A SYSTEM FOR THE CLINICAL STAGING OF LUNG CANCER*

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STAGING of neoplastic disease is the procedure of assigning a simple coded designator to a patient in accordance with an established set of rules. Its purpose is to classify patients and group them with respect to the anatomic extent or biologic severity of their disease. Clinical staging is based only on those measures of disease extent which are available from diagnostic or evaluative studies undertaken prior to instituting therapy. This classification of patients into relatively homogeneous groups, with respect to estimates of their prognosis, is essential if different modalities of treatment are to be compared and if results are to be communicated in meaningful terms.

The central problems in designing a meaningful staging system are: (1) to identify and give proportionate weight to those factors which will reliably and validly predict survival; and (2) to develop rules which, when applied to these factors, will permit assignment of an index of disease extent. The essential character of such an index is that patients within any stage-group who survive equivalent treatment will demonstrate a generally similar age-adjusted life expectancy. A major constraint on any system of classifying the extent of disease is that it must be easily understood and remembered; therefore, it must be based on relatively few predicting factors. Only a relatively uncomplicated system will lend itself to widespread utilization.

Among the systems of classification proposed by international organizations and congresses[3,8,10,14,17] and individuals[6] are classification schemes applicable specifically to lung cancer.[1,12] Some of these have been found wanting,[5,9,11,13] and none have achieved wide acceptance to date. The TNM classification scheme, first proposed by Denoix,[4] meets many of the criteria and constraints noted above, and its principles are well established internationally.[16] Therefore, the general rules of the TNM system were adopted in this investigation, undertaken under the auspices of the Task Force on Lung Cancer[2] of the American Joint Committee on Cancer Staging and End Results Reporting.

When using the TNM system, the letter T represents the primary tumor with appropriate subscripts to describe increasing sizes of tumor and/or the involvement by direct extension. The letter N represents regional lymph node involvement with appropriate subscripts to describe the absence of involvement or increasing degrees of such involvement. The letter M represents distant metastasis with appropriate subscripts to describe the absence of such metastasis or increasing degrees of such dissemination of the tumor. The various categories of T, N, and M are then grouped into appropriate combinations to create a small number of stages of the disease.

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METHOD

Information was collected in computer-compatible format on 2,155 histologically proved cases of bronchogenic carcinoma. Patients were included in the study only if the cancer had been diagnosed 4 or more years prior to the start of the study and if follow-up information was available, either to the time of death or to survival for at least 4 years.

The stage classification is based on an analysis of 28 clinical factors, including: (1) findings on physical examination; (2) roentgenographic studies; (3) endoscopic studies including mediastinoscopy; (4) results of thoracentesis; and (5) any special examinations required to demonstrate the presence of extrathoracic metastases. The data included size, location, and margination of each primary tumor, the presence of extrapulmonary extension, and complications such as obstructive pneumonitis, atelectasis, and pleural effusion. The presence of spread of carcinoma to lymph nodes in the hilar region and in the mediastinum and the presence of more distant metastases were recorded. The results of exploratory thoracotomy were only used to verify the histologic proof of disease where it was necessary to do so, but these results were not used to measure the extent of the primary tumor or the extent of regional spread to the hilar lymph nodes or mediastinum.

More than 300 survival curves[7] were plotted[15] for various characteristics of the primary tumor, the spread to the regional lymph nodes, and the presence of distant metastases in various combinations. The relative contribution of each clinical variable to the force of mortality in lung cancer was assessed. Those anatomic factors most highly predictive of survival were identified for each T, N, and M descriptor. Subsequently, the various combinations and permutations of these descriptors were assigned to a stage of disease such that each stage would be substantially homogeneous with respect to survival and so that the force of mortality would be Stage I < Stage II . . . <Stage N.

CLINICAL DATA

AGE, SEX DISTRIBUTION

The age distributions for the total series (median 59 years) and for each cell type followed a normal distribution for lung cancer. The median age in patients with adenocarcinoma and small cell carcinoma is 2 to 3 years less than for the other cell types. In the total series, 88 per cent were male squamous cell 95 per cent, adenocarcinoma 75 per cent, large cell and small cell carcinoma 90 per cent.

