell lung cancer? No. *Cancer Treatment Reports* 67:217-221, 1983.
114. Comis, R.L.: Small cell carcinoma of the lung. *Cancer Treatment Reviews* 9:237-258, 1982.
115. Peschel, R.E., Kapp, D.S., et al.: Long term survivors with small cell carcinoma of the lung. *Int. J. Radiation Biol. Phys.* 7:1545-1548, 1981.
116. Hansen, H.H., Dombernowsky, P., et al.: Chemotherapy versus chemotherapy plus radiotherapy in regional small-cell carcinoma of the lung--a randomized trial. *Proc. AACR* 20:277, 1979.
117. Bunn, P., Cohen, M., et al.: Randomized trial of chemotherapy versus chemotherapy plus radiotherapy in limited stage small cell lung cancer (SCLC). *Proc. ASCO* 2:200, 1983.

118. Perez, C.A., Einhorn, L., et al.: Preliminary report on a randomized trial of radiotherapy (RT) to the thorax in limited small cell carcinoma of the lung treated with multiagent chemotherapy. Proc. ASCO 2:190, 1983.
119. Mira, J.G., Kies, M.S., et al.: Influence of chest radiotherapy (RT) in response, remission duration, and survival in chemotherapy (CT) responders in localized small cell lung carcinoma (SCLC): A Southwest Oncology Group (SWOG) study. Proc. ASCO 3:212, 1984.
120. Abeloff, M.D., Klastersky, J., et al.: Complications of treatment of small cell carcinoma of the lung. Cancer Treatment Reports 67:21-26, 1983.
- 121a. Aisner, J., Wiernik, P.H.: Complications of treatment and of improved survival in patients with small cell carcinoma of the lung, in Greco, F.A., Oldham, R.K., Bunn, P.A., Jr.: Small Cell Lung Cancer (Clinical Oncology Monographs). New York, Grune and Stratton, 1981, pp. 381-398.
- 121b. Rubin, P.H., Scarantino, C.H.: The bone marrow organ: The critical structure in radiation/drug interaction. Int. J. Radiat. Oncol. Biol. Phys. 4:3-23, 1978.
122. Comis, R., Meyer, J., et al.: The current results of chemotherapy (CTH) plus adjuvant surgery (AS) in limited small cell anaplastic lung cancer (SCALC). Proc. ASCO 1:147, 1982.
123. Comis, R., Meyer, J., et al.: The impact of TNM stage on results with chemotherapy (CT) and adjuvant surgery (AS) in small cell lung cancer (SCLC). Proc. ASCO 3:226, 1984.
124. Foster, J.M., Prager, R.L., et al.: Limited-stage small-cell carcinoma (SCC): Prospective evaluation regarding the feasibility of adjuvant surgery. Proc. ASCO 2:196, 1983.
125. Friess, G., McCracken, J., et al.: Improved long term survival associated with surgery in limited small cell cancer of the lung (SCCL). A Southwest Oncology Group (SWOG) study. Proc. ASCO 3:219, 1984.
126. Ihde, D.C., Lichter, A.S., et al.: Late intensive combined modalitiy therapy (LIRX) with autologous bone marrow (ABM) infusion in extensive stage small cell lung cancer (SCLC). Proc. ASCO 2:198, 1983.

127. Valdivieso, M., Cabanillas, F., et al.: Effects of intensive induction chemotherapy for extensive-disease small cell bronchogenic carcinoma in protected environment-prophylactic antibiotic units. *American Journal of Medicine* 76:405-412, 1984.
128. Smith, I.E., Evans, B.D., Harland, S.J.: High dose cyclophosphamide (HDC) (7 G/M^2) + autologous bone marrow rescue (ABMR) after conventional chemotherapy in patients with small cell lung cancer (SCLC). *Proc. ASCO* 2:186, 1983.
129. Aroney, R.S., Bell, D.R., et al.: Alternating non-cross-resistant combination chemotherapy for small cell anaplastic carcinoma of the lung. *Cancer* 49:2449-2454, 1982.
130. Evans, W.K., Feld, R., et al.: VP-16 alone and in combination with cisplatin in previously treated patients with small cell lung cancer. *Cancer* 53:1461-1466, 1984.
131. Cohen, M.H., Ihde, D.C., et al.: Cyclic alternating combination chemotherapy for small cell bronchogenic carcinoma. *Cancer Treatment Reports* 63:163-170, 1979.
132. Johnson, D.H., Wolff, S.N., et al.: High-dose VP-16-213 (HDE) treatment of extensive small cell lung cancer (SCC). *Proc. ASCO* 2:193, 1983.
133. Woods, R.L., Fox, R.M., Tattersall, M.H.N.: Treatment of small cell bronchogenic carcinoma with VM-26. *Cancer Treatment Reports* 63:2011-2013, 1979.
134. Natale, R.B., Gralla, R.J., Wittes, R.E.: Phase II trial of vindesine in patients with small cell lung carcinoma. *Cancer Treatment Reports* 65:129-131, 1981.
135. Petruska, P., Luedke, D., et al.: Phase II study of vindesine (v) in refractory small cell carcinoma of the lung (SCC). *Proc. AACR/ASCO* 21:500, 1981.
136. Gregor, A., Cornbleet, M., et al.: Vindesine and VP-16-213 as primary therapy for poor prognosis small cell carcinoma of bronchus (SCCB). *Proc. ASCO* 2:186, 1983.
137. Schabel, F.M., Trader, M.W., et al.: Cis-dichlorodiammineplatinum (11): Combination chemotherapy and cross-resistance studies with tumors of mice. *Cancer Treatment Reports* 63:1459-1473, 1979.

138. Livingston, R., Mira, J.: Extensive small cell lung cancer: Combined alkylators for induction with cisplatin + VP-16 consolidation. A Southwest Oncology Group study. Proc. ASCO 3:210, 1984.
139. Zekan, P., Jackson, D., et al.: Cyclophosphamide, Adriamycin, and Vincristine (CAV) versus VP-16-213 + CAV (VCAV) in the treatment of small cell carcinoma of the lung (SCC). Proc. ASCO 2:193, 1983.
140. Messeih, A., Schweitzer, J.M., et al.: The addition of VP-16-213 to Cytoxan, Adriamycin and Vincristine for remission induction, and survival in patients with small cell lung cancer. Proc. ASCO 2:201, 1983.
141. Rome, L.S., Portlock, C.S., et al.: Cyclophosphamide, Adriamycin, vincristine (CAV) vs. cyclophosphamide, Adriamycin, vincristine alternating with VP-16 (Etoposide) (CAV/E) in the treatment of small cell cancer (SCC) of the lung. Proc. ASCO 4, 1985 (in press).

Ex-cigarette smokers	<1 pack a day	1-2 packs a day	2+ packs a day
14.5%	19.2%	23.9%	31.1%

Total subjects = 163

From: Auerbach, O., Garfinkel, L., and Parks, V.R.^[14]

Table 1 -- Age Standardized Percentage Distribution of SCCL by
Cigarette Smoking Habit

<u>Exposure Group</u> +	<u>Excess Cases</u>
1 - 359	8.27*
360 - 1779	22.07*
> 1800	33.69*
Combined groups	64.03*

* = significantly different from expected number of cases ($p < .01$)

+Exposure is quantified by "Working Level Month" (WLM) Groups. One WLM is a month's work performed in an atmosphere containing a standard radiation dose per liter of air.

