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NON-SMALL CELL LUNG CANCER - AN UPDATE

MEDICAL GRAND ROUNDS

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EPIDEMIOLOGY

Excluding non-melanoma skin cancer, lung cancer is the most common type of cancer in man and is the leading cause of cancer deaths in humans. (1)

There will be approximately 91,000 new cases and 80,000 deaths in males in 1982 and 38,000 new cases and 31,000 deaths in females. (1)

The death rate in both sexes continues to increase at a greater rate than any other cancer and with the present trend will also be the most common cause of cancer mortality in females by 1985-1990. (1,2) Fig 1, Table 1.

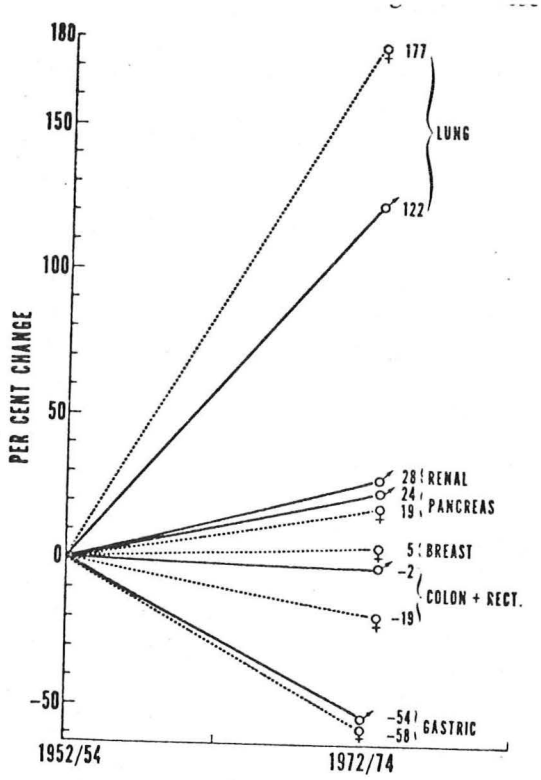


FIG. 1. Changing cancer death rates, U.S.A. From Silverberg, E.: Cancer statistics, 1977. CA, *26*:41, 1977.

Figure 1

TABLE I

RELATIVE FREQUENCY OF CANCER DEATHS BY SELECTED SITES

(% of Total Cancer Deaths)

	1977		1982	
	Male	Female	Male	Female
Lung	32	11	34	16
Breast	0.1	19	0.1	19
Colon-Rectum	9	13	12	15
Prostate	10	-	10	-

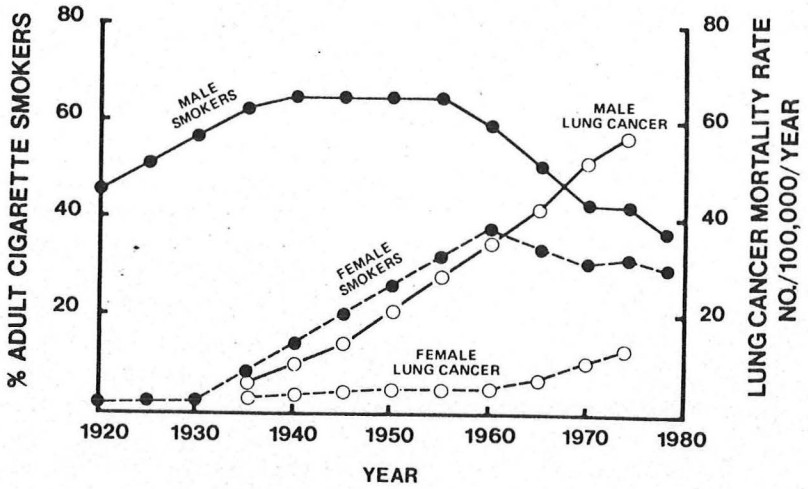
ETIOLOGY

Tobacco smoke, ionizing irradiation, certain industrial exposures to chemicals and asbestos are all accepted as carcinogens, cocarcinogens or promoters of bronchogenic malignancies. (3-5)

TOBACCO SMOKING

Inhaled tobacco smoke is the most serious etiologic agent in the development of lung cancer. Suggested contents which may be carcinogenic, cocarcinogenic or promoters include benzo (a) pyrene and other polycyclic hydrocarbons, nitrosamines and radioactive lead and polonium.

