SMALL CELL ANAPLASTIC CARCINOMA OF THE LUNG

(OAT CELL CARCINOMA)

Richard G. Sheehan, M.D.

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Introduction

The malignant lung tumor, popularly termed oat cell carcinoma, is a disorder worthy of discussion for a number of reasons. It is a common neoplasm. Its cellular origin and its recognized potential for paraneoplastic phenomena provide an interesting insight into the embryologic and functional interrelationships of physiologic systems that, on the surface, have little anatomic or functional connections. The progress, over a short span of time, in the management of this tumor demonstrates the clinical applications of basic observations regarding malignant cell growth, and the impact of cooperative interdisciplinary clinical approaches that is a model of the concepts of modern clinical oncology.

Definition

Walter and Bryce were among the first to recognize that this tumor was a separate and unique form of lung cancer both in terms of its clinical behavior and perhaps separate cellular origin (1). Histologically, it is comprised of relatively small cells with hyperchromatic nuclei and scanty cytoplasm that superficially resembles a lymphoma. The World Health Organization classification of lung tumors is shown in Table 1. The proper designation is small cell anaplastic carcinoma. Subtypes of this tumor are recognized histologically, and one of these, the lymphocyte-like appearing cells, is termed oat cell carcinoma. However, these different subtypes may be seen in different sections of the same tumor (2).

In addition, there is no evidence that the subclasses differ in their clinical behavior (3, 4). It has thus become popular terminology to use interchangeably the terms small cell anaplastic carcinoma and oat cell carcinoma of the lung. The popular term will be utilized in this discussion.

WHO CLASSIFICATION OF LUNG CANCER

HISTOLOGIC TYPE	% TOTAL
I. Epidermoid (Squamous Cell)	40
II. Small Cell Anaplastic	20
1. Fusiform cell 2. Polygonal cell 3. Oat cell	
III. Adenocarcinoma	15
IV. Large Cell Undifferentiated	20
V. - XIII. Others	5

TABLE 1

Incidence

Oat cell carcinoma accounts for approximately 20% of all malignant lung tumors. Table 2 demonstrates the impact of lung cancer as a public health problem. In particular, it is predominantly a tumor of middle-aged to elderly males. The oat cell type is one of the two histologic forms of lung cancer (the other being squamous cell) which has the highest association with cigarette smoking and other environmental and occupational inhalants (5). Table 3 indicates the frequency of lung cancer, and specifically oat cell carcinoma in relation to other forms of malignant disease. It is apparent that the tumor is as common as many of the more frequently emphasized cancers in man. These incidence data translate into a case incidence of approximately 175 new diagnoses per year in the Dallas-Ft. Worth area (6).

LUNG CANCER INCIDENCE - ANNUAL

TOTAL POPULATION	38/100,000
Males	63/100,000
Females	15/100,000
Males age 50	150/100,000
Males age 70	560/100,000

TABLE 2, Reference 6

ANNUAL CANCER INCIDENCE PER 100,000 POPULATION

SITE	INCIDENCE RATE
Colorectal	42
Breast	39
Lung	38
Uterus (including cervix)	24
Prostate	24
Bladder	12
Oro-pharynx	10
Stomach	10
Lymphomas - all	9
Leukemias - all	9
Pancreas	9
Ovary	7
Oat Cell of Lung	8

TABLE 3, Reference 6

Cellular Origin and Paraneoplastic Manifestations

Until approximately fifteen years ago, the major interest in this tumor revolved around its high propensity to be associated with a number of paraneoplastic and ectopic hormonal syndromes. These observations led to a large number of studies aimed at elucidating the cell of origin, its embryologic relationship to other cells in remote areas of the body, and the functional interrelationships of these cells. Indeed, this tumor continues to be a prime model for studying aspects of hormonal production and control and kinetic aspects of malignant cell growth.

Feyrter first proposed the presence of cells in the bronchial mucosa which might have an endocrine function (7). By electron microscopic methods, Bensch first identified a specific cell in the bronchial mucosa which fits this hypothesis (8). These cells were located near the basement membrane below the ciliated epithelium and mucous cells. He noted that the presence of secretory type granules, the tendency to form pseudopods, the tendency to be argentaffinic and their location in the mucosa was strikingly similar to the Kultschitzky cells of the gastrointestinal tract (7). Thus he termed these Kultschitzky-like cells of the bronchi or K cells. The endocrine function of these cells has not been proven. On the other hand, a number of lines of evidence suggest this role. The ultramicroscopic features of these cells are extremely similar to those of other neuroendocrine cells (9). The same type of anatomical interrelationships of the pulmonary K cells and neural elements has now been shown as exists for the gastrointestinal Kultschitzky cells (10). In addition, two pulmonary tumors have the same ultrastructural and histochemical characteristics as this cell, namely bronchial carcinoid and oat cell carcinoma. Both of these tumors have a high frequency of "ectopic" syndromes associated with the production of polypeptide hormones and fluorogenic amines.

Pearse first emphasized that a number of polypeptide producing cells of both endocrine origin and non-endocrine tissues shared a number of cytochemical and ultrastructural properties (11, 12). These are listed in Table 4. The first three features, that is the fluorogenic amines (catecholamines and serotonin) in these cells, the ability to take up their precursors (DOPA and 5 hydroxytryptophan) and the ability to decarboxylate these precursors to form the product, led him to coin the term APUD cells. Of the several ultrastructural features, the presence of neuro-secretory granules is the most regular and important. Finally, Tischler has demonstrated that cells of this series as well as tumors derived therefrom are capable of undergoing electrical excitability (13, 14). Based on the presence of these features, many cells located throughout the body, not only in endocrine organs, were felt to possess neuroendocrine functions. Those cells, which are presently classified as part of the APUD system, are listed in Table 5 along with the specific polypeptide hormone which they are known to produce. In some instances, a specific polypeptide product has not been positively identified.

Pearse and later Weichert (11, 12, 15) proposed that embryologically, these cells arise from the neural crest derivative of the neuroectoderm and then migrate to their various anatomic sites and there give rise to their

specific functional capacities. Pearse has more recently modified this embryologic concept to propose that these cells arise from neuroendocrine-programmed ectoblasts without necessarily having migrated from the neural crest (16).

CHARACTERISTICS OF APUD CELLS

1. Fluorgenic Amines
2. Amine Precursor Uptake
3. Aminoacid Decarboxylase
4. Masked metachromasia
5. Non-specific esterase and cholinesterase
6. Alpha glycerophosphate dehydrogenase
7. Polypeptide hormones
8. Electrical excitability
9. Membrane bound secretory granules

TABLE 4, Reference 11-14

APUD CELLS

Cell	Polypeptide Hormone
Adenohypophysis	ACTH, MSH, LPH, Endorphin
Neurohypophysis	ADH, Oxytocin
Pancreatic Islet Cells and Gastrointestinal Cells	
A	Glucagon
B	Insulin
D	Somatostatin
D_1	VIP
D_2	Pancreatic polypeptide
I	CCK
G	Gastrin
K	GIP
EC_2	Motilin
EC_1	Substance P
EG	Enteroglucagon
H	Bombesin
S	Secretin
Thyroid C cell	Calcitonin
Adrenal chromaffin cells	--
Autonomic neurons	--
Lung Kultschitzky cells	--
Melanocytes	--

TABLE 5, Reference 12

Benign and malignant tumors felt to arise from any of these cells have thus been termed APUDomas (Table 6). These include the multiple endocrine adenoma syndromes, functioning tumors of endocrine organs, as well as certain tumors of non-endocrine tissues. One of the striking features of these tumors is the high propensity to be associated with the production of polypeptide hormones or fluorogenic amines. In some instances, this is the hormone normally produced by the cell of origin (e.g., insulinomas, gastrinomas and calcitonin by medullary carcinoma of the thyroid). In other instances, the hormone is "ectopically" produced. Oat cell carcinoma of the lung is a classic example of the latter. Nevertheless, even in the case of the ectopic hormone producing APUDomas, the hormones produced are, in the vast majority of instances, hormones normally produced by other cells of the APUD series.

APUDOMAS

1. Pancreatic Islet Cell Tumors
2. Foregut carcinoids
3. Medullary carcinoma thyroid
4. Thymomas - epithelioid cell
5. Pheochromocytomas
6. Neuroblastomas
7. Oat cell carcinomas
8. Melanoma (?)

TABLE 6, Reference 12

In contrast, tumors of other cell types, including other lung tumors, are felt to arise from cells of different embryologic origin and give rise to ectopic hormones syndromes specific for their group (for example, ectopic parathormone production) (17).

Ectopic Manifestations of Oat Cell Carcinoma

As mentioned previously, the pulmonary K cell as well as the tumors felt to derive from it (bronchial carcinoid and oat cell carcinoma) share most of the cytochemical and ultrastructural features of APUD cells with the exception that a specific polypeptide product for the K cell has not been identified. Oat cell carcinoma of the lung is the tumor with the highest frequency of ectopic production of polypeptide hormones, and in addition, has occasionally been associated with syndromes produced by excess fluorogenic amines (17, 18). Table 7.