CELL TYPE

Of the 2,155 cases, 996 were diagnosed as squamous cell, 521 as adenocarcinoma, 195 as undifferentiated large cell, 368 as undifferentiated small cell, and 75 as undifferentiated with a cell type not specified. The diagnosis was established by exfoliative sputum cytology or by direct endoscopic biopsy in 80 per cent and by other biopsy methods in 6 per cent. The histologic pattern of disease was confirmed at autopsy in 14 per cent. In the most recent years of patient accessions, a definitive objective diagnosis was confirmed in most cases prior to death. This reflects the introduction of mediastinoscopy and bronchial brush biopsy, and the increased utilization of percutaneous needle biopsy, bone marrow biopsy, and mediastinotomy.

SITE AND EXTENT OF INVOLVEMENT

The right lung was involved in 55 per cent of the patients. The primary lesion was peripheral in 28 per cent, apical in 7 per cent, hilar in 49 per cent, and involved the main bronchus proximal to the upper lobe orifice in 13 per cent. On roentgenologic examination, $\frac{1}{2}$ of the lesions were described as solitary and circumscribed and $\frac{1}{3}$ as solitary and noncircumscribed. Cavitation was relatively rare (6.6 per cent). Some degree of atelectasis or obstructive pneumonitis was present in 44

per cent of all patients. Pleural effusion was observed in 12.8 per cent; fluid was examined cytologically in 50 per cent of these with malignant cells demonstrated in $\frac{2}{3}$. On the basis of roentgenographic and other clinical examinations, the hilar lymph nodes were regarded as definitely involved in 25 per cent and questionably involved in 10 per cent. With respect to mediastinal lymph nodes, 30 per cent were regarded as questionably or definitely involved. Some evidence suggestive of direct mediastinal extension was present in 22 per cent. The scalene and/or supraclavicular lymph nodes were palpable and were biopsied in 16.6 per cent of the patients; metastatic spread was found in $\frac{2}{3}$ of those biopsied. The next most common sites of suspected or proved metastatic disease were liver (10.1 per cent), bone (9.3 per cent), brain (4.5 per cent), and contralateral lung (4.5 per cent). It should be stressed that all of the above findings are based on clinical judgment derived from all sources of information available to the time of initial diagnosis and prior to any major surgical intervention.

RESULTS

HISTOLOGY

As shown in Figure 1, the over-all prognosis in squamous cell carcinoma is superior to that in other major cell types, regardless of any other factor of disease. The relative survival rates for patients with adenocarcinoma and undifferentiated large cell carcinoma are intermediate and are almost identical. The survival experience with undifferentiated small cell (oat cell) carcinoma is universally disastrous. Because of these differences in biologic behavior, data were analyzed separately for each cell type before attempting to apply TNM descriptors. It was also concluded that any patient with undifferentiated small cell carcinoma should be assigned to the worst clinical stage of disease regardless of the TNM classification (Tables I, II, III and V).

PRIMARY TUMORS (T factor)

The survival analysis demonstrates that prognosis is principally related to the size of the primary tumor, its location, external margination, complications such as atelectasis or obstructive pneumonitis, pleural effusion, and its extensiveness with respect to direct invasion. As shown in Table 1 there is a direct relationship between the measurable clinical anatomic extent of the primary tumor and survival in squamous cell carcinoma, adenocarcinoma, and undifferentiated large cell carcinoma. The survival experience in undifferentiated small cell carcinoma bears no relationship to the clinically recognized anatomic extent of disease. The most favorable variables are small size of primary tumor, peripheral location, and absence of invasion of adjacent structures. On the basis of the analysis, the definitions of the T factor are as follows:

T—*Primary Tumors*

- T_0 No evidence of primary tumor
- T_X Tumor proved by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically
- T_1 A tumor that is 3.0 cm. or less in greatest diameter surrounded by lung or visceral pleura and without evidence of invasion proximal to a lobar bronchus at bronchoscopy
- T_2 A tumor more than 3.0 cm. in greatest diameter or a tumor of any size which with its associated atelectasis or obstructive pneumonitis extends to the hilar region. At bronchoscopy the proximal extent of demonstrable tumor must be at least 2.0 cm. distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung, and there must be no pleural effusion
- T_3 A tumor of any size with direct extension into an adjacent structure such as the chest wall, diaphragm, or mediastinum and its contents; or demonstrable bronchoscopically to be less than 2.0 cm. distal to the carina; any tumor