From: Archer, J.E., Saccomano, G., and Jones, J.H.^[16]

Table 2 -- Distribution of Excess (Presumably Radiation-Induced) Bronchogenic Cancers by Radiation Exposure Group

Percentage of patients with the symptom

<u>Symptom</u>	Cohen and Matthews ^[12]	Friesenhahn, et al. ^[44]
Cough	76	37
Chest pain	36	28
Dyspnea	34	31
Pneumonitis	25	NR
Wheeze	22	NR
Hemoptysis	15	17
Fatigue	NR	21
Hoarseness	15	NR
SVC syndrome	12	NR

NR = Not Reported

Table 3 -- Symptoms of SCCL

<u>Site</u>	At Presentation ^[45] (<u>total pts = 375</u>)	At Autopsy ^[14] (<u>total pts = 163</u>)
Liver	32	61.7
Bone	30	35
Bone marrow	16	NR
Brain	14	50
Skin, soft tissue, nodes	16	75.5 (excluding "chest wall")
Effusion/pleura	15	22.7
Heart	NR	20.3

NR = Not Reported

From: Livingston, R.B., Trauth, C.J., Greenstreet, R.L.^[45] and
Auerbach, O., Garfinkel, L., Parks, V.^[14]

Table 4 -- Percent Distribution of Metastases at Presentation and
at Autopsy in Two Studies

Site	Procedure	Recommended	If positive initially	If signs/symptoms
Primary	Chest X-ray	+		
	Fiberoptic bronchoscopy	+		
Mediastinum	Mediastinoscopy*	+		
	Gallium scan		+	
Bone marrow	Biopsy and aspiration	+		
	Bilateral biopsies		+	
	Scintigrams		+	
Liver	Peritoneoscopy and liver biopsy		+	
	Ultrasonography		+	
	CT scan		+	
Lymph nodes and skin	Fine-needle aspiration			+
CNS	CT scans		+	
	Scintigrams		+	
	Lumbar puncture		+	
	Myelograms		+	
Retroperitoneal organs	CT scans		+	+
	Ultrasonography		+	+
	Laparotomy			+

*Whenever possible.

From: Osterlind K., Ihde, D.C. et al. [57]

Table 5 -- Recommendations for Restaging

<u>Definite</u>	Stage of disease Performance status
<u>Probable</u>	Liver or CNS metastases Laboratory parameters
<u>Possible</u>	Weight loss Number of metastatic sites Age Sex Size of lesion ("very limited" vs. other)
<u>None</u>	Histologic subtype (1977 WHO classification)
<u>Investigational</u>	Histologic subtype (small cell-large cell vs. classic small cell)+

Adapted from Ihde D.C., and Hansen, H.H.[48]

+Proposed by pathology panel of the International Association for the Study of Lung Cancer.[73b]

Table 6 -- Prognostic Factors in SCCL

<u>Treatment</u>	<u>Number of Pts</u>		<u>Complete Response</u>		<u>Median Survival (weeks)</u>	
	LD	ED	LD	ED	LD	ED
Placebo ^[47]	38	108	+	+	11.7	5.0
Placebo ^[88]	29	+	+	+	>16	+
Surgery ^[90]	68	+	+	+	28.5 ^a	+
Radiation ^[90]	70	+	*	+	44 ^a	+
Radiation ^[88]	53	+	*	+	>16	+
CAV + RT ^[94]	108	250	41%	14%	52	26
CME + RT ^[95]	(38 LD + ED)		86%	27%	56	20
CAVE + RT ^[96]	33	11	76%	34%	92	36
CAVE + RT ^[97]	28	29	61%	21%	60	37
MEV/ CAV/ ^[98] MEV - CAV	+	453	+	16%	+	31

+ = Inapplicable
 * = Not Reported
 a = Mean Survival

C = cyclophosphamide
 A = Adriamycin
 V = vincristine

M = methotrexate
 RT = Radiation Therapy
 E = Etoposide
 (VP 16-213)

Table 7 -- Treatment Results in SCCL: Selected Studies

<u>Treatment</u>	<u>Number of Patients</u>	<u>Patient Characteristics</u>	<u>Long-Term Survivors</u>
Surgery ^[90]	58	All LD	0% LD
Radiation ^[90]	70	All LD	5% LD
Chemotherapy \pm RT ^[84]	255	+	6% LD + ED
CAV + RT ^[86]	400	100 LD 300 ED	4% (LD + ED) 11% LD 2% ED

+ = Not Reported

C = cyclophosphamide

RT = Radiation Therapy

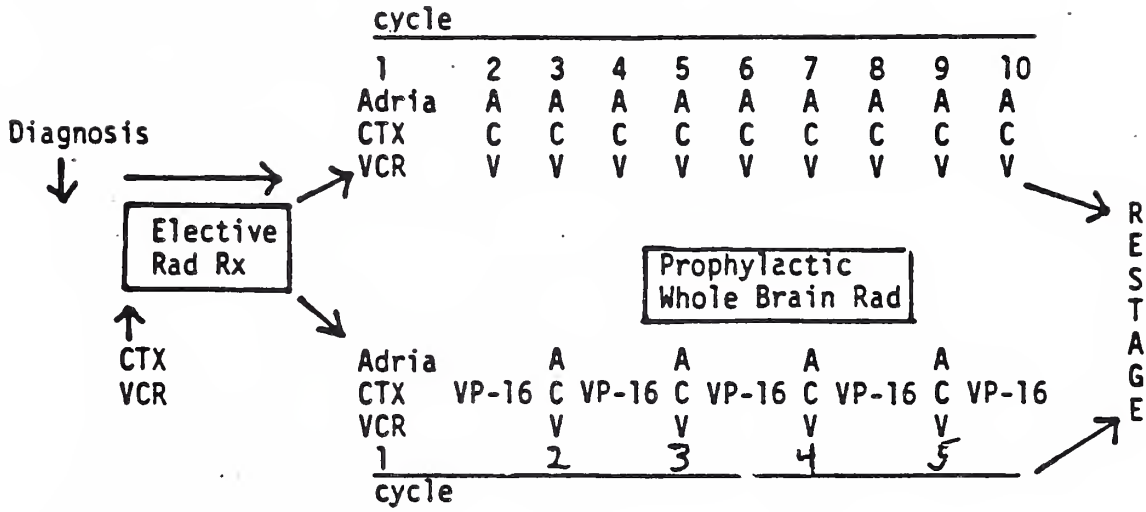
A = Adriamycin (doxorubicin)

V = vincristine

Table 8 -- Long-Term Survival (≥ 5 years) in SCCL

Treatment Schema

GROUP 2 = Extensive Disease



- Adria : Adriamycin 40 mg/m² IV day 1
- CTX : Cyclophosphamide 1000 mg/m² IV day 1
- VCR : Vincristine 1.4 mg/m² IV day 1 (each dose limited to 2 mg total)
- VP-16 125 mg/m² IV days 1, 3, 5

Table 10 -- Treatment Protocol for Extensive Disease

CAV Therapy Patients n = 21 (54%)

10 females: 11 males

Median age (range): 59 years (49-71)

Subgroup: CAV - Limited Disease Patients n = 8 (38%)

P.S. 0 = 1 ————— 6 pts. fully ambulatory
P.S. 1 = 5 ————— (75%)

P.S. 2 = 0 ————— 1 pt. not fully
P.S. 3 = 1 ————— ambulatory
P.S. 4 = 0 ————— (12%)

P.S. unknown = 1

Subgroup: CAV - Extensive Disease Patients n = 13 (62%)

P.S. 0 = 0 ————— 8 pts. fully ambulatory
P.S. 1 = 8 ————— (62%)