The most common, clinically manifest, ectopic hormone syndrome in oat cell carcinoma is that of the inappropriate secretion of antidiuretic hormone. SIADH has been reported in as many as 12% of patients in two series (19, 20). Proof of production of the hormone by the tumor, in several instances, has been firmly established. Not only have serum levels of vasopression been

elevated, but tumor extracts revealed excessive levels of the hormone (2, 21, 23). In addition, George, et al., have demonstrated synthesis by tumor cells with short term incubation studies (24) and Pettengill, et al., have established a long term tissue culture of an ADH producing oat cell carcinoma (25). Patients without the clinical syndrome do not appear to have increased plasma levels of vasopression by immunoassay (22). This syndrome appears to be very specific for oat cell carcinoma as opposed to other malignant lung tumors.

ECTOPIC HORMONES AND BIOGENIC AMINES
PRODUCED BY OAT CELL CARCINOMA

Substance	Clinical Syndrome
Proven	
ACTH	Uncommon
β-MSH	Rare
ADH	Common
Serotonin	Rare
Insulin	None
Calcitonin	None
Oxytocin	None
Possible	
Glucagon	
Gastrin	
β Lipotropic Hormone (β-MSH, Endorphin)	
VIP	

TABLE 7, References 17-30

Serotonin has also been extracted from a large proportion of oat cell carcinomas tested (2, 26, 27). However, elevated levels of serotonin in the serum or increased 5HIAA excretion in the urine are rare. Carcinoid syndrome has been reported in oat cell carcinoma, but again, this is rare (2, 17). Other forms of lung cancer have not had demonstrable increases in serotonin content (2).

Silva, et al., noted that 50% of patients with lung cancer of various cell types, who were normocalcemic, had elevated serum levels of calcitonin. In two patients with oat cell carcinoma, tumor extraction or venous sampling of the tumor indicated tumor production of the hormone (28). No clinical syndrome appeared to be produced. Another group was unable to confirm this incidence of hyper-calcitoninemia, however (20). Recently, Ellison, et al., have demonstrated calcitonin synthesis by oat cell carcinomas in short and long term tissue culture (29).

Increased levels of insulin and oxytocin have been reported in tumor extracts of oat cell carcinoma in at least one report (17). Glucagon and insulin levels were elevated in tissue extracts of an "undifferentiated" lung carcinoma metastasis by Unger, et al. (30). It is not known if this was an oat cell carcinoma. Clinical syndromes attributable to these hormones in this tumor have not been described.

One of the more recently characterized peptide hormones has been shown to be present in elevated concentrations in the plasma of patients with lung cancer. Dr. Sami Said has demonstrated elevated levels of plasma vasoactive intestinal peptide (VIP) in 16/55 patients with lung cancer. This appeared not to be specific for oat cell carcinoma, since all four major histologic types are represented in his series (unpublished observations). A few patients appeared to have a clinical syndrome associated with the presence of this peptide.

The greatest interest has been in the production of ACTH by oat cell tumors. Ectopic ACTH syndromes are the most commonly reported for APUD tumors as a whole. A review of patients with clinically apparent Cushing's syndrome by Azzopardi indicated that all of those that he considered validated were in association with tumors that fell into the category of APUDomas (31). Oat cell carcinoma of the lung was the most frequently reported tumor.

Extensive studies of the association of ectopic ACTH production with lung tumors have, more recently, resulted in a more complex and less easily explained pattern of observations. As noted, clinical manifestations of ectopic ACTH production have been reported almost exclusively in oat cell carcinoma and carcinoid tumors as opposed to other histologic types of lung cancer. The syndrome is manifested by weakness, hypokalemia, frequent hypertension, edema and glucose intolerance. Centripetel obesity is generally not seen. The elevated plasma ACTH activity is not dexamethasone suppressible (32). In such patients, Liddle's group and Rees' group have demonstrated the presence of increased levels of ACTH-like material in tumor extracts and plasma that is chemically, immunologically, and biologically indistinguishable from normal human (39 residue) ACTH (33, 34). Additionally, both groups have demonstrated an excess of smaller N-terminal and C-terminal peptides of ACTH in these tumors. Bloomfield, et al., also found immunoreactive and biologically active ACTH as well as fragments in oat cell tumors from patients without the ectopic syndrome, but insignificant levels of these in non-oat cell lung tumors (35). Rees' group and Imura's group have demonstrated actual synthesis of bioactive ACTH by these tumors in cell culture (36, 37). On the other hand, Imura's group and Yalow's group have both demonstrated ACTH immunoreactivity in tumor extracts of all histologic types of lung tumor examined (patients without the ectopic syndrome). In the patients studied by Yalow, essentially all of the immunoreactivity was due to a larger molecular weight material than the natural 39 residue hormone (26, 38). This "big" ACTH is almost devoid of bioactivity but can be converted to bioactive ACTH peptides by trypsin treatment (39). Table 8 summarizes these points. A major problem inherent in all of these studies is that extraction procedures and antisera for detection of immunoreactive material varies between the groups. Thus, for example, Yalow's assay will not detect small N and C terminal fragments of ACTH, and Liddle's and Rees' extraction procedures

probably exclude or degrade nearly all of the "big" ACTH material (33-38).

It is apparent that, at the present time, differences in technical approaches preclude a clear understanding of the significance of ectopic ACTH production by lung tumors. It is possible that differences in the types of ACTH peptides formed or other cellular factors of a catabolic or secretory nature govern the observation that ACTH-like immunoreactive material appears to be synthesized by all lung tumors, but ectopic Cushings syndrome is almost exclusively seen with the oat cell or carcinoid cell types.

ECTOPIC ACTH PRODUCTION IN LUNG CANCER

Clinical State	TUMOR ACTH Big	Natural	Fragments	Bioactive	Tumor Type
Ectopic Cushings	+	++	++	++	Oat Cell Carcinoid
No Ectopic Cushings	++	+	+	+	Oat Cell Carcinoid
	++	0	0	0	Non-Oat Cell

TABLE 8

Additional advances in the understanding of the ectopic hormonal syndromes seen in oat cell carcinoma are evolving from the elucidation of the biochemistry and physiology of production and secretion of certain other pituitary hormones. It has been known for sometime that β-MSH immunoreactivity is commonly seen in tumors and plasma of patients with ectopic ACTH production (17). Normally, β-MSH is not seen as a single species in the plasma of normal persons. It appears as a part of a larger (91 amino acid) peptide, β-lipotropin (β-LPH). This peptide actually contains the entire biological and immunoreactive sequence of β-MSH (residues 41-58), β-enkephalin (residues 61-65) and β-endorphin (residues 61-91). The latter two substances are naturally occurring, pituitary produced, endogenous opiate agonists. Recent studies have indicated that β-MSH activity found in patients with ectopic production is actually a β-LPH like substance (40). Furthermore, recent preliminary assays for β-endorphin immunoreactivity, in cooperation with Dr. Roger Unger, have shown increased immunoreactivity in 5/5 patients with oat cell carcinoma. A further chapter in this story is the observation by Mains, et al., that human pituitary extracts and mouse pituitary tumors contain a single molecule containing both a large ACTH antigenic determinant and β-LPH (41). It is possible, therefore, that tumors may produce any portion or all of these closely related peptide materials and thus explain the frequency of finding these multiple markers in the same patient population.