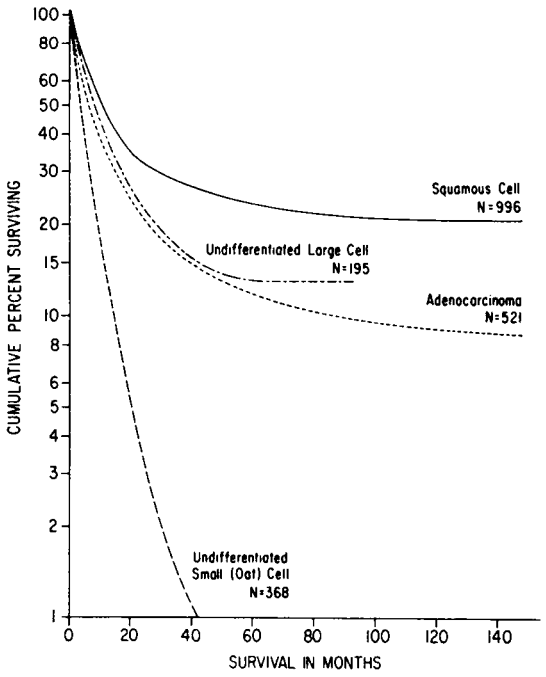

FIG. 1. Proportion of patients surviving lung cancer stratified by the histologic pattern of disease.

associated with atelectasis or obstructive pneumonitis of an entire lung or pleural effusion

Figure 2 demonstrates the relationship between T_1-T_3 and survival based on observations recorded in 1,678 patients. At this time we have inadequate data regarding the survival of patients with T_X lesions.

LYMPH NODES (N factor)

Table II shows the relationship of regional lymph node metastases to survival by cell type. Involvement of both the hilar and mediastinal nodes has more serious implications in adenocarcinoma and in undifferentiated large cell than in squamous cell carcinoma. Again, no relationship is seen between the estimated clinical extent of lymph node disease and survival in small cell tumors. On the basis of this analysis, the definitions of the N factor are as follows:

N—*Regional Lymph Nodes*

- N_0 No demonstrable metastasis to regional lymph nodes
- N_1 Metastasis to lymph nodes in the ipsilateral hilar region (including direct extension)
- N_2 Metastasis to lymph nodes in the mediastinum

Figure 3 demonstrates the survival relationships between these categories based on observations in 1,568 cases.

DISTANT METASTASES (M factor)

With current therapy, lung cancer must be regarded as essentially hopeless, regardless of cell type, once the disease has ex-

TABLE I

THE RELATIONSHIP OF PRIMARY TUMOR EXTENT (T factor) AND SURVIVAL IN LUNG CANCER BY CELL TYPE

Clinical Measure of Disease Extent	Relative Percentage Surviving 5 Years			
	Squamous cell	Adeno-carcinoma	Undifferentiated large cell	Undifferentiated small cell
Size <3 cm.	48	32	18	<5
Size >3 cm.	29	14	18	<2
Site peripheral	30	16	20	<2
Site main bronchus >2 cm. distal to carina	23	10	3	<1
Site proximal main bronchus	9	1	0	<1
Atelectasis/pneumonitis of segment or lobe	25	8	very rare	<4
Atelectasis/pneumonitis entire lung	7	0	not seen	<1
Pleural fluid	7	2	8	0
Direct chest wall invasion	<1	5	uncommon	<1
Mediastinal extension	<2	<2	uncommon	<1

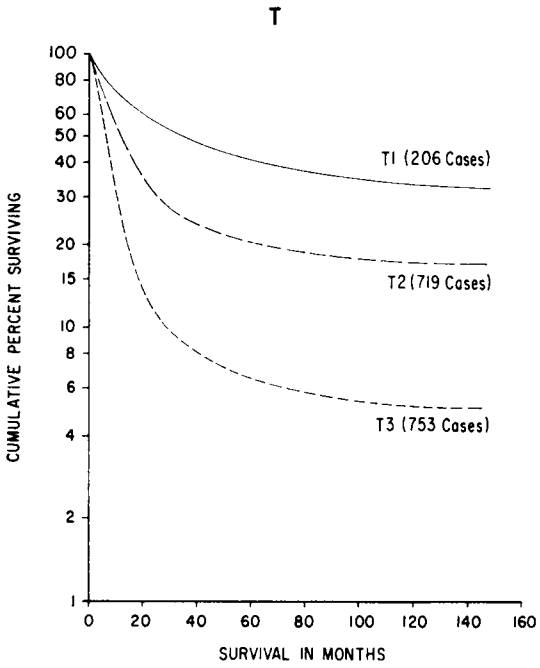

FIG. 2. Survival in lung cancer stratified by the anatomic extent of the primary tumor (T factor), excluding undifferentiated small cell carcinoma.

