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Causes of Treatment Failure and Death in Carcinoma of the Lung

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Studies of patterns of failure and causes of death have been undertaken based upon the WHO histopathologic classification. In a randomized trial of thoracic irradiation ± chemotherapy (hydroxyurea and CCNU), patterns of failure did not seem to differ by cell type; the largest group was "death without progression." A subsequent clinical trial of thoracic irradiation ± cranial irradiation permitted a more detailed evaluation. Patients with squamous cell carcinoma had a higher rate of local failure than distant metastasis. Those with small cell carcinoma had a lower local failure rate and a high rate of distant spread. Patients with adenocarcinoma and large cell carcinoma had the lowest local failure rate, but had a high rate of distant metastasis. In 300 consecutive patients with autopsies, 75 percent with squamous carcinoma died of complications of the thoracic tumor and only one-quarter had extrathoracic dissemination; 30 percent with small cell carcinoma died of local tumor complications and 70 percent had carcinomatosis; 40 percent of patients with adenocarcinoma and large cell carcinoma died of intrathoracic complications, and 55 percent had distant metastases. Half the patients with small cell carcinoma, large cell carcinoma, and adenocarcinoma had brain metastases at autopsy. Future clinical trials should emphasize better control of the most common sites of failure.

Virtually all clinical studies, whether surgical, radiotherapeutic, or chemotherapeutic, use survival as an endpoint. Although survival is an important parameter to evaluate, it often does not provide information that would suggest better approaches to treatment. When comparing different treatments, unless the groups of patients are completely comparable with respect to important prognostic factors, survival may be relatively meaningless.

In order to evaluate approaches to treatment of carcinoma of the lung in a manner that might suggest ways to improve therapy, several studies were undertaken to evaluate patterns of failure and causes of death. The first study attempted to determine patterns of failure in a prospective randomized trial conducted by the Veterans Administration Lung Group. This study has previously been reported [1,2]. It involved the comparison of standard radiation therapy (4000–5000 rad in four to six weeks) to the primary pulmonary tumor and regional lymph nodes versus the same irradiation plus hydroxyurea, 1 g/M^2 twice weekly and CCNU, 100 mg/M^2, every six weeks, both drugs administered orally. Overall survival was not different for

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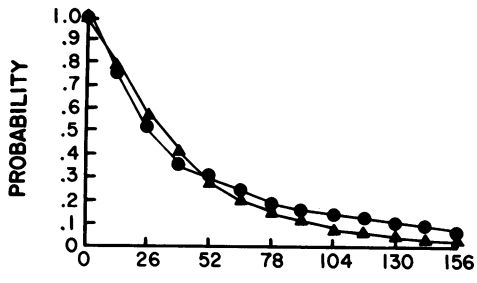
the two treatment groups (Fig. 1A). Long-term survival of patients who lived at least one year showed that treatment with irradiation alone was superior to combined treatment (Fig. 1B).

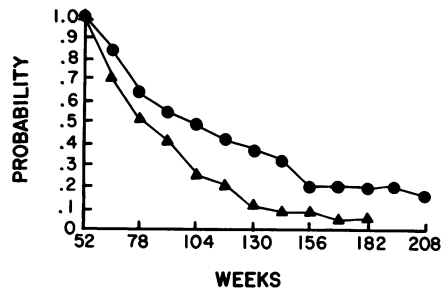
The study forms for this trial permitted evaluation of survival for the entire group of patients. However, the forms were changed midway in the point of the trial so that they included much more detailed information. Patterns of failure could only be assessed from the study forms of the latter half of the trial. Table 1 shows the clinical failure pattern by histopathologic type based on the final interpretation after review by a three-member panel. Local failure was a common phenomenon regardless of cell type, as was distant spread. There was a suggestion that distant metastases were more frequent in adenocarcinoma, but the numbers were too small to be significant. The largest category was "death without progression." This group included all patients who had no clinical metastases and stable (< 50 percent regression or < 25 percent progression) intrathoracic disease. This category prompted a search for a more precise delineation of causes of death. Final report forms included clinical assessment of actual cause of death for a small number of patients but the numbers where this information was available were too small to associate causes of death with specific cell types.

In a more recently completed study, with larger numbers of patients and more detailed report forms, it was possible more clearly to identify clinical patterns of failure. The slides from this study were also reviewed by the three-member panel of pathologists directed by Dr. Raymond Yesner. The results of this trial have been published [3,4,5]. In order to permit comparisons among the cell types, each histopathologic sample was normalized to 100 patients entering on study; squamous cell carcinoma, small cell carcinoma, and the combined group of adenocarcinoma and large cell carcinoma (between which there were no significant differences), constituted the three sub-groups for comparison. Figure 2 shows the failure sequence for the patients with squamous carcinoma. It is apparent that local failure was a common problem, both initially and subsequently. Initial failure by distant spread occurred in 20 percent of patients, a small proportion of whom eventually also had local failure. Death without clinical evidence of progression occurred in 23 percent of patients. A similar set of 100 patients with small cell carcinoma (Fig. 3) is traced from entry on study until the time of death. Local persistence or recurrence as the initial



TREATMENT	ALIVE	DEAD	TOTAL	MEDIAN
RT	15	166	181	27.4
RT + CHEMO	7	173	180	30.8

FIG. 1A. Survival after randomization by treatment group. VALG Protocol 13 L.