P.S. 2 = 4 ————— 5 pts. not fully
P.S. 3 = 0 ————— ambulatory
P.S. 4 = 1 ————— (38%)

CAV/E Therapy Patients n = 18 (46%)

10 females: 8 males

Median age (range): 66 years (53-72)

Subgroup: CAV/E - Limited Disease Patients n = 7 (39%)

P.S. 0 = 3 ————— 5 pts. fully ambulatory
P.S. 1 = 2 ————— (71%)

P.S. 2 = 2 ————— 2 pts. not fully
P.S. 3 = 0 ————— ambulatory
P.S. 4 = 0 ————— (29%)

Subgroup: CAV/E - Extensive Disease Patients n = 11 (61%)

P.S. 0 = 1 ————— 3 pts. fully ambulatory
P.S. 1 = 2 ————— (27%)

P.S. 2 = 4 ————— 8 pts. not fully
P.S. 3 = 3 ————— ambulatory
P.S. 4 = 1 ————— (73%)

E = Etoposide (VP-16-213)
A = Adriamycin (doxorubicin)

C = cyclophosphamide
V = vincristine

Table 11 -- Patient Characteristics by Treatment Arm

<u>Site</u>	Number of pts with disease at site+		% of ED pts with disease at site		Number of pts with this site as only involvement beyond <u>primary tumor</u>
	<u>CAV</u>	<u>CAV/E</u>	<u>CAV</u>	<u>CAV/E</u>	
Liver	8	6	62%	55%	3
Bone	7	5	54%	45%	1
Bone Marrow	6	1	46%	9%	2
Nodes (excluding chest)	3	2	23%	18%	-
Pleura	2*	2**	15%	18%	-
Bilateral Lung	1	1	8%	9%	-
Subcutaneous Nodules	2	-	.5%	-	-
Brain	-	1	-	9%	-

* Neither confirmed by cytology
 ** 1 of 2 confirmed by cytology

+ Total ED patients = 24
 ED-CAV = 13
 ED-CAV/E = 11

Table 12 -- Metastatic Sites at Diagnosis in Extensive Disease (ED)
 Patients by Treatment Arm

<u>Site</u>	<u>Number of patients with relapse at site+</u>	<u>% of all patients who who relapsed at this site</u>
Chest (excluding pleura)	9	23%
Liver	7	18%
Bone	5	13%
Brain	5	13%
Nodes (excluding chest)	4	10%
Pleura	2*	5%
Bone Marrow	1	3%
Subcutaneous Nodules	1	3%
Others CNS (choroidal)	1	3%

* Neither confirmed by cytology; one recurrent +Total pts = 39

Relapses at Sites of Initial Disease*

<u>Site</u>	<u>Number of Relapses</u>
Liver	4
Bone	3
Nodes (excluding chest)	2
Pleura	1

* Excludes chest relapses, except in pleura

Table 13 -- Sites of Relapse

Response to Therapy by Stage and Treatment Arm

	CR	PR	NR
All patients (n=39) (no.(%))	15 (38%)	13 (33%)	11 (28%)
Limited Disease (n=15)	12 (80%)	1 (7%)	2 (13%)
Extensive Disease (n=24)	3 (12%)	12 (50%)	9 (38%)
CAV-LD (n=8)	7 (88%)	1 (12%)	0
CAV/E-LD (n=7)	5 (71%)	0	2 (29%)
CAV-ED (n=13)	2 (15%)	7 (54%)	4 (31%)
CAV/E-ED (n=11)	1 (9%)	5 (45%)	5 (45%)

Time to Relapse

<u>Group</u>	<u>Median (projected)</u>	<u>p-value</u>
LD- CR+PR	361 days	p = .0001
ED- CR+PR	188 days	
ED- NR	71 days	
CAV-LD	334 days	p = .55
CAV/E-LD	361 days	
CAV-ED	193 days	p = .04
CAV/E-ED	109 days	

LD = Limited-stage disease

CR = Complete response

NR = Non-responders

C = cyclophosphamide

V = vincristine

ED = Extensive-stage disease

PR = Partial response

A = Adriamycin (doxorubicin)

E = Etoposide (VP-16-213)

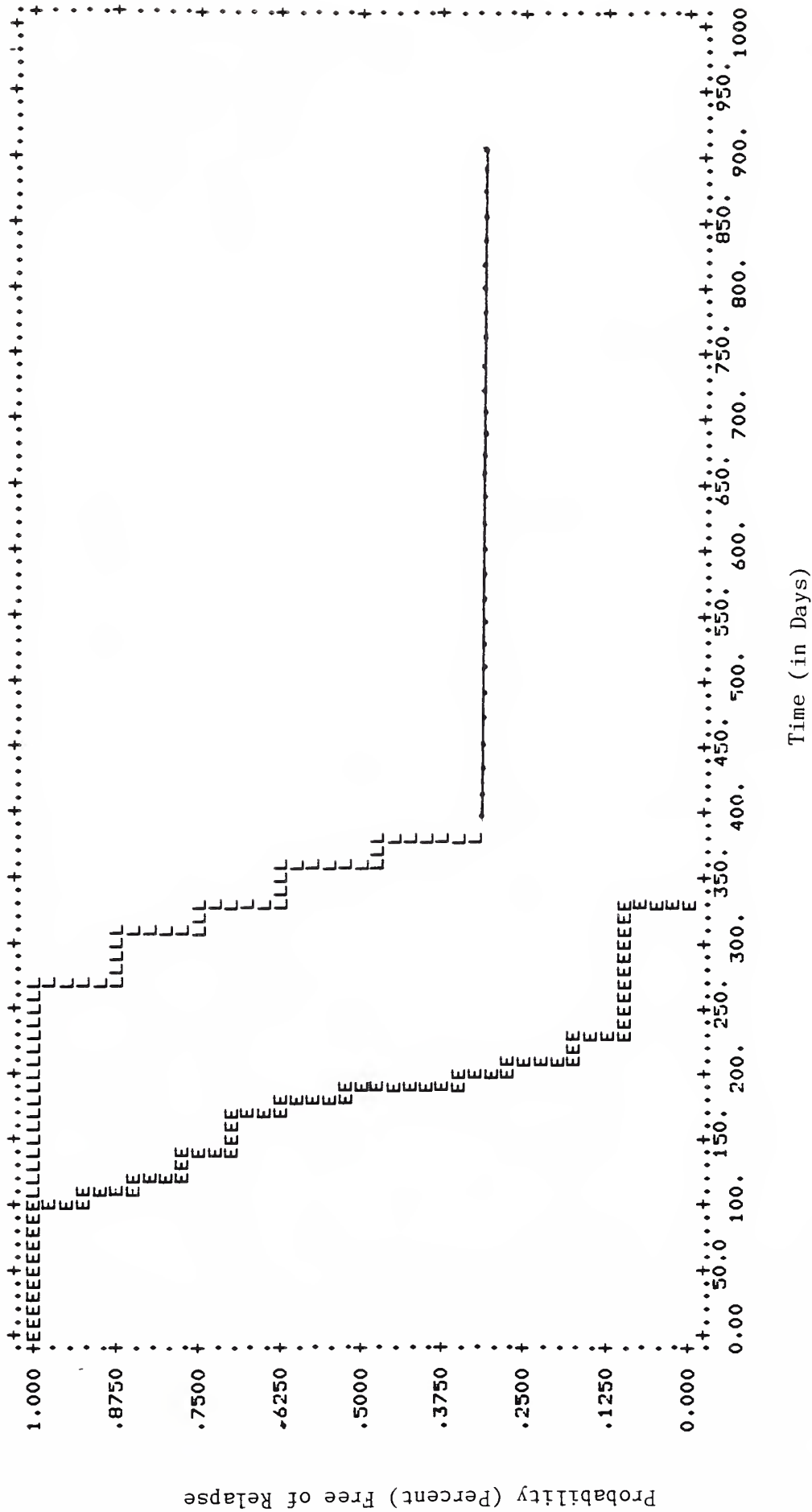
Table 14 -- Treatment Results: Response and Time to Relapse