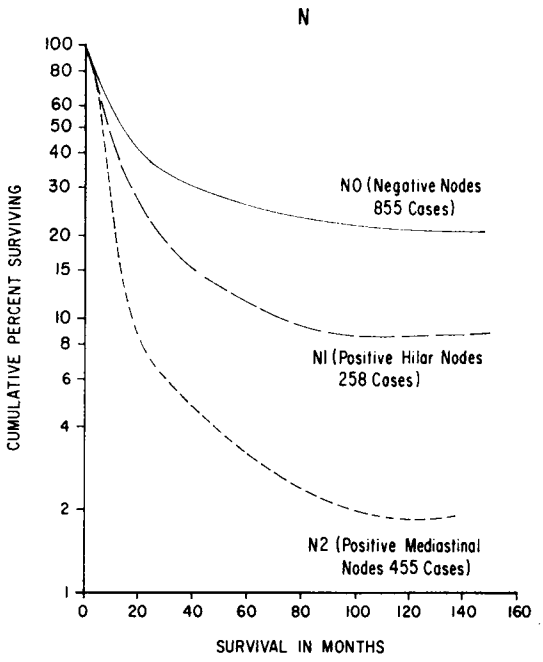

FIG. 3. Survival in lung cancer stratified by the extent of regional lymph node involvement (N factor), excluding undifferentiated small cell carcinoma.

tended beyond the hemithorax of origin and beyond the mediastinal lymph nodes. This is demonstrated in Table III. Based on this analysis, the definitions of the M factor are as follows:

M—*Distant Metastases*

M_0 No distant metastasis

M_1 Distant metastasis such as in scalene, cervical, or contralateral hilar lymph nodes, brain, bones, lung, liver, etc.

Figure 4 demonstrates the survival relationship between M_0 and M_1.

STAGE-GROUPING (TNM combinations)

The characteristics of survival curves for each permutation of the TNM descriptors were subsequently analyzed. The various TNM sets were assigned to stage-groups in a manner intended to minimize intragroup variability in survival and to create the greatest prognostic differences between stage-groups. Table IV indicates the number of patients in each combination and the composition of each stage. An estimate

TABLE II

THE RELATIONSHIP OF LYMPH NODE INVOLVEMENT (N factor) AND SURVIVAL IN LUNG CANCER

Clinical Measure of Disease Extent	Relative Percentage Surviving 5 Years			
	Squamous cell	Adeno-carcinoma	Undifferentiated large cell	Undifferentiated small cell
Lymph nodes negative	30	18	20	<3
Hilar lymph nodes involved	16	8	6	<1
Mediastinal lymph nodes involved	5	2	<2	<1

TABLE III

THE RELATIONSHIP OF DISTANT METASTASIS (M factor) TO SURVIVAL IN LUNG CANCER

Clinical Measure of Disease Extent	Relative Percentage Surviving 5 Years			
	Squamous cell	Adeno-carcinoma	Undifferentiated large cell	Undifferentiated small cell
No metastases	30	19	17	2
Scalene/cervical lymph nodes positive	0	<1	<1*	0
Distal metastases, all sites	<1	<1	0†	0

* Fairly common.
† Rare.

of survival is given with its error estimate at 12 months and 18 months. A survival gradient is seen within each stage and a significant survival gradient is demonstrated between stages. The number of T_1 lesions associated with either N_2 or M_1 extensions of disease was insufficient to make meaningful estimates of survival. The survival estimates for $T_3\ N_0\ M_0$ lesions seems high compared to other Stage III disease. This group, however, contains superior sulcus tumors which have a known unique biologic behavior as compared to other bronchogenic carcinomas. With current therapeutic practice, the prognosis associated with these tumors is distinctly superior to that with all other types of

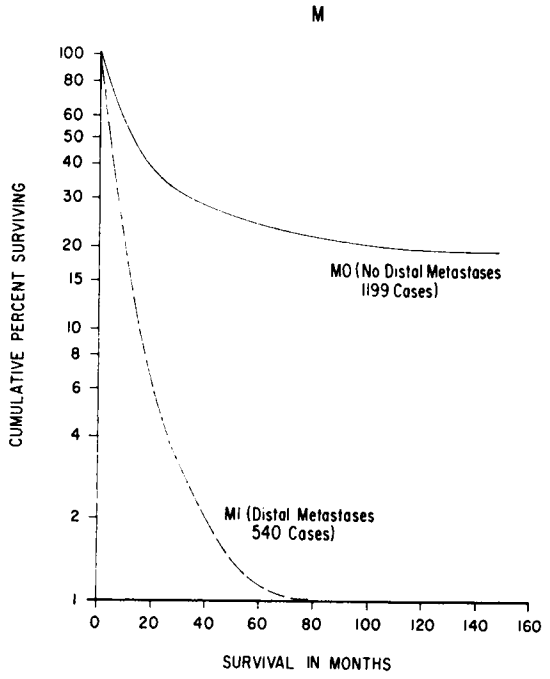

FIG. 4. Survival in lung cancer stratified by absence or presence of distant metastases (M factor), excluding undifferentiated small cell carcinoma.