TREATMENT	ALIVE	DEAD	TOTAL	MEDIAN
RT	11	39	50	48.9 } +52
RT + CHEMO	4	45	49	27.1 }

FIG. 1B. Long-term survival of patients who lived at least one year, by treatment group. VALG Protocol 13 L.

TABLE 1
First Site of Progression (Clinical) by Cell Type After Irradiation ± Chemotherapy VALG 13 L

Site of Progression	Squamous	Small Cell	Adenocarcinoma	Large Cell	Total
Local	20% (17)	23% (7)	13% (4)	23% (9)	20% (37)
Distant	21% (18)	29% (9)	40% (12)	28% (11)	27% (50)
Multiple sites	5% (4)	0	3% (1)	5% (2)	4% (7)
Death without progression	49% (41)	39% (12)	43% (13)	35% (14)	43% (80)
Not failed	5% (4)	10% (3)	0	10% (4)	6% (11)

( ) = Number of patients

type of failure was relatively infrequent, whereas distant metastases clearly predominated. However, a large proportion of patients failed both within the thorax and with extra-thoracic disease. The combined group with adenocarcinoma and large cell carcinoma had an intermediate failure pattern (Fig. 4). A small proportion of patients failed locally when compared to squamous carcinoma. Distant metastases were found almost as frequently as with small cell carcinoma and much more frequently than with squamous cell carcinoma.

A review of the literature comparing clinical patterns of failure to autopsy data [6] showed that the distributions of metastases were different and little could be said about actual cause of death. The diagnosis of metastasis in some sites was associated with a much shorter survival interval, but it was unclear whether this reflected clinical detection very late in the course of the disease or relative effectiveness of therapy once metastases were documented. A report from Memorial Hospital in New York, based on autopsy data, suggested that local factors were of considerable importance as the immediate cause of death. However, comparisons by histopathologic subtype were not undertaken [7].

In order to assess causes of death by cell type, a consecutive group of 300 patients who came to autopsy and had been a part of VALG studies, was analyzed [8]. Of

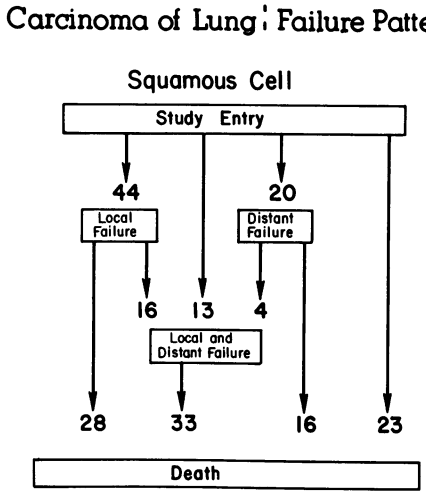


FIG. 2. Pattern of initial and subsequent failure after irradiation for inoperable squamous cell carcinoma.

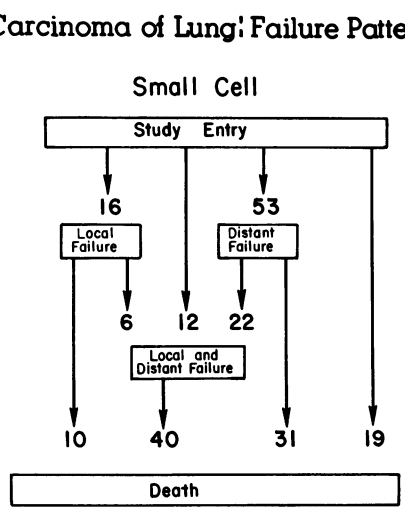


FIG. 3. Pattern of initial and subsequent failure after irradiation for inoperable small cell carcinoma.

course, patients die as the result of several concomitant factors and separation of these factors is somewhat arbitrary. In order to try to delineate the major factors contributing to death, patients who died with any evidence of extrathoracic metastases were said to have died from "carcinomatosis." The "CNS" patients had metastatic disease confined to the central nervous system without any other evidence of extrathoracic spread. The combination of infection, hemorrhage, and respiratory

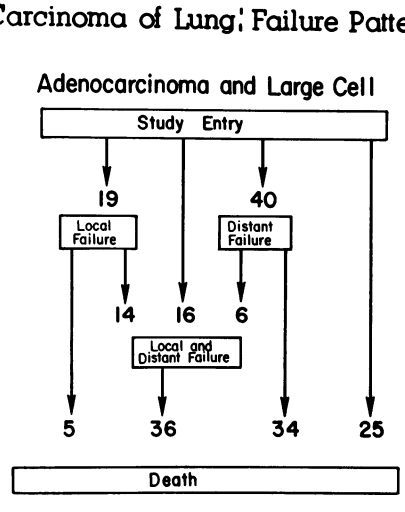


FIG. 4. Pattern of initial and subsequent failure after irradiation for inoperable large cell carcinoma and adenocarcinoma.

and cardiac failure could be taken as a measure of failure to overcome the intrathoracic disease. This latter group of patients had no evidence of extrathoracic metastasis. The results (Table 2) showed that a large proportion of patients with squamous cell carcinoma died from complications of the local tumor, while a very high proportion of patients with small cell carcinoma had extrathoracic dissemination documented at autopsy. Again, adenocarcinoma and large cell carcinoma were intermediate in regard to local factors and carcinomatosis when compared to squamous cell carcinoma and small cell carcinoma.