<u>Group</u>	<u>Median (projected)</u>	<u>p-value</u>
All patients	301 days	
LD - CR	560 days	
LD- CR+PR	560 days	p = .0007
ED- CR+PR	230 days	
ED- NR	198 days	p = .24
CAV-LD	560 days	p = .24
CAV/E-LD	424 days	
CAV-ED	230 days	p = .23
CAV/E-ED	186 days	

LD = Limited-stage disease
 CR = Complete response
 NR = Non-responders
 C = cyclophosphamide
 V = vincristine

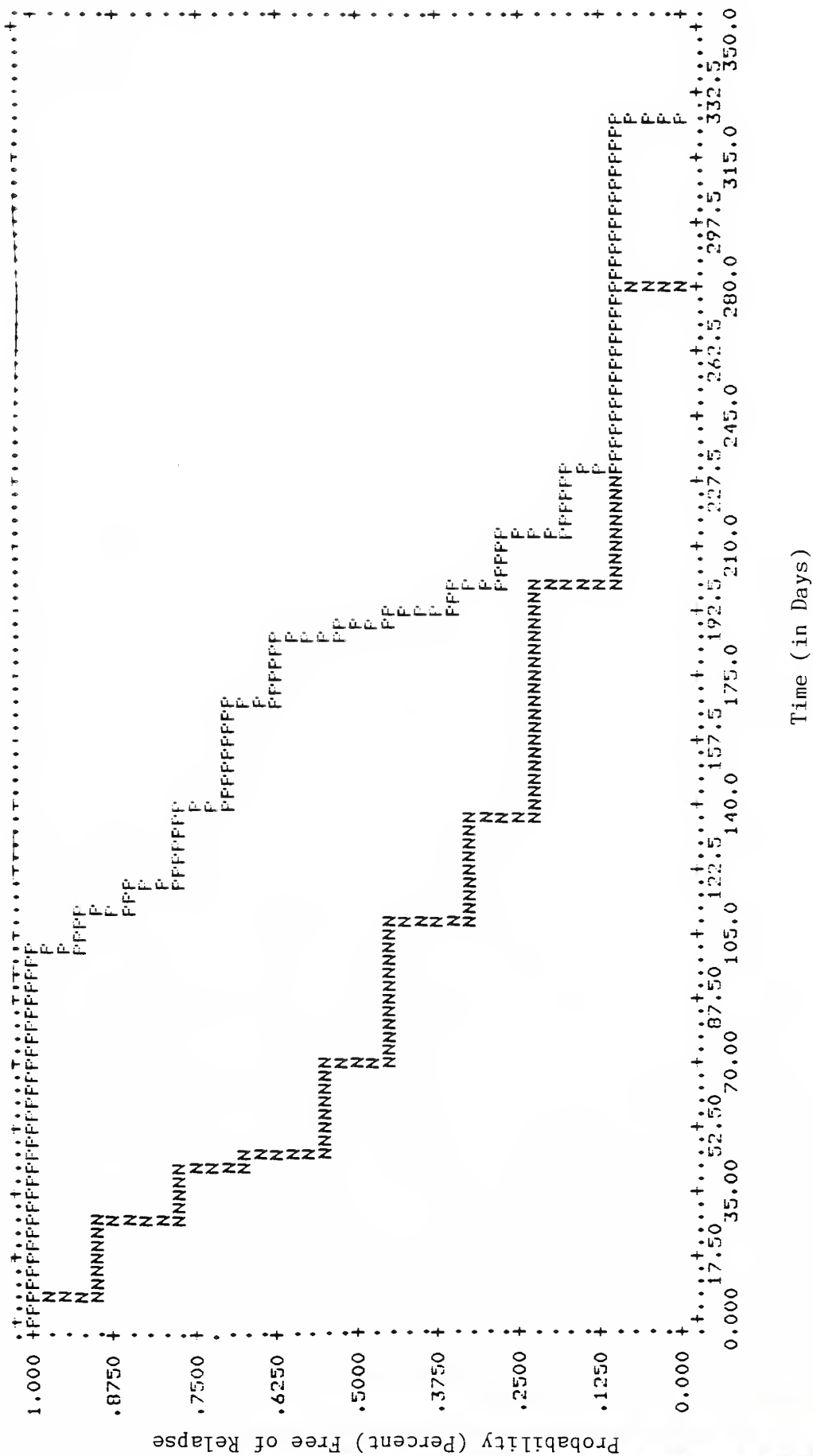
ED = Extensive-stage disease
 PR = Partial response
 A = Adriamycin (doxorubicin)
 E = Etoposide (VP-16-213)

Table 15 -- Survival



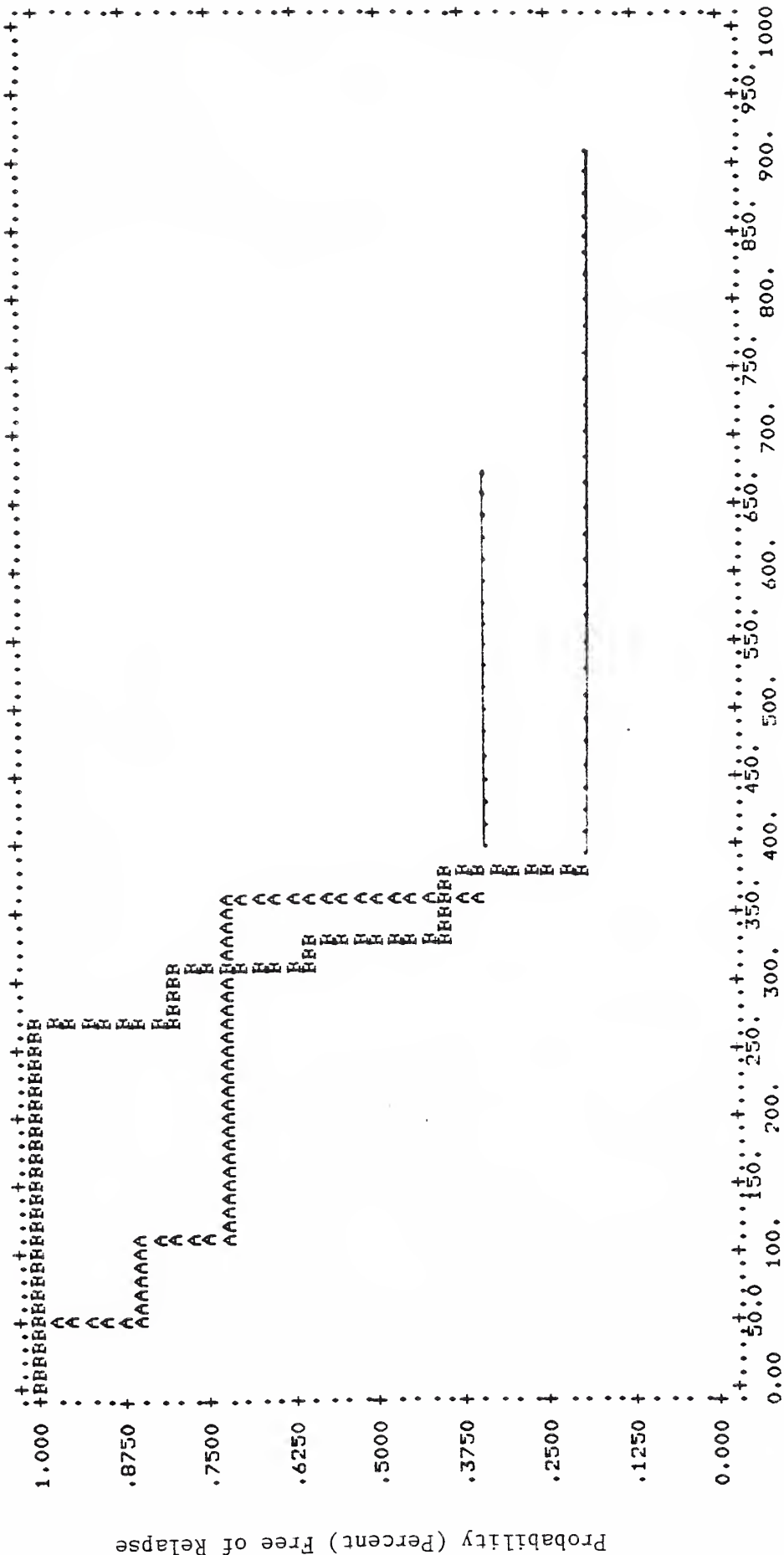
L = Limited Disease
 E = Extensive Disease