There is an approximately 30-40 year latency period from beginning exposure to development of bronchial malignancies. (5-7) Fig 2.



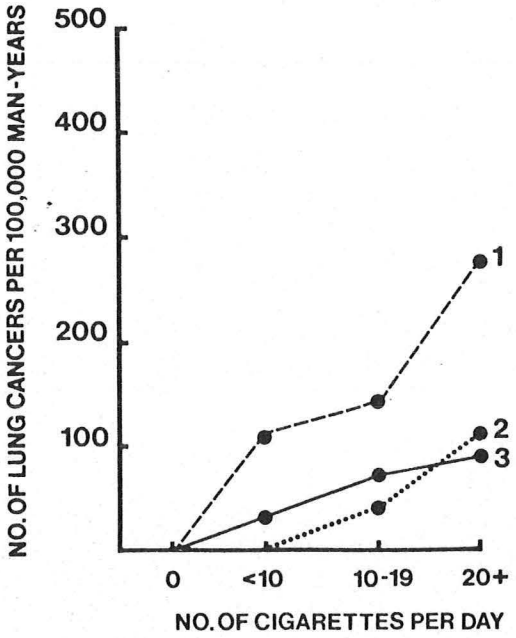
Temporal trends in the estimated percentage of current cigarette smokers in the U.S. adult population by sex[30,31] and trends in the U.S. age-adjusted (to the 1950 population) lung cancer mortality rates by sex.[32]

Figure 2, Reference 5

There is a definite dose-response relationship between the number of cigarettes smoked and the relative risk of developing lung cancer. Cellular atypia in bronchi at autopsy also obey this dose response relationship. (5, 8,9) Fig 3.

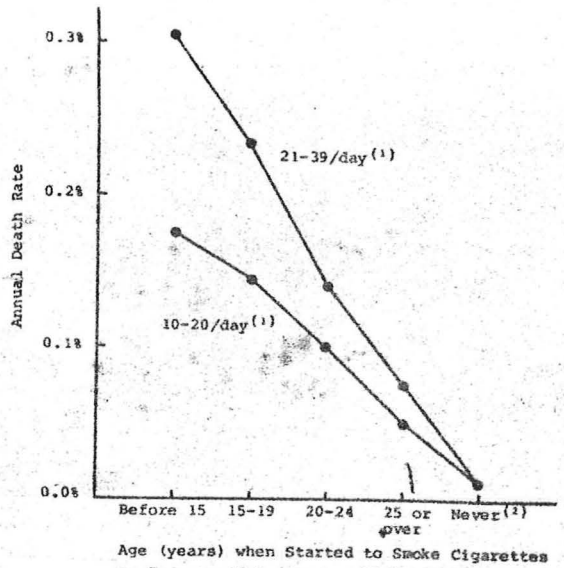
All cell types occur, but small cell carcinoma is rare in non-smokers and increases in relative frequency in very heavy smokers. (5,8,10) Fig 3.

The relative risk for developing lung cancer for a given exposure history increases the earlier the age at which smoking was initiated. (4) Fig 4.



Dose–response curves for lung cancer by cell type in relation to the number of cigarettes smoked per day by males aged 45 and over in the Philadelphia Pulmonary Neoplasm Research Project.[34] *Cancer types: 1, squamous cell carcinoma; 2, small cell carcinoma; 3, adenocarcinoma. Rates are adjusted for age and race.*

Figure 3, Reference 5



—Data on U.S. veterans (Kahn, 1966). Lung cancer mortality at ages 55-64 among current smokers of cigarettes only, in relation to the age when cigarette smoking first began (though this was perhaps not when regular consumption of substantial numbers of cigarettes first began).

(1) *The figures 10-20 and 21-39/day refer to the maximum rate at which the subject ever normally smoked cigarettes; the lifelong average may, of course, be much less than this.*