Brain metastases can be considered separately for the individual cell types for two reasons. The central nervous system represents a "sanctuary" area which is relatively poorly penetrated by cytotoxic agents. Even the most sensitive cell type to chemotherapeutic agents, small cell carcinoma, was unaffected in regard to frequency of CNS metastasis when comparing the lipid soluble nitrosoureas to other chemotherapeutic agents [9]. Second; prophylactic cranial irradiation has been tried and found to be tolerated and might be considered for any group of patients at sufficiently high risk to justify this approach [3]. Table 3 shows the frequency of brain metastasis as determined in 400 consecutive autopsies of patients with cancer of the lung in which the brain was examined. Approximately 50 percent plus or minus 5 percent of patients with small cell carcinoma, large cell carcinoma, and adenocarcinoma have brain metastasis at autopsy. When patients are evaluated according to whether the brain metastasis occurred concomitant with other metastases as opposed to the brain being the only site of metastasis (Table 4), adenocarcinoma seems to be different in that single organ brain metastases are found in over 10 percent of patients. This suggests that prophylactic cranial irradiation should be more extensively investigated in patients with adenocarcinoma, and perhaps those with large cell carcinoma. It also suggests that survival is not likely to be altered by the prophylactic cranial irradiation except, perhaps, in patients with adenocarcinoma where this may represent the only site of distant spread. In fact, recently completed studies have shown that prophylactic irradiation with low total doses has reduced the frequency of brain metastasis in patients with "non-small cell" carcinoma of the lung [5]. Although long-term survival data are not available, a favorable effect on survival might be expected in patients with adenocarcinoma. In the other patients, CNS metastases co-exist with other sites of dissemination, and improved survival from prophylactic irradiation would be unlikely.

TABLE 2
Causes of Death by Cell Type: 300 Consecutive VALG Autopsies

Cause of Death	Squamous	Small Cell	Adenocarcinoma	Large Cell	Combined
Carcinomatosis	25% (21)	70% (40)	48% (49)	47% (23)	(2)
CNS	2% (2)	–	9% (9)	8% (4)	–
Infection	36% (30)	11% (6)	19% (19)	27% (13)	(6)
Hemorrhage	8% (7)	7% (4)	4% (4)	2% (1)	–
Respiratory failure	6% (5)	3% (2)	7% (7)	8% (4)	–
Heart failure	20% (17)	9% (5)	8% (8)	6% (3)	–
Pulmonary emboli	–	–	4% (4)	2% (1)	–
Other malignancy	1% (1)	–	2% (2)	–	

( ) = Number of patients

TABLE 3
Frequency of Brain Metastases by Cell Type 400 Autopsies from VALG and West Haven VA Hospital

	Brain Metastases		
Cell Type (No. cases)	Number	% of total brain mets	% of cell type
Squamous (123)	16	10.5	13.0
Small cell (82)	37	24.2	45.1
Adenocarcinoma (129)	69	45.1	53.5
Large cell (54)	28	18.3	52.0
Combined (12)	3	1.9	25.0
Total	153	100.0	

TABLE 4
Frequency of Brain Metastases Alone at Autopsy by Cell Type

	Brain Metastases		
Cell Type	Number	% of total brain mets	% of cell type
Squamous	5	16.1	4.1
Small cell	5	16.1	6.1
Adenocarcinoma	16	51.7	12.4
Large cell	5	16.1	9.3
Total	31	100.0	

In summary, clinical patterns of failure, as well as patterns of failure and causes of death determined from autopsies, suggest three basic groups of patients with carcinoma of the lung. Those with squamous cell carcinoma have progression of disease within the thorax and are most likely to die as a result of compromise of vital intrathoracic organs. It is justifiable in these patients to pursue vigorous efforts to control the local-regional disease. Higher doses of irradiation, radiotherapy plus hypoxic cell sensitizers, and high LET (linear energy transfer) radiations such as neutrons deserve investigation. Patients with small cell carcinoma are subject to widespread dissemination early in the course of the disease. It is now recognized that systemic chemotherapy is an important part of the management of these patients as is prophylactic cranial irradiation and thoracic irradiation. Patients with large cell carcinoma and adenocarcinoma are at high risk for failure both within the thorax and in extrathoracic sites. Adenocarcinoma is especially likely to disseminate to the brain, perhaps as the only site of spread. Prophylactic cranial irradiation may be especially helpful in these patients. In addition, continued search for effective combinations of chemotherapeutic agents is important as it is clear that many patients will require systemic treatment.

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