Figure 1 -- Time to Relapse for Responders (CR + PR) by Disease Extent



P = Responders (CR + PR)
 N = Nonresponders

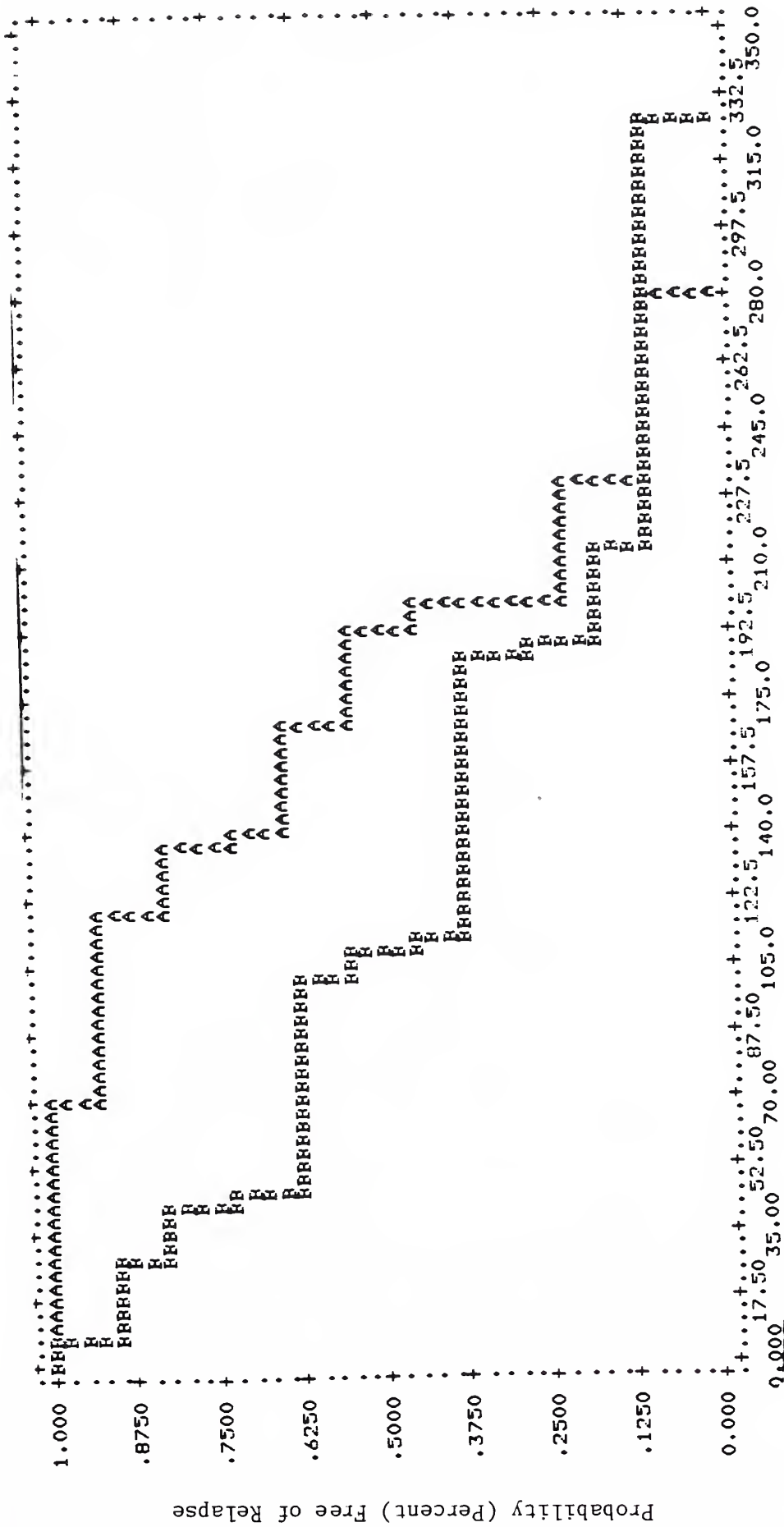
Figure 2 -- Time to Relapse for Extensive Disease Patients by Response Group



Time (in Days)