Use of Ectopic Hormones as Tumor Markers

One reason for major interest in the ectopic hormone syndromes is that they have the potential for serving as means of identifying the presence of malignancy, perhaps at a very early stage of development, and also as a means for ascertaining response to treatment and a signal of early relapse. Yalow has published a series of observations of plasma ACTH levels in patients with lung cancer and other lung disorders (42). Ninety percent of patients with untreated lung cancer had elevated plasma levels of ACTH-like immunoreactive material (Figure 1). As was true for their studies of tumor content, there was no specificity for cell type and essentially all of the material was biologically inactive "big" ACTH by chromatography. The incidence of elevated levels was lower in treated patients and tended to fall following therapy when serial observations were available. Of interest was that they noted increased levels in a few patients with evidence of chronic obstructive lung

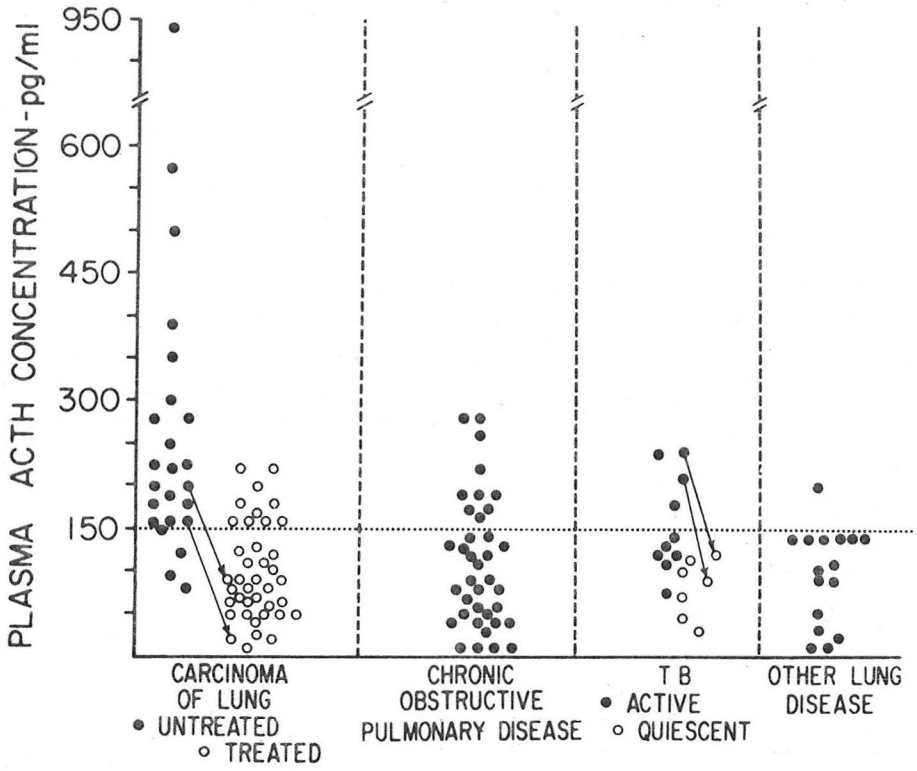

FIGURE 1, Reference 42

disease only. In 3 such patients, the diagnosis of carcinoma eventually was apparent in a period of 5 months or less. The explanation for the elevated levels in other patients with COPD or tuberculosis is unclear, but Gould, et al., have described dysplasia of the neuroendocrine cells (K cells) in bronchi

of patients with non-oat cell lung tumors as well as in some patients with non-neoplastic lung processes (43). They proposed that these dysplastic cells might occasionally produce hormone substances in the transformed state. Presently, more studies will be necessary to determine which peptide markers (or other substances), alone or in concert, may become useful for early diagnosis and serial evaluation in patients with lung carcinoma and also, perhaps, serve as specific markers for the oat cell tumor type. In this context, it is of interest to note that only oat cell carcinoma of the lung has been implicated in the simultaneous ectopic production of both ADH and ACTH (44).

Tumor Kinetics

Oat cell carcinoma is a rapidly growing tumor relative to most solid neoplasms. This feature carries significant implications regarding clinical behavior and potential therapeutic approaches. The tumor doubling time compared to other histologic types of lung cancer is shown in Table 9. Although this is a rather crude measure of tumor growth characteristics, it does correlate with a number of other clinical features. Thus, it has been shown that the time from diagnosis of the primary tumor to first evidence of metastases, the time from a solitary focus to multiple foci, and patient survival times all are proportional to the doubling time (46, 47). In addition, tumors with short doubling times may be more radiosensitive than those with longer *in vivo* doubling times (48).

TUMOR DOUBLING TIMES
FOR LUNG CANCER

Histology Type	Average D.T. (Days)
Oat Cell	33
Large Cell Undiff	92
Epidermoid	103
Adenocarcinoma	187

TABLE 9, Reference 45

The doubling time of a tumor is a composite result of a number of parameters including the size of the lesion when first measured, the growth rate of the tumor cells and the spontaneous cell loss (death) within the tumor. The latter two parameters are not easily measured, especially cell loss. Nevertheless, certain kinetic parameters of malignant tumors have been measured and some broad conclusions can be drawn that are applicable to oat cell carcinoma. The growth rate of a tumor cell population is a function of the characteristics of its cell cycle and the proportions of the cells in various

kinetic compartments (Figures 2 and 3). In general, a tissue, normal or neoplastic, can be shown to have at least four such compartments (49-51). 1) A rapidly proliferating cohort which enters DNA synthesis within 48 hours of measurement; 2) a slowly proliferating fraction which demonstrates DNA synthesis over a longer period of observation; 3) non-cycling cells which retain their potential for proliferation (resting cells) and 4) non-cycling cells which can never proliferate (end stage cells). The resting cell population is of major clinical importance. These cells (either in a quiescent post-mitotic stage, G_0, or in a post-mitotic phase of the cycle, G_1) contribute to overall growth rate, and the G_1 duration will affect the apparent cell cycle time or generation time (Tc). The relative proportion of cells in these various compartments not only will be, in part, responsible for the rate of tumor doubling, but also will generally indicate the potential for chemotherapeutic responsiveness. A number of chemotherapy agents are so called cycle specific, that is, they are effective in inducing cell death only when the cells exposed are in the cell cycle or a specific portion (e.g., DNA synthesis phase, G_2 or mitosis). Also, agents which are non-cycle specific often demonstrate an increased dose-related effect on cells in cycle versus the resting cell population (52). Kinetic parameters that have been measured in oat cell carcinoma are shown in Table 10.