TABLE IV

STAGE-GROUPING IN CARCINOMA OF THE LUNG

TNM Set	No. of Patients	Cumulative Percentage Surviving ± S.E.	
		12 Months	18 Months
Stage I			
$T_1\ N_0\ M_0$	135	.72 ± .04	.65 ± .04
$T_2\ N_0\ M_0$	358	.64 ± .02	.53 ± .03
$T_1\ N_1\ M_0$	24	.62 ± .10	.49 ± .10
Stage II			
$T_2\ N_1\ M_0$	109	.49 ± .05	.35 ± .01
Stage III			
T_1 Lesions	Insufficient Data	—	—
$T_2\ N_2\ M_0$	44	.26 ± .07	.14 ± .07
$T_2\ N_2\ M_1$	51	.24 ± .06	.10 ± .06
$T_2\ N_0\ M_1$	74	.10 ± .04	.04 ± .04
$T_2\ N_1\ M_1$	28	.11 ± .06	.07 ± .06
$T_3\ N_0\ M_0$	216*	.38 ± .03	.24 ± .03
$T_3\ N_1\ M_0$	96	.26 ± .05	.15 ± .05
$T_3\ N_2\ M_0$	210	.21 ± .03	.11 ± .03
$T_3\ N_0\ M_1$	116	.14 ± .04	.11 ± .04
$T_3\ N_1\ M_1$	57	.09 ± .04	.06 ± .04
$T_3\ N_2\ M_1$	306	.10 ± .02	.04 ± .02

* Superior sulcus tumors included.

lung cancer in an invasive stage. The definitions of the various stages are as follows:

Occult Carcinoma

$T_X N_0 M_0$ An occult carcinoma with bronchopulmonary secretions containing malignant cells but without other evidence of the primary tumor or evidence of metastasis to the regional lymph nodes or distant metastasis

Invasive Carcinoma

Stage I

$T_1 N_0 M_0$ A tumor that can be classified T_1 without any metastasis or with metastasis to the lymph nodes in the ipsilateral hilar region only, or a tumor that can be classified T_2 without any metastasis to lymph nodes or distant metastasis

$T_1 N_1 M_0$

$T_2 N_0 M_0$

(*Note:* T_X, N_1, M_0 and T_0, N_1, M_0 are also theoretically possible, but such a clinical diagnosis would be difficult if not impossible to make. If such a diagnosis is made, it should be included in Stage I)

Stage II

$T_2 N_1 M_0$ A tumor classified as T_2 with metastasis to the lymph nodes in the ipsilateral hilar region only

Stage III

T_3 with any N or M Any tumor more extensive than T_2 or any tumor with metastasis

N_2 with any T or M to the lymph nodes in the mediastinum or

M_1 with any T or N with distant metastasis

Figure 5 demonstrates the survival relationships between the 3 stage-groups based on an analysis of 1,633 patients with all information available to permit clinical staging. The survival curves for patients with undifferentiated small cell (oat cell) carcinoma indicate a disastrous clinical course regardless of the demonstrable anatomic extent of the disease. It was concluded, therefore, that stage-grouping for this cell type lacked meaning at this time.