A = CAV/E
B = CAV

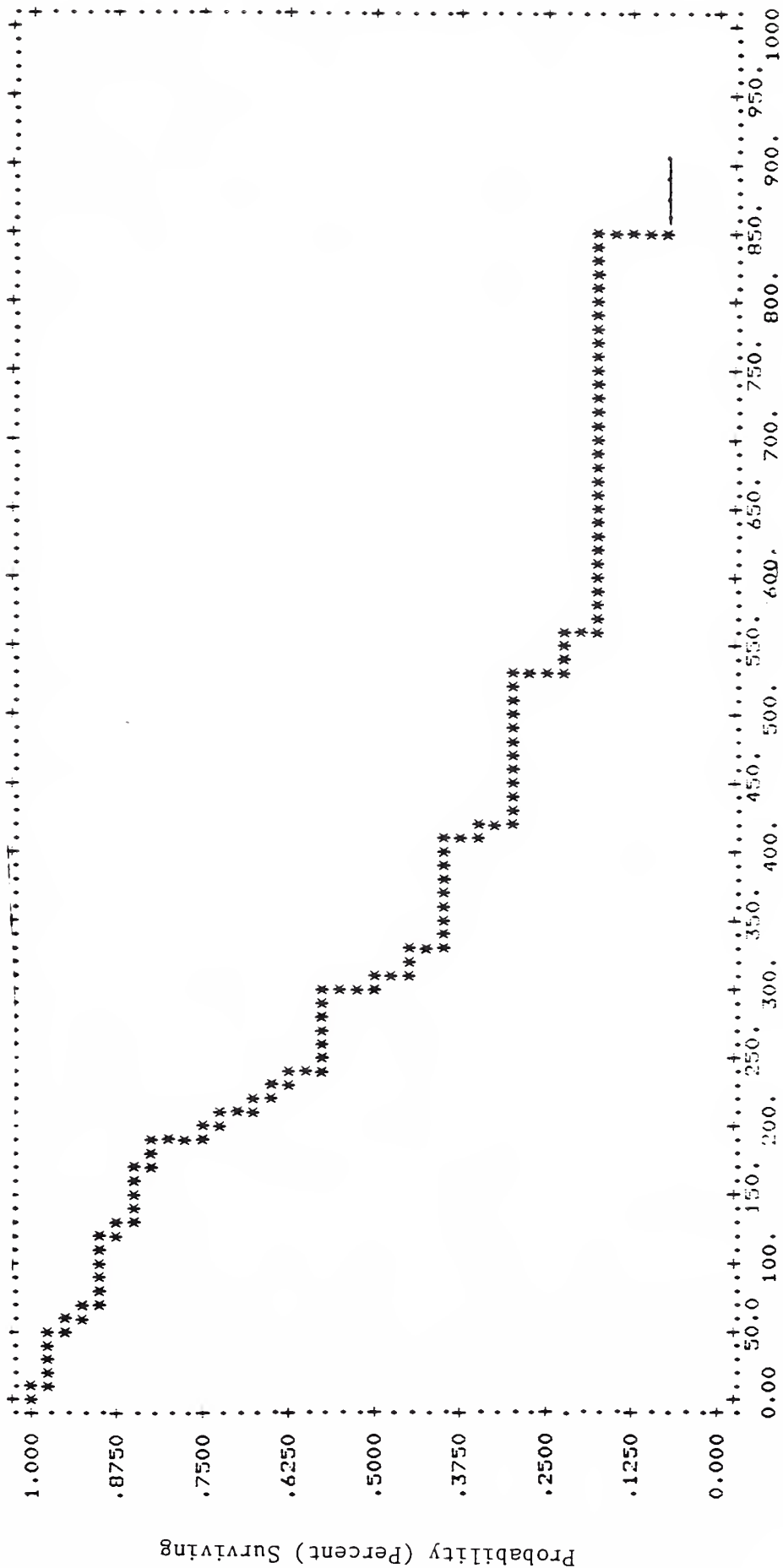
Figure 3 -- Time to Relapse for Limited Disease Patients by Treatment Group



A = CAV
 B = CAV/E

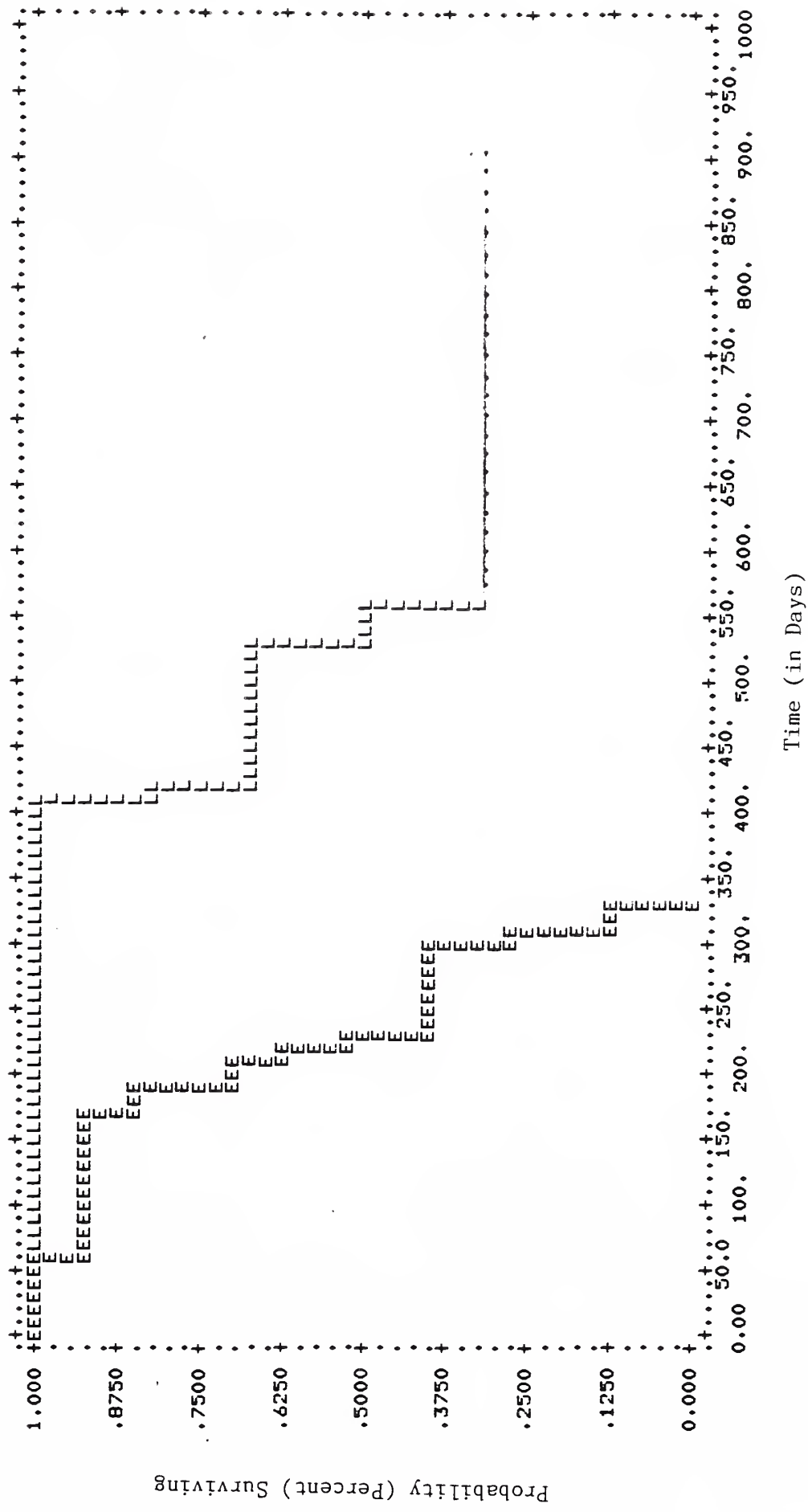
Time (in Days)

Figure 4 -- Time to Relapse for Extensive Disease Patients by Treatment Group



Time (in Days)