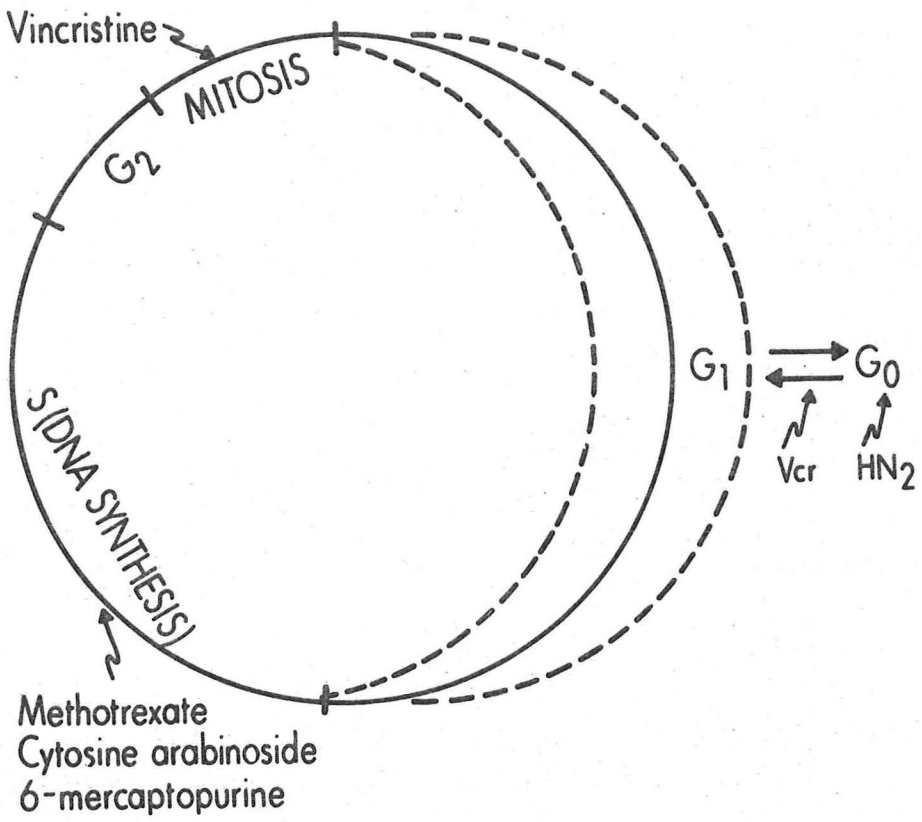

FIGURE 2

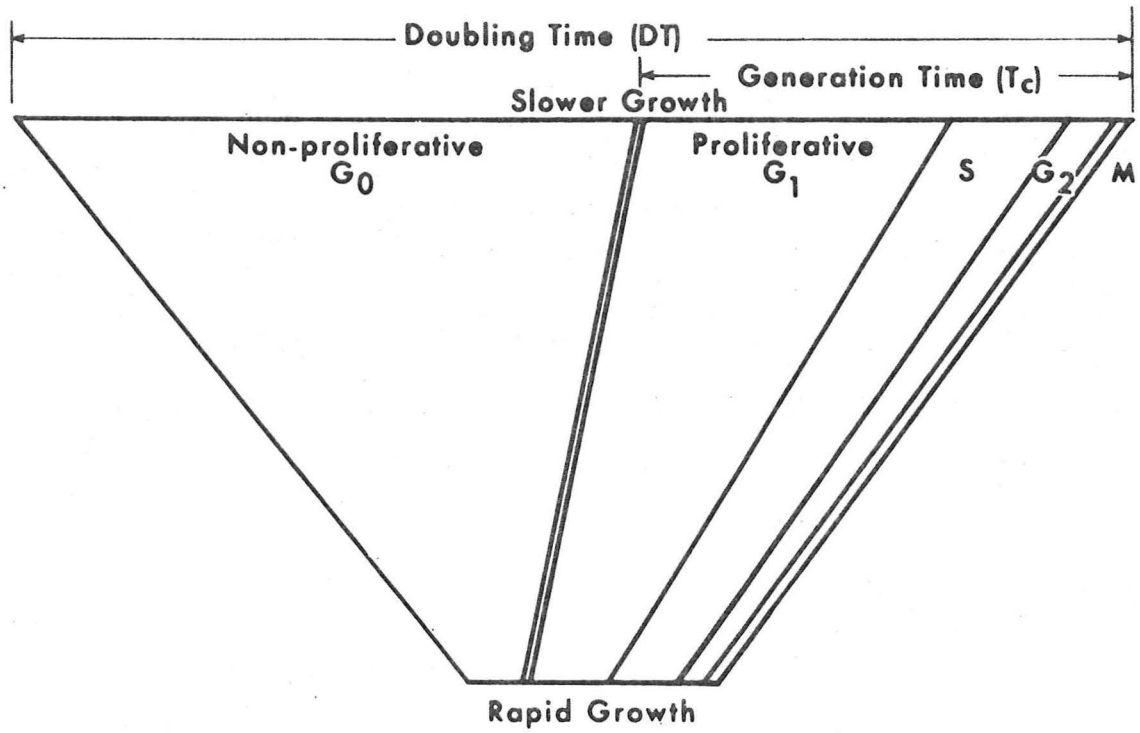

FIGURE 3, Reference 50

The median labelling index of twelve tumors was 17% (53). This is a measure of the proportion of cells in DNA synthesis phase at a given single point in time. This value is very high for a solid tumor and approximates those found in certain leukemias and lymphomas (54). The values for duration of DNA synthesis (Ts), G_2+M, G_1 and Tc are not significantly different from many tumors and normal tissues. The percentage of cells labelled at 48 hours was 44-55% indicating a high proportion of cells in the rapidly proliferating compartment. The growth fraction has been calculated to be 0.5.

CELL CYCLE DATA FOR OAT CELL CARCINOMA

1. Labelling index 7.2-29.5% (Median 17)
2. Percent labelled cells at 48 hours: 44-55%
3. Generation time (Tc) 64 hours
4. Post Mitotic GAP (G_1) 38 hours
5. DNA Synthesis Time (T_3) 19 hours
6. Post Synthesis GAP + Mitosis (G_2/M) 7 hours
7. Growth Fraction 0.5

TABLE 10, Reference 53

These values indicate a larger growth fraction and larger percentage of cells in the rapidly proliferating compartment than with most solid tumors. Thus, one might predict that oat cell carcinoma would be a rapidly progressive, early metastisizing tumor which could, however, be relatively radiosensitive and also responsive to a number of cycle specific and cycle nonspecific chemotherapeutic agents.

Staging of Oat Cell Carcinoma:

One of the features which sets oat cell carcinoma apart from other lung tumors, and also from almost all other solid tumors is its high propensity for metastases at the time of presentation. As will be seen, this feature is so prominent that even in patients in whom metastases cannot be demonstrated, surgical resection is not curative; and only rarely is intensive radiotherapy successful. This clearly implies that micrometastases are essentially universally present at presentation. This characteristic negates the use of the standard staging system for lung carcinoma, since it is predicated on the assumption that certain patients will have a potentially operable lesion (55). At the present stage of our knowledge it is clear that the most significant determinants of potential therapeutic benefit and survival prolongation are simply the presence or absence of demonstrable distant metastases. The terms limited or loco-regional disease versus extensive disease are applied to differentiate these two situations.

Limited disease is defined as disease demonstrable only in the primary hemithorax and the mediastinum. It is as yet unclear as to whether ipsilateral supraclavicular lymph node involvement dictates a prognosis more in keeping with extensive or limited disease. Pleural effusions are considered limited disease.

Extensive disease is defined as demonstrable disease in the contralateral hemithorax or beyond the confines of the thoracic contents. Figure 4 demonstrates an example, from a series at this institution, of the difference in prognosis based on this delineation alone (unpublished observations).

The frequency of these two categories of extent of disease is unclear and may be changing due to earlier recognition and evaluation of patients with oat cell carcinoma as effective therapeutic approaches are emerging. In general, approximately 30% of any series of patients with this diagnosis will be classified as limited disease when careful staging procedures are performed.

The following sections will discuss the frequency and approaches to detection of various anatomic sites of metastases of oat cell carcinoma of the lung.

Bone

Bone involvement is the most common site of distant metastases in patients with oat cell carcinoma of the lung. Table 11 demonstrates the relative frequency of bone marrow involvement in a series of 200 consecutive patients with lung cancer studied at the NCI-VA Medical Oncology Service (56). Table 12

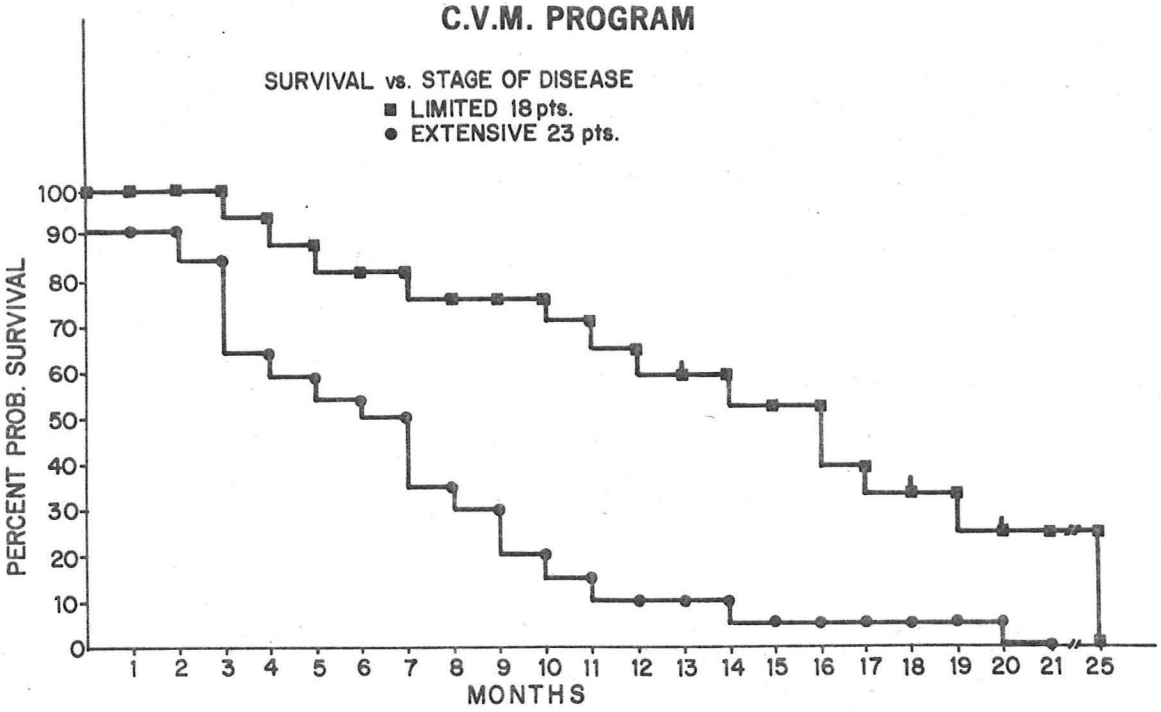

FIGURE 4

indicates the relative utility of various parameters for identifying bone metastases (3, 56). It is clear that the bone scan and bone marrow are complementary techniques for identifying spread to bone. Skeletal films are uncommonly abnormal, but when so, there is a unique propensity for the lesions to be osteoblastic as opposed to the usual osteolytic nature in other lung tumors (57, 58). Hypercalcemia is rare in oat cell carcinoma (59).

BONE MARROW METASTASES
IN LUNG CARCINOMA

Cell Type	% Positive
Oat Cell	43
Large Cell Undiff	17
Squamous Cell	3
Adenocarcinoma	18

TABLE 11, Reference 56

DIAGNOSIS BONE METASTASES
IN OAT CELL CARCINOMA

Bone Involvement	59%
Marrow Positive Only	30%
Scan Positive Only	16%
Both Positive	13%
Bone Radiography Abnormal	4%
Hypercalcemia	<0.1%

TABLE 12, References 3, 56

Recently, the frequency of positive bone marrow examinations appears to have declined, perhaps due to earlier referral of patients with this cell type for definitive therapy (3). This latter study revealed, also, that bone marrow aspirates were positive alone in 38% of involved marrows as opposed to the biopsy alone being positive in 8%. In 54%, both procedures were positive. This is in contrast to most tumors when bone marrow metastases are present. An additional point emphasized in that study was that the abnormal bone marrow examination was the only site of distant metastases identified in 77% of patients when liver biopsy by peritoneoscopy was excluded.