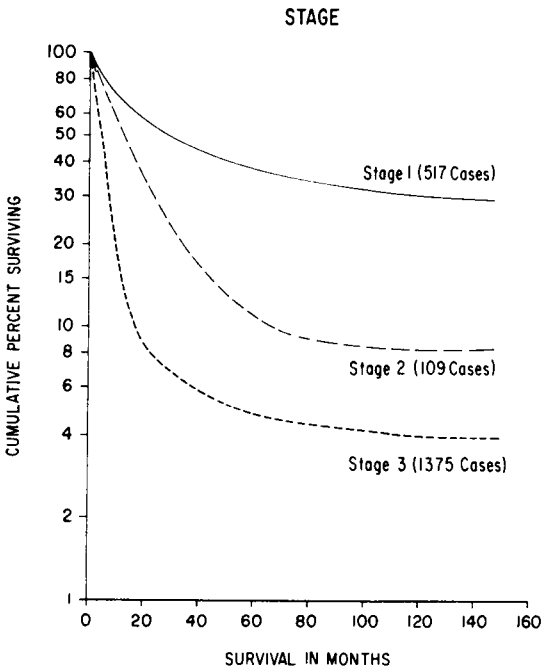

FIG. 5. Survival in lung cancer stratified by Stage (TNM combinations), with undifferentiated small cell carcinoma specified as Stage III.

The importance of grouping together only patients with a common histologic pattern of disease is demonstrated when the survival data are stratified by cell type within stage-groups, as in Table V. Metastases to the hilar lymph nodes, when the primary tumor is greater than 3 cm. in diameter, have much more grave prognostic implications in adenocarcinoma and in undifferentiated large cell carcinoma than in squamous cell carcinoma.

DISCUSSION

It is a basic principle of general semantics that no 2 objects are completely similar, and that they can never be completely described. They can be grouped together or classified, and said to be alike, only by abstracting certain common features and omitting or disregarding other aspects which are dissimilar. The problem is to identify those characteristics which allow one to classify each patient by some very simple scheme that reflects the prognostic implications of his disease.

TABLE V

SUMMARY TABLE OF RESULTS OF FIELD TRIALS FOR CARCINOMA OF THE LUNG—2 YEAR CUMULATIVE PERCENTAGE SURVIVING

Histologic Type	Stage					
	I		II		III	
	Per Cent	No.	Per Cent	No.	Per Cent	No.
Squamous Cell	46.6	331	39.8	66	11.5	524
Adenocarcinoma	45.9	151	14.3	28	7.9	334
Undifferentiated Large Cell	42.8	61	12.9	17	12.9	103
Undifferentiated Small Cell (Oat Cell)	6.0	38	5.0	20	3.8	302

At any given point in time, such as at the date of diagnosis, the actual stage of disease in a given patient is, in fact, a reflection of a large number of complex interacting biologic variables. These include: (a) the basic behavioral nature of a specific cell type of tumor; (b) its growth and extension in the host; (c) delays in recognition and in diagnosis of the disease; and (d) host-tumor relationships about which we have very little current understanding. In the present state of knowledge we cannot measure many of these parameters and we must be content in dealing with those which are measurable. Such factors pose an almost insurmountable obstacle to any perfect system of classification. These problems must be recognized and their limitations kept in mind.

The TNM system utilizes a common language to provide a basis for categorizing the extent of disease. The principles of the TNM system have, therefore, been utilized and applied to a method for describing the extent of bronchogenic carcinoma and to a stage-grouping, as presented.

Such a system of classification of patients with lung cancer serves to meet a number of related objectives: (1) to aid the clinician in the planning of treatment; (2) to make a quantitative estimate of prognosis; (3) to add validity to the clinician's end result evaluation which thus serves for continuing selfassessment; and (4) perhaps most important, to facilitate the exchange of information between centers of study.

The clinical classification of lung cancer makes it possible to compare the results of different modalities of treatment. Thus the survival experience for one population of a given cell type and stage of disease may be compared with another of a similar cell type and stage. Once the extent of disease has been established, the original description of the extent of tumor or its stage-grouping is not altered during the subsequent course of the malignancy. It is appreciated that the clinical estimate of disease is, to some degree, judgmental in nature and subject to error. It is important, therefore, to utilize the most objective sources of information available to minimize this type of misinterpretation. The extent of mediastinal involvement, for example, may be more validly assessed by utilizing the complementary value of mediastinoscopy and pulmonary arteriography than by reliance on the standard chest roentgenogram. Biopsy of a palpable lymph node is a more reliable index of disease extent than palpation, etc. Up to the point of employing major surgery, all types of objective evaluative information may be employed within the context of the clinical classification.

CONCLUSION

Even more definitive types of evaluative evidence may be used for classifying the

extent of disease. When information obtained at exploratory thoracotomy is utilized to describe the extent of disease, the stage-grouping is termed a "surgical evaluative classification." If the information is based on examination of a therapeutically resected specimen, it is termed a "post-surgical treatment classification." Our further studies, to be published later, indicate that the proposed scheme for describing the TNM sets and for their grouping into stages is equally applicable to each of the 3 types of classification.

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