Figure 5 -- Overall Survival



L = Limited Disease
 E = Extensive Disease

Figure 6 -- Survival for Responders (CR + PR) by Disease Extent

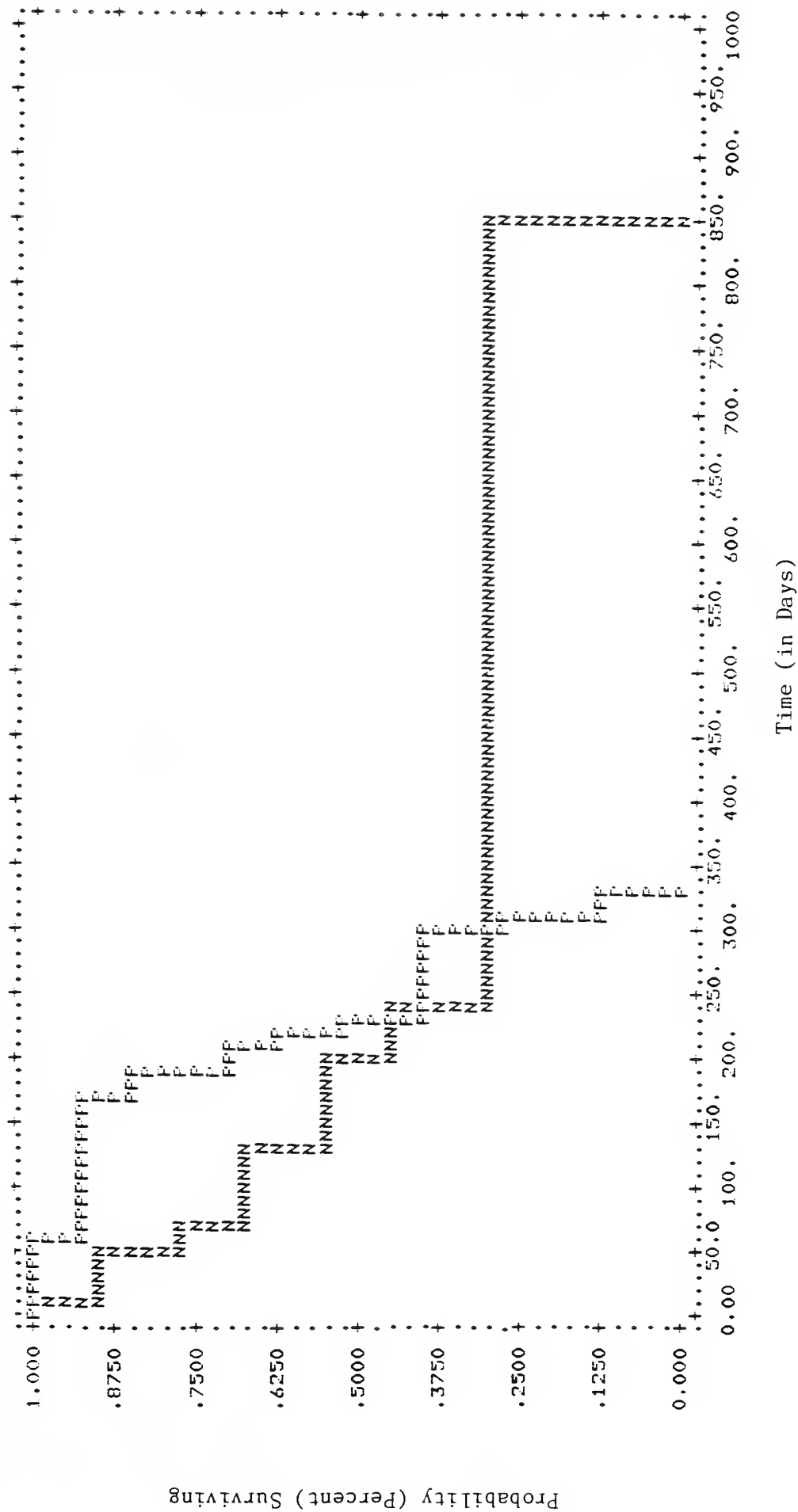
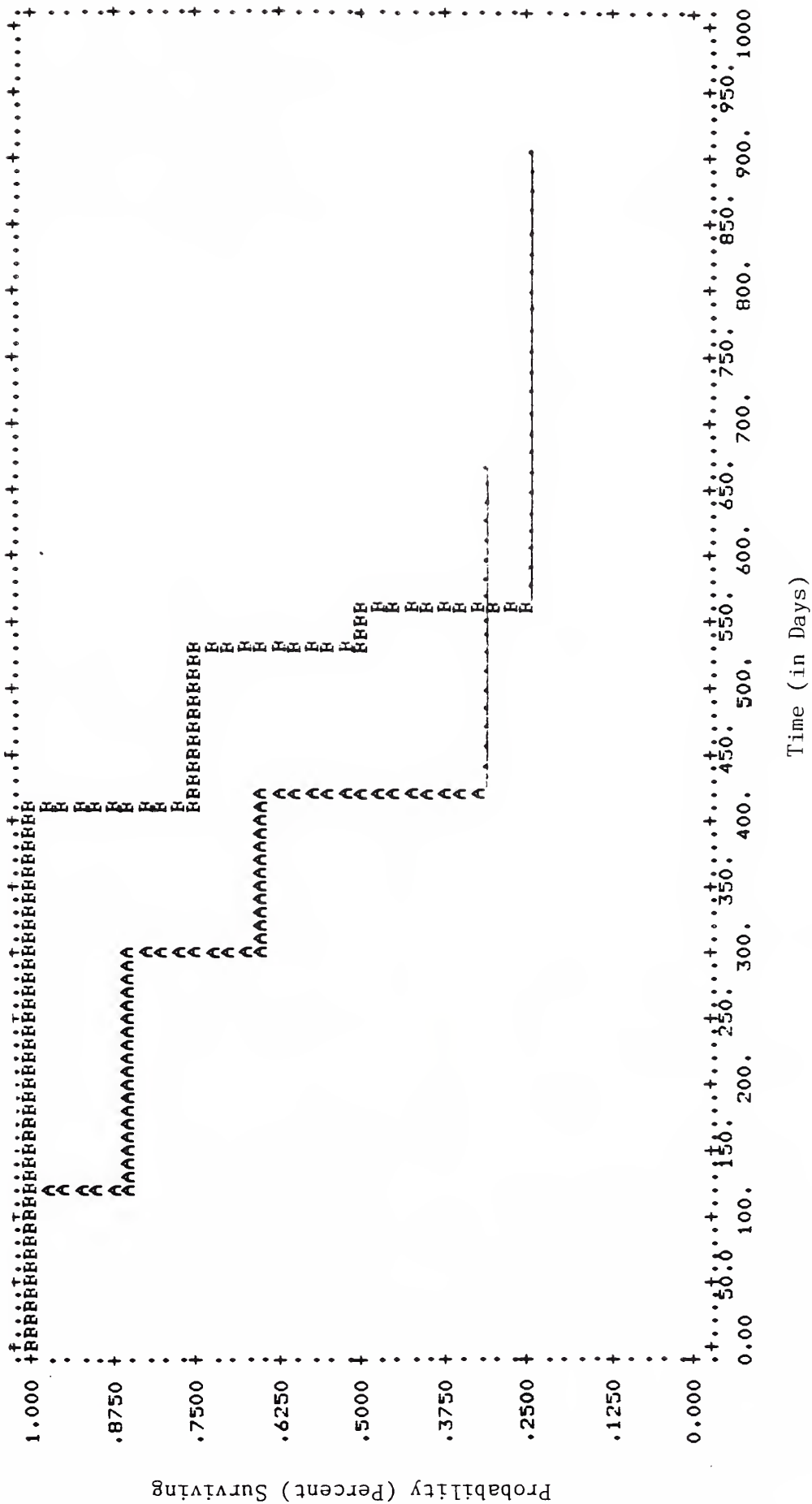
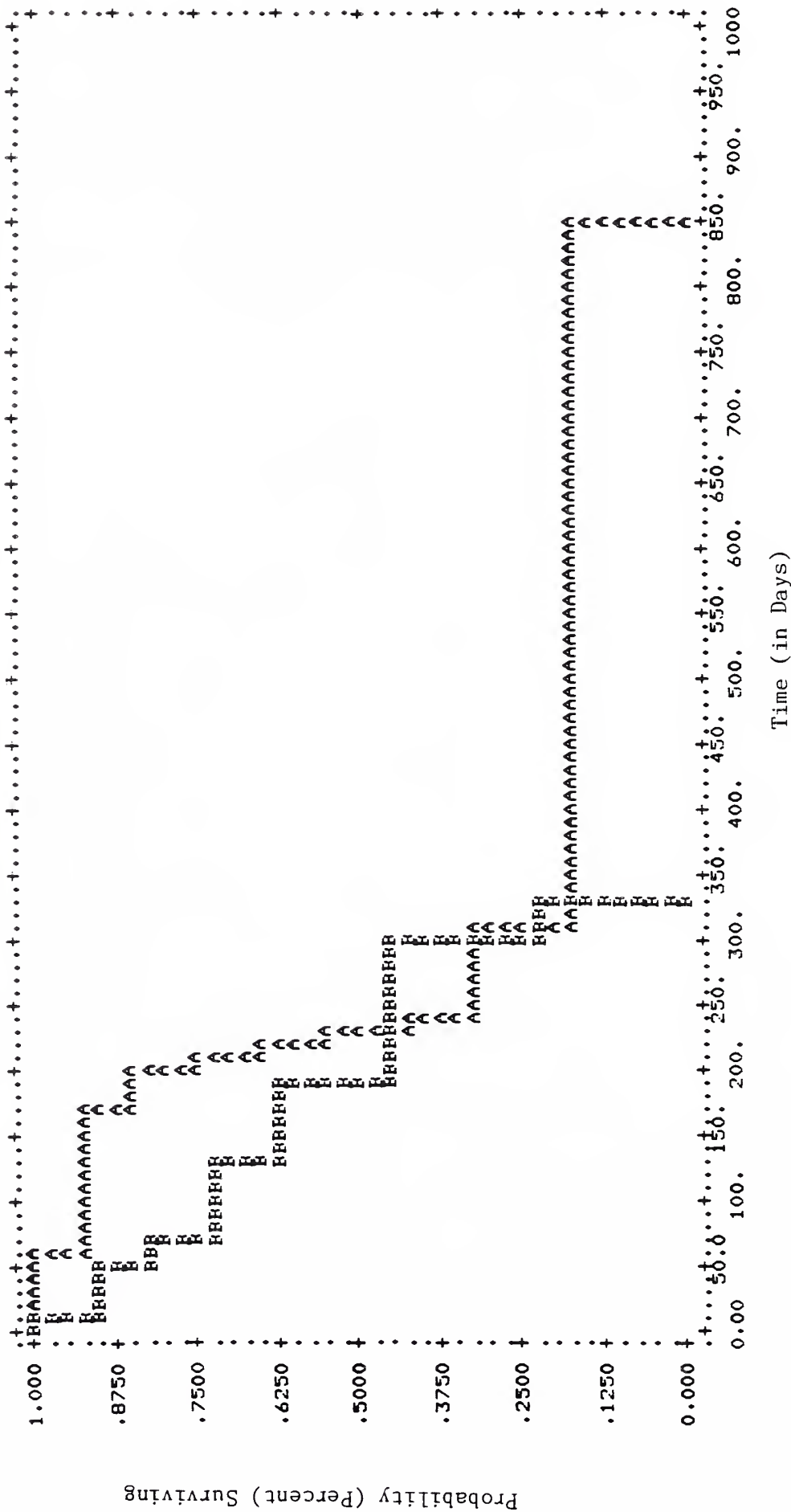