Liver

The liver is a common site of metastatic disease in oat cell carcinoma of the lung. It is the most frequent site at autopsy, being present in over 60% of patients at the time of demise (56). Of more importance to the question of clinical management is the frequency of this site of involvement at the time of diagnosis. Several lines of evidence indicate that this is in the range of 30-40% of patients when invasive attempts at evaluation are made. 37% of patients dying within one month of diagnosis have autopsy proven liver metastases (60). Transdiaphragmatic exploration of the liver in apparently operable patients with lung carcinoma at the time of thoractotomy revealed 25% of "undifferentiated" tumors to have spread to the liver (61). Two separate studies of patients, utilizing peritoneoscopy with direct visualization and biopsy, demonstrated that 30% and 40% of patients with oat cell carcinoma had liver metastases (4, 62). This frequency is considerably higher than in other cell types of lung cancer (Table 13). This will be the only site of metastasis in approximately 10% of patients at the time of staging procedures. As a result of these studies, it is apparent that the pre-biopsy evaluation of liver metastases is more reliable in oat cell carcinoma than in other tumors; nevertheless, not without false positive and false negative assessments. In the series of Margolis, et al., no patients with metastases from this cell type had entirely normal liver functions, and two had normal liver scans (62). Thus, the liver scan was falsely negative in 2 of 11 patients. The liver scan was, however, falsely positive in one-third of patients.

INCIDENCE OF HEPATIC METASTASES
IN LUNG CANCER AT DIAGNOSIS

Cell Type	% Involved
Oat Cell	30 - 40
Epidermoid	2
Adenocarcinoma	4
Large Cell Undiff.	<1

TABLE 13, References 4, 62

In the 162 oat cell patients biopsied by Dombernowsky, et al., 68% that had a positive liver biopsy had 2 or more abnormal liver function tests and only 3% of those with negative biopsies had this degree of liver function abnormality (4). These observations are similar to those of Margolis, et al.

A summary of the evaluation of liver involvement in oat cell carcinoma of the lung is shown in Table 14. Based on these data, we have utilized, as non-invasive criteria for hepatic metastases, the presence of a positive or suspicious liver scan and two or more abnormal liver function tests (one of which is the alkaline phosphatase). This should produce an approximate 10-20% false negative result. The false positive rate will be in the range of 5-10%. However, since the number of patients with hepatic metastases only is relatively low, this results in an acceptable alternative to invasive procedures if patient management is not based on this criteria. If treatment programs are, as is likely in the near future, to be different in patients with extensive versus regional disease, then biopsy approaches may be necessary in those with apparently localized disease in whom simpler studies have not demonstrated other areas of metastases. Unfortunately, evaluable percutaneous liver biopsy results, in which this tumor is specified, are not available. Also the use of alternate means of evaluating liver metastases for this specific tumor, such as C.T. scans and ultrasonography, have not been adequately evaluated.

EVALUATION OF LIVER INVOLVEMENT
IN OAT CELL CARCINOMA

1. Only site of metastasis in 10% of patients.
2. Two or more abnormal liver function tests in 70% of positive biopsies; 3% false positives.
3. Normal liver function tests in 7% of positive biopsies
4. Alkaline phosphatase elevated in 80% of positive biopsies; 14% false positive.
5. Liver scan positive or suspicious in 75% of positive biopsies; 20% false negatives and 25% false positives.

TABLE 14

Local Nodal Metastases

As is true of all lung tumors, the most common first site of metastases will be the hilar and mediastinal lymph nodes. Involvement of mediastinal nodes is an indication of lack of operability. Goldberg, et al., carefully staged the mediastinum in a large series of lung tumor patients by either mediastinoscopy or exploratory thoracotomy (63). Mediastinal lymph node

involvement was found in 70% of the patients with oat cell carcinoma. Seventy percent of these (50% of all patients) had bilateral mediastinal node metastases. These findings are consistent with those of Kato, et al., who noted 72.5% of oat cell patients to have hilar and mediastinal mode metastases at diagnosis (64).

Other Metastatic Sites

Table 15 lists other common sites of metastases identified in oat cell lung cancer patients and the approximate frequency of observation at presentation or at autopsy.

Central nervous system metastases occur during the course of the disease in 30-45% of patients as judged by autopsy results (19, 65). Newman and Hansen noted brain metastases at diagnosis in 8% of their cases and Kato, et al., noted a similar incidence of 12% for brain lesions at the time of initial diagnosis (64, 65). Williams, et al., noted the development of brain metastases during treatment in one-third of their series (66). Of primary therapeutic importance is that in perhaps 20% of patients in complete clinical remission, the brain is the first site of disease recurrence (19).

As with other widely metastisizing tumors, extradural cord compression and meningeal carcinomatosis are also not infrequently observed during the course of these patients (67). Diagnosis of brain metastases is usually made by scanning techniques. It has been stated that up to 5% of patients with no clinical evidence of brain lesions will have positive brain scans (68). This number may be somewhat high. At a recent conference, several investigators indicated that the yield of this procedure in oat cell carcinoma was essentially nil when there were no signs or symptoms pointing to the CNS. On the other hand, when brain lesions are suspected clinically, scanning procedures will demonstrate metastases in the brain approximately 50% of the time (68).

Skin metastases and metastases to lymph nodes outside of the thoracic cage are seen in 15-20% of patients at presentation. The most commonly observed sites of these nodal metastases are the ipsilateral supraclavicular and scalene nodes. In the NCI-VA series, 16% of patients had node or skin metastases at diagnosis (56). In the series of Takita, et al., 18% of the patients actually had their tissue diagnosis made by supraclavicular lymph node biopsy (69). Biopsy of such lesions often saves the patient bronchoscopy or thoracotomy. In addition, when necessary for staging purposes, they are readily accessible sites to demonstrate extensive disease.

Abdominal lymph node and retroperitoneal metastases are common at autopsy. Fifty-seven percent of one series had abdominal lymph node metastases at postmortem (56). In the same series, adrenal metastases were present in 40%. Up to 20% of patients may have metastases to the pancreas (19). This may be clinically manifest during life by abdominal pain and occasionally hyperamylasemia. Ultrasonography can often assist in making this diagnosis. How frequently these various sites are abnormal at the time of diagnosis is unknown. No significant series of exploratory laparotomies or lymphoangiography have been published. Clinically, it does not appear that these sites are commonly the

only site of early metastasis and thus are not routinely examined by invasive techniques for staging purposes.

OTHER METASTATIC SITES IN OAT CELL CARCINOMA OF THE LUNG

	% at Diagnosis
Central Nervous System	
Brain	10
Cord Compression	--
Meningeal Carcinomatosis	--
Skin and Supraclavicular Lymph Nodes	20
Hilar and Mediastinal Nodes	70
Bilateral	50
Adrenal (Autopsy)	(40)
Abdominal Nodes and Pancreas (Autopsy)	(55)

TABLE 15

Another important parameter which significantly relates to prognosis irrespective of any others is the evaluation of the patient's clinical performance status. This is generally true for all lung tumors as well as many other malignant neoplasms (70).

A simple, applicable and clinically relevant performance classification is that developed by the Eastern Cooperative Oncology Group. This is recorded on a scale of 0-4 as follows: 0 = normal activity; 1 = symptoms but ambulatory; 2 = in bed less than half the time; 3 = in bed more than half the time; 4 = completely bedridden. Observation of this variable is important when attempting to test or interpret clinical trial data as well (71).

Table 16 lists the recommended staging procedures for patients with oat cell carcinoma of the lung as indicated by the data reviewed in the preceding section.

SUGGESTED STAGING EVALUATION OF OAT CELL CARCINOMA

Physical Examination - Functional Status	
Chest X-Ray	
CBC - Platelet Count	
Serum Electrolytes	
Liver Function Tests	
Bone Marrow Aspirate and Biopsy	
Bone Scan	
Liver Scan	
Brain Scan	(Metastasis Suspected)
Peritoneoscopy - Liver Biopsy	(Optional)
Peptide and Amine Markers	(Optional)
Biopsy Skin/Nodes	(Optional)

TABLE 16

Therapy

The treatment of oat cell carcinoma at the present time, and its effect on the natural history of the disease, is an excellent model of how the collaboration of multiple clinical disciplines utilizing well-designed clinical trials has made a significant impact in the area of malignant disease. Less than a decade and a half ago, the outlook for patients with neoplasm was dismal. Figure 5 demonstrates the survival of untreated patients; that is, the natural history of the disease. In addition, the impact of various therapeutic modalities in this disease were unknown. Collaborative efforts of surgeons, radiation therapists and medical oncologists have led to the design of ever improving combined modality programs with a major improvement of prognosis for this disorder. At a recent meeting of the American Society of Oncology, it was generally agreed that it was now appropriate to use the word "curable" for a segment of patients with oat cell lung cancer. The following sections will summarize the roles of surgery, radiotherapy and chemotherapy in this disease and conclude with a resume of the present results of ongoing combined therapy trials in oat cell carcinoma.

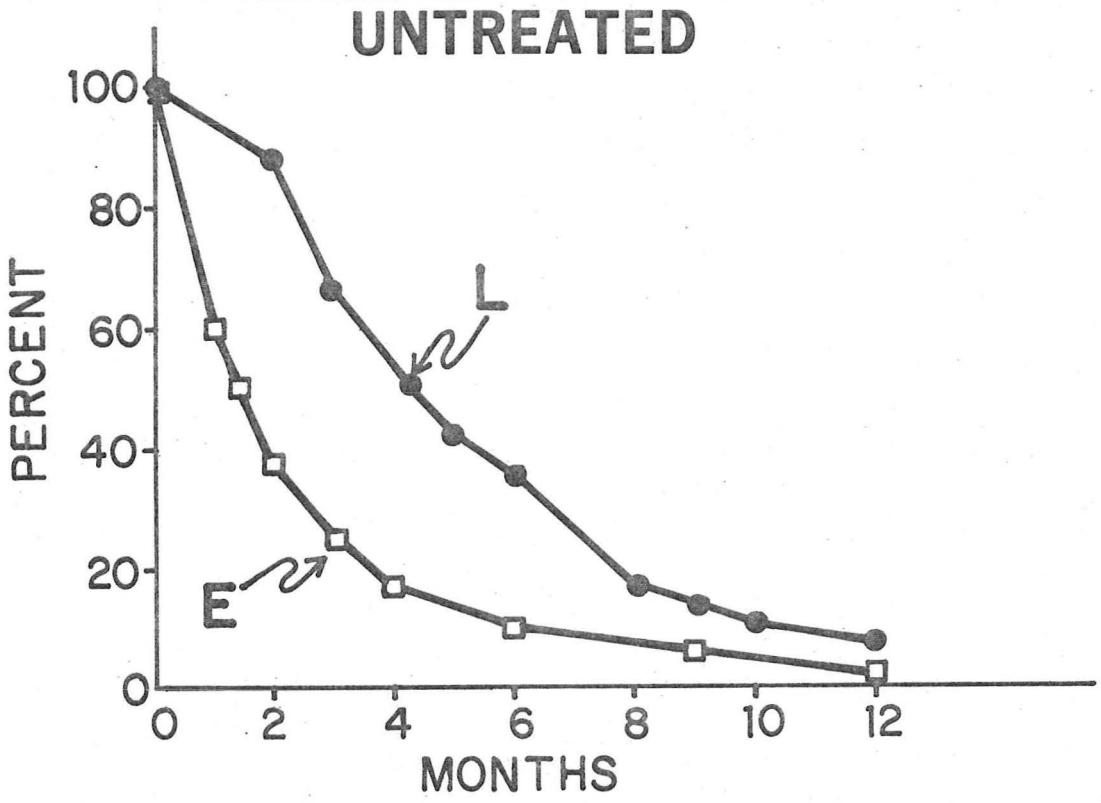

FIGURE 5, References 73, 77

Surgery

In 1973, a British Medical Research Council report laid to rest the question of the role of surgery in this disease. As noted above, inoperable disease was recognized as the rule in the majority of these patients, but surgeons still expressed the feeling that a select group of patients might benefit by attempts at curative resection. Patients at 29 thoracic surgical centers in England entered into a randomized study of the role of surgery and radical radiotherapy in oat cell carcinoma. Patients who were considered operable by all pre-thoracotomy evaluation, and who were felt to be healthy enough to undergo either of these two modalities of treatment, were then randomized to thoracotomy for attempted curative resection or radical radiation therapy. These criteria would apply, at the very most, to 10% or less of all patients at presentation. This represents the most localized and healthy group. Survival was the major endpoint of the study. The report of the 10-year results appeared in 1973 (72). Salient features were as follows:

1. Of 71 patients randomized to surgery, only 34 were able to undergo a curative resection when the chest was opened.

2. Eight of the resected patients were alive at 1 year, two at 2 years, and none at 5 years. The average survival time was 6 months.

3. The results are only slightly better than no treatment at all for patients with localized but inoperable disease as demonstrated by the VA Cooperative trial comparing radiotherapy to no treatment (73). In that study, inoperable localized disease patients, given supportive therapy only, had a median survival of 4 months and 3.5% were alive at one year.

4. The conclusion of the BMRC study was that surgery is not of benefit as a therapeutic modality in oat cell carcinoma of the lung.

Radiotherapy

As noted previously, one might predict that oat cell carcinoma would be a relatively radio-responsive tumor. This fact has been demonstrated clinically by a number of approaches. Salazar, et al., demonstrated that oat cell patients receiving 4000 - 6000 rads of megavoltage therapy had better than an 80% incidence of reduction of tumor mass by greater than 50% (Figure 6) (74). This response rate is considerably different than for other cell types of lung carcinoma. (Note also the correlation with doubling times as discussed in a previous section). In the British MRC study reviewed above, the very select "operable" group of patients (representing 10% or less of all patients) who were treated by radical radiotherapy had a small cohort of long-term survivors. There was a 4% disease-free survival rate at 5 and 10 years (3/37 patients). However, the average survival was only 10 months for the group as a whole (72). Thus, a rare (probably 1/200) patient with oat cell carcinoma will be cured by radiotherapy alone. The VA Cooperative trial comparing radiotherapy to supportive therapy in patients with localized but inoperable disease demonstrated no significant difference between these two approaches. There was a 4 months median survival in

both groups and 7% vs 3.5% 1 year survivals (73). Choi, in a group of similarly localized but inoperable patients treated with technically better radiation therapy, reported a 9 month median survival and 1-of-19 5 year survivors (75). The major problems with this approach are death from distant metastases and a 30% local recurrence rate. The rate of local recurrence is a function of total dose and the local control rate at 4 months for 3000, 4000, and 4800 rads was 60%, 79%, and 88% respectively (75).

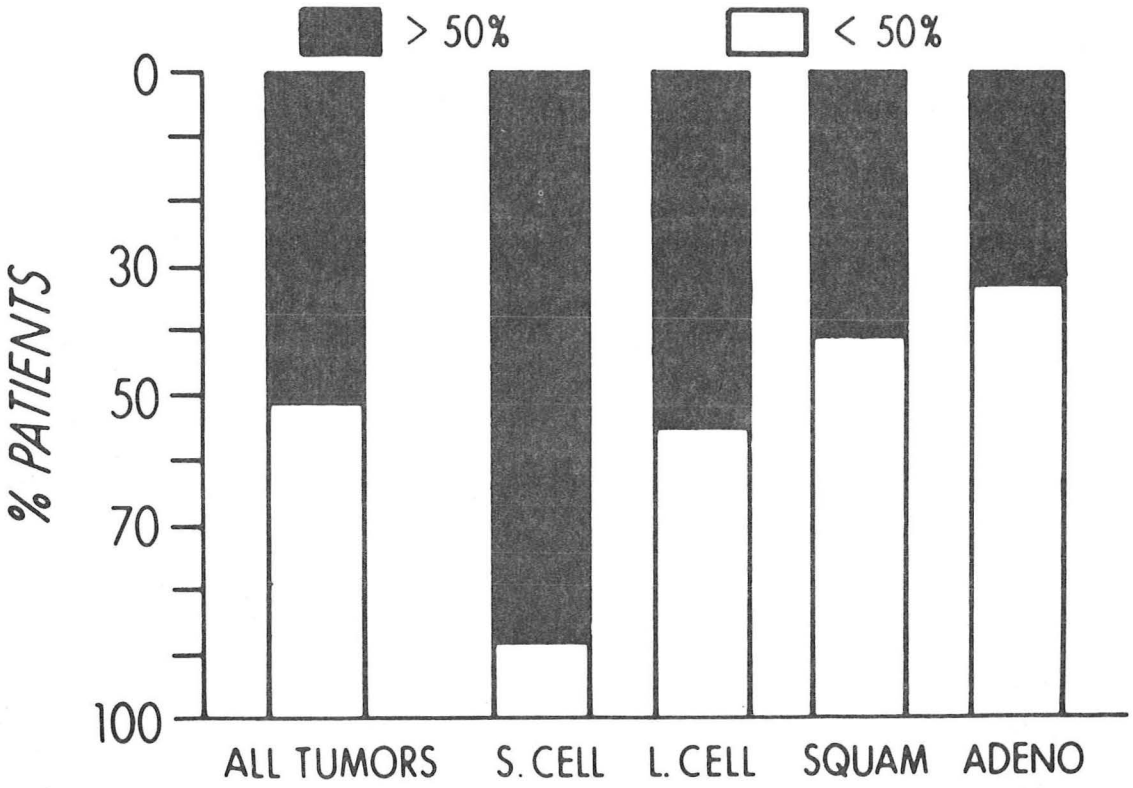

FIGURE 6, Reference 74

Rissanen, et al., also demonstrated that local sterilization of oat cell carcinoma can be accomplished (76). Autopsy studies in patients who had received prior radiotherapy demonstrated that approximately 1/3 of patients receiving 4800 rads or more had no microscopic evidence of malignancy in previously irradiated sites. Thus, radiation therapy does afford significant tumor regression and the opportunity for local eradication. Nevertheless, as a single modality, except in a rare patient, it affords little or no benefit regarding long-term survival.