Figure 7 -- Survival for Extensive Disease Patients by Response Group



A = CAV/E
 B = CAV

Figure 8 -- Survival for Limited Disease Patients by Treatment Group



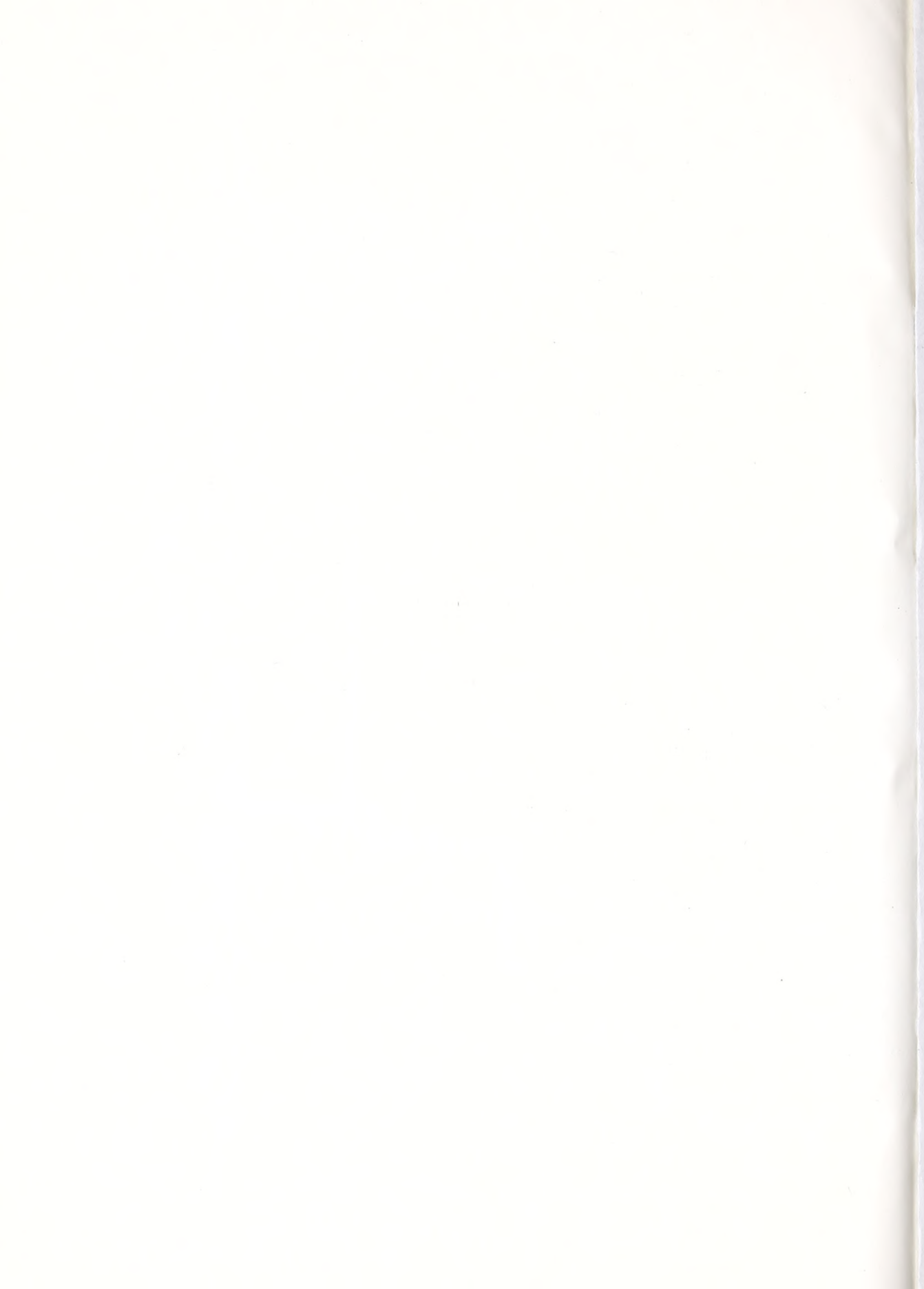
A = CAV
 B = CAV/E

Figure 9 -- Survival for Extensive Disease Patients by Treatment Group

and
the
lit

e

--
--





YALE MEDICAL LIBRARY

Manuscript Theses

Unpublished theses submitted for the Master's and Doctor's degrees and deposited in the Yale Medical Library are to be used only with due regard to the rights of the authors. Bibliographical references may be noted, but passages must not be copied without permission of the authors, and without proper credit being given in subsequent written or published work.

This thesis by _____ has been used by the following persons, whose signatures attest their acceptance of the above restrictions.

NAME AND ADDRESS	DATE
------------------	------