Chemotherapy

The role of chemotherapy as a therapeutic modality in oat cell carcinoma was first appreciated in a VA Cooperative study published in 1969. Patients with extensive disease were randomized to no treatment or single agent chemotherapy with the alkylating agent cyclophosphamide. An effect on the median survival was appreciated, increasing from 6 weeks to 4 months (Figure 7) (77). Data from another VA Cooperative Study, in which patients considered operable (again, a very select group) were randomized to attempted resection only versus attempted resection plus post-operative cyclophosphamide, also demonstrated a significant effect on survival (78). Subsequently, a large number of chemotherapeutic agents have been demonstrated to produce an acceptable response rate in this tumor (Table 17) (79).

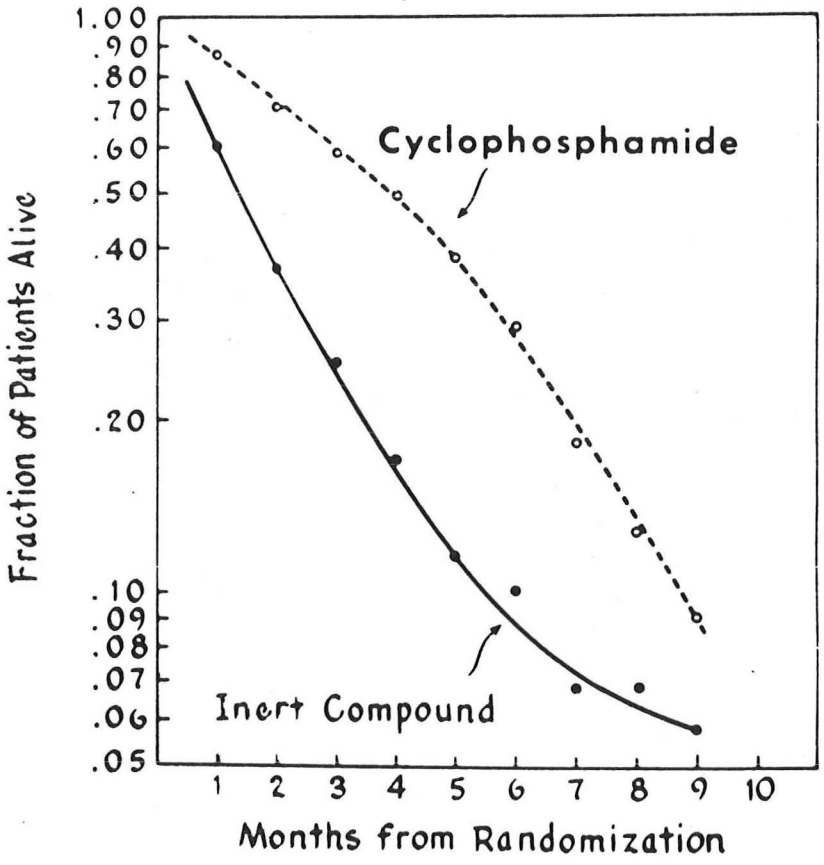

FIGURE 7, Reference 77

As might be predicted from kinetic data, these include both cycle specific and cycle non-specific agents. The concept of combination chemotherapy has also been effectively applied to the treatment of oat cell carcinoma. In general, the principles underlying this concept include the potential of utilizing more than one agent that is effective in a disease in an attempt to achieve additive or even synergistic effects of the agents and to avoid, in part, the problem of drug resistant subclones of tumor cells causing an inadequate degree of response.

In addition, when possible, drugs with different forms of toxicity are combined in order to achieve additive therapeutic benefit without the problem of additive toxicity (80). Hansen, et al., initially demonstrated the improvement in therapeutic benefit of drug combinations in oat cell carcinoma (81). Over the past five years, a number of studies of combination chemotherapy in oat cell carcinoma have been published. Many of these are difficult to evaluate because the numbers of patients were small, the followup was very short and/or the separation of limited disease from extensive disease patients was not made (79, 82). Nevertheless, significant conclusions can be drawn and these will be discussed subsequently in terms of limited and extensive disease management.

SINGLE AGENT ACTIVITY
IN
OAT CELL CARCINOMA

Drug	Objective Responses (%)
Vincristine	40
Methotrexate	39
Epipodophyllotoxin (VP-16)	37
Cyclophosphamide	31
Hexamethylmelamine	30
Adriamycin	25
Procarbazine	25
CCNU	15

TABLE 17, Reference 79

Combined Modality Therapy

Since both radiation therapy and chemotherapy are effective modalities in this tumor, it is logical to assume that the combination of these modalities might afford even greater benefit than chemotherapy alone. Bergsagel, et al., first published data indicating that the median survival of localized, inoperable disease patients could be approximately doubled by the use of these two modalities together (83). It should be kept in mind, however, that radiation therapy alone has not been shown to have a beneficial effect on survival except in those patients with extremely limited disease (see above). Unfortunately, almost no studies have been done in a controlled randomized fashion in order to assess whether radiotherapy to the primary lesion adds any beneficial effect to combination chemotherapy results.

The thesis behind combined modality therapy is primarily the attempt to better control local disease in the primary and immediate nodal regions and lower the local relapse rate in those sites. As discussed previously, radiotherapy is capable of major reduction of mass disease in most patients and has a significant chance of local eradication. For this approach to be valid, one must demonstrate

a higher complete remission rate in the local site, a lower local recurrence rate and, finally, and most importantly, this should have significant impact on survival outcome.

Therapy Results

The present status of therapeutic endeavors will be discussed in terms of the general stage of disease. In interpreting therapeutic results, several parameters must be judged. The complete remission rate (disappearance of clinically apparent disease) has a major impact on survival for most tumors. That is, complete responders usually have longer survival times as a group than partial or non-responders. The median survival rate (time at which 50% of patients are dead) is a means of judging improvement in life expectancy where the survival curve demonstrates a fairly constant decline and numbers of patients are acceptable. Finally, long term survival is a major end point in all therapeutic studies, since this value carries the inherent possibility of cure of a disorder, particularly when the survival curve reaches a "plateau".

Treatment of Extensive Disease

The impact of therapy on patients with extensive disease is real but, so far, only modest. Table 18 lists the historical data including survival with no treatment and compares that with selected representative examples of series treated with combination chemotherapy or combined modality therapy. Combination chemotherapy and combined modality therapy show remarkably similar figures for response and survival despite a variety of approaches. Complete response rates occur in around one-third to one-half of patients. Median survivals are in the range of 6 - 12 months. Two year survivals (not shown) are negligible. An advantage to the addition of radiotherapy to the primary site is not really apparent. Actually, the PVCCN and PVCCN-RT regimens were a randomized study of this question (94, 95). It is apparent that survival is not affected for the group by the addition of radiotherapy. Actually, sites of relapse were not significantly different in the two groups. The study has not been in existence long enough to determine whether any long-term survivals will occur and if they will be weighted towards one or the other approach. At this time, however, the routine use of radiation therapy in these advanced stages of the disease has not been shown to be advantageous. Since this modality contributes to the problems associated with subsequent chemotherapy (see below), its major role may be limited to palliation of local obstructive, compressive or pain problems. It is clear that other approaches, either more aggressive forms of chemotherapy or more unconventional strategies, will be necessary to further improve the outlook for far-advanced oat cell carcinoma.

THERAPY OF OAT CELL CARCINOMA

EXTENSIVE DISEASE

Modality	Complete Response (%)	Median Survival (Mos)	References
No Rx	--	1.5	77
C	--	4	77
C-V-P-Pr	22	9	84
B-A-C-V	8	5	85
C-M	64	12	86
C-M-CN	--	8	88
C-M-C-V-A-P	36	--	96
P-V-C-CN	--	10	94, 95
C-V-M-RT	--	7	87
C-A-V-RT	14	6	89
C-A-V-RT	52	9	90, 91
C-A-V-RT	48	10	92, 93
C-A-V-RT	55	11	97
P-V-C-CN-RT	--	9	94, 95

C=Cyclophosphamide M=Methotrexate V=Vincristine
P=Procarbazine CN=CCNU A=Adriamycin VP=VP-16
B=Bleomycin Pr=Prednisone RT=Radiotherapy

TABLE 18

Treatment of Limited Disease

The approximately one-third of patients who present to the oncologist with loco-regional disease demonstrate the most remarkable effects of modern therapeutic advances on this tumor. Table 19 shows selected representative examples of several reported trials. A reasonable expectation is that 70+% of patients should achieve a complete clinical remission. One series has proven this by re-bronchoscoping most of their patients and demonstrating pathological proof of local disappearance of disease (97). Those regimens with the highest response rates have not, generally, reached a median survival with more than half of the patients in several series living at 12+ - 27+ months (as computed by actuarial survival methods). In addition, the most dramatic observations are those related to frequency of long term, disease free status.

Einhorn has 5 of his original 19 patients with limited disease now greater than two years in a disease-free survival status off all therapy (unpublished). Cohen, et al., have 12 patients at risk for two years or more and 3 are alive

without evidence of disease for 2 - 5 years. Their actuarial prediction is that 13% of all patients (only 1/3 were limited disease) will be disease free at 28 months (unpublished). Similar observations are reported by Oldham (unpublished). Johnson's series has 36% of their limited disease patients alive and disease free at 27 months. That program stopped all therapy at 3 - 4 months from its initiation (93). Problems encountered in achieving these remarkable results will be discussed in the next section.

THERAPY OF OAT CELL CARCINOMA

LIMITED DISEASE

Modality	Complete Response (%)	Median Survival (Mos)	References
No Rx	--	4	73
Radiotherapy (RT)	--	4 - 5	72, 73
C + RT	--	9 - 10	83
B-A-C-V	100	12+	85
C-M-CN-V-A-P	74	--	96
C-V-M-RT	--	16	87
C-A-V-RT	41	12	89
C-A-V-RT	97	12+	97
C-A-V-RT	88	19+	90, 91
C-A-V-RT	79	27+	92, 93

C=Cyclophosphamide M=Methotrexate V=Vincristine
P=Procarbazine CN=CCNU A=Adriamycin VP=VP-16
B=Bleomycin Pr-Prednisone RT=Radiotherapy

TABLE 19

Whether radiotherapy to the primary lesion is a necessary component of these programs is unclear. No randomized studies have been reported.

The primary purpose, reduction of bulk disease and potential eradication, and a reduction of local recurrence rates, has been discussed. Most programs have utilized combined modality therapy. One of the most effective chemotherapy-only series (in terms of remission and survival) reports that two-thirds of relapses have been intra-thoracic (96). Whether this will have an important impact on survival is unknown and is a question worthy of testing in a randomized clinical trial.

Problems Encountered in the Treatment of Oat Cell Carcinoma

As advances in the management of this tumor have occurred, problems affecting therapeutic results have emerged. Solutions of these problems will, for the most part, be necessary in order for further significant progress to take place.

Toxicity

Toxicity from the therapeutic modalities is presently the most significant barrier to the treatment of any tumor which is managed by chemotherapy and/or radiotherapy (79, 82). Gastrointestinal toxicity is the most frequently encountered side effect of chemotherapeutic agents. Although this problem is usually manageable in terms of mortality, it frequently becomes dose limiting from the standpoint of patient compliance and continued participation in a treatment program. Lack of successful prevention of this nuisance has remained a major obstacle to the chemotherapist.

Myelotoxicity is the most common dose limiting complication of any chemotherapeutic regimen. The development of non-myelotoxic agents or compounds or methods of delivery with greater tumor to normal tissue selectivity is a major area of clinical pharmacologic investigation. In terms of oat cell carcinoma, the therapeutic regimens which have demonstrated the most remarkable survival prolongation have been associated with severe myelotoxicity, in some instances intolerable, because of the rate of severe or treatment-related mortality (90-97). These factors have been compounded by the simultaneous use of chemotherapeutic drugs and radiotherapy, both of which have at least additive myelotoxic manifestations. This has led to attempts at modifying the timing and total dose of radiotherapy to minimize the potentiation (see below).

Next to myelotoxicity, esophageal complications have been the greatest barrier to the combined chemotherapy-radiotherapy programs. In Johnson's series, severe esophagitis occurred in 60% of the patients including stricture formation in 14% (92, 93). This is primarily due to the radiation potentiating effects of the drugs, especially adriamycin. Normally the esophagus is tolerant of 5000 to 6000 rads before significant esophagitis occurs. These side effects were seen at a dose of 3000 rads. Chebora, et al., reviewed the literature and noted only 7 radiation therapy induced instances of esophageal stricture reported to 1972. Subsequently 7 further cases were reported in the next 5 year period, all in association with either simultaneous chemotherapy or exposure to agents (usually adriamycin) within 1 week of radiation therapy despite doses of generally 3000 rads maximum (98). These additive or potentiating effects of radiation and chemical agents have led to attempts to modify doses and timing of the modalities. Two such studies did reduce the frequency and severity of complications, but still not to an acceptable level (90, 97). Good survival results appeared to be maintained. In the past 1½ years, we have initiated a program at this institution, utilizing further modifications of timing of the same drugs and radiation, and have succeeded in essentially eliminating esophageal problems and markedly

reducing significant myelosuppression (unpublished data). Complete response rates were as good but survival results are too early to assess.

Pulmonary fibrosis is a recognized accompaniment of radiation exposure of the lung. Again, potentiation by drugs seems to occur (99). In most persons, the degree of this problem might be tolerated, but the lung carcinoma population has a high frequency of significant pulmonary functional embarrassment from chronic obstructive disease and these patients are often unable to withstand much further reduction in lung function. This again places a limitation on the use of radiation therapy.

Brain Relapse

As high as 20% of patients in complete remission may have their first site of clinical recurrence in the brain (See section on staging). As with acute leukemia, this suggests that the brain is a sanctuary protected from the effects of chemotherapy on micrometastases. Both retrospective analyses of patients receiving prophylactic whole brain irradiation as well as randomized clinical trials of this approach have demonstrated a significant reduction in the brain as a site of relapse (75, 100, 101). At this time, no effect on median survival has been seen, but this relates to the high rate of general relapse in this disease. As improved frequencies of long term survival occur, this approach seems very likely to have an effect on survival, appropos of childhood acute leukemia.

Long Term Survival

It is apparent that long term survival rates are becoming sufficiently frequent in limited disease patients to project the possibility of cure. Careful assessment of the factors that are associated with the development of or failure to maintain long term survival will hopefully lead to further refinements of approach. On the other hand, long term survivals are not being achieved in patients with extensive disease (Table 18). Additionally, the use of radiotherapy as an adjunctive modality does not appear to affect survival in this group of patients (94, 95). Therefore, the use of this modality in these patients may be seriously questioned, particularly when one takes into account the prominent toxicity of combined modality therapy. Totally different approaches to management of these patients is likely to be necessary. Such innovative strategies as autologous bone marrow replacement after otherwise lethal mega-dose chemotherapy shows some promise (102). Obviously, developing techniques of earlier detection remains the paramount goal.

Local Relapse After Radiation Therapy

The primary purposes of local radiotherapy are to reduce bulk disease to a size more likely to respond to chemotherapy and also, in some instances, to achieve local eradication (see section on radiotherapy). Unfortunately, maximum benefits of radiotherapy require doses that produce intolerable toxicity when combined with chemotherapy. Thus, as noted, programs have attempted to balance

these two aspects. In extensive disease, local relapse rates appear not to be affected by adding this modality (94, 95). On the other hand, the role of radiotherapy in controlling local relapse in the lung in patients with initially localized disease is unknown. Certainly, in exclusively chemotherapy regimens, local relapse is the most frequent initial recurrence site (96). Nevertheless, some of those regimens have a good survival prediction. It seems appropriate that randomized studies be carried out to delineate a clearer appreciation of this question.

Role of Immunotherapy

Little useful information has been published to determine whether various forms of immunotherapy have a role in the treatment of oat cell carcinoma of the lung (79, 82). The only positive trial reported is that from the NCI-VA study utilizing thymosin at varying doses. At the highest dose, thymosin appeared to produce a longer disease free survival than in patients who received placebo or lower doses (103). Several other trials have included BCG, etc., in a non-randomized fashion, and whether the promising results of those programs overall was enhanced by the immunotherapy cannot be established.

Early Diagnosis

It is clear that the treatment of this tumor is most successful at the earliest stages of development. Traditional attempts at early diagnosis of lung cancer by chest radiography or even sputum cytology in high risk groups have not made a significant impact. The greatest therapeutic advances will probably be achieved as a result of identifying the disease sooner. It is this goal that has led to a major interest in developing techniques of serological identification of tumor markers (see above). An all-out effort to pursue these approaches seems justified. If such approaches are to be successful, oat cell carcinoma of the lung seems an excellent candidate due to the unusual frequency of production of peptides and other substances by this tumor.

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