(2) *Subject may previously have smoked "once in a while but not every day."*

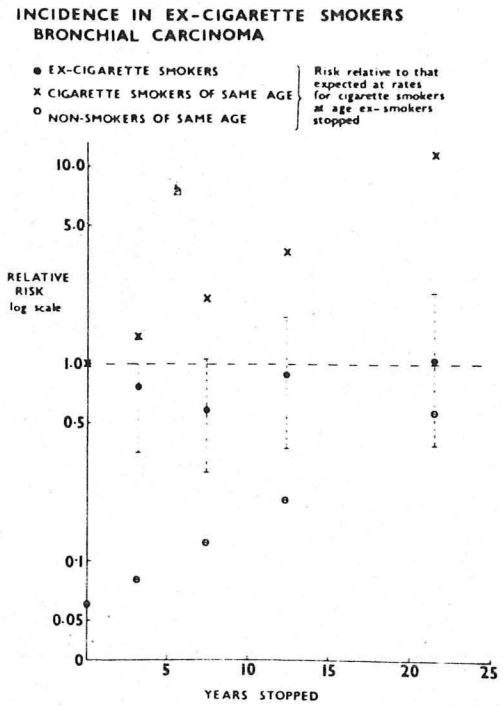
Figure 4, Reference 4

The relative risk of smokers over non-smokers is 10-20 fold for developing lung cancer. (4) Fig 5.

The relative risk of developing lung cancer diminishes in smokers who stop with a sudden decrease in the first two years then with a more gradual decline, but it never reaches the risk of "never" smokers. The same relationship exists for degrees of bronchial atypia at autopsy. (10,11) Fig 5.

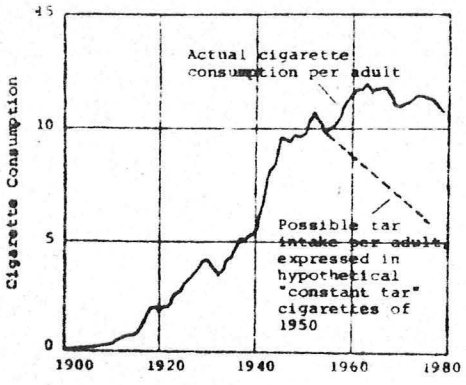
Two large studies have reached separate conclusions regarding the risk of "passive" smoking causing lung cancer in non-smoking wives of smokers versus non-smokers. The Japanese study noted a significant increased risk whereas an U.S. study could not demonstrate this phenomenon. (12,13)

The use of filter cigarettes may be reducing the risk of developing lung cancer for a given cigarette dose exposure (4,14,15) Fig 6 and 7.

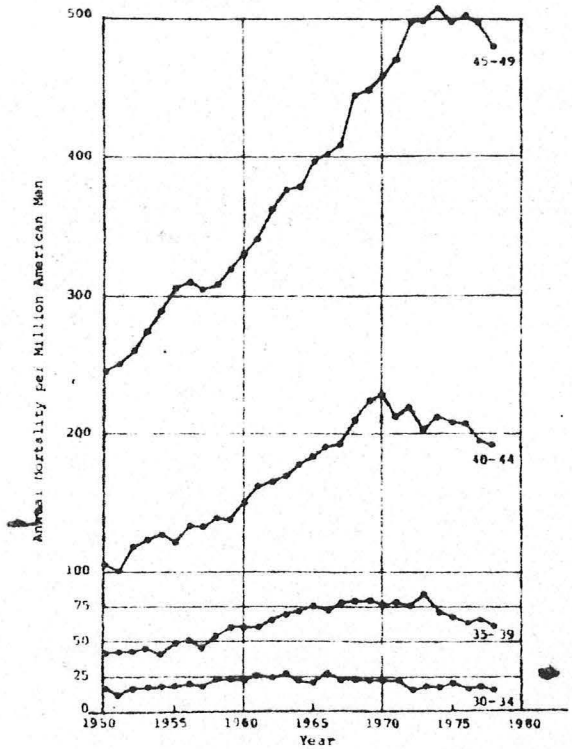


Numbers of cases of lung cancer in exsmokers, expressed as proportions of the numbers expected on the assumption that the rate remained the same as in regular cigarette smokers at the ages at which smoking was stopped: by time since smoking was stopped (double logarithmic scale). For comparison, similar proportions are shown estimated on the assumption that exsmokers would have continued to show the same incidence as (*a*) regular cigarette smokers of the same age and (*b*) lifelong nonsmokers of the same age.

Figure 5, Reference 10



—Mean daily sales of manufactured cigarettes per U.S. adult over 18 years of age (Surgeon General, 1980), together with a crude estimate of tar yield per adult, based on Owen, 1976. *The estimate of tar yield allows approximately for decreases since 1954 in tar yield per cigarette smoked in a standard manner (but not for any hypothetical compensatory increases in number of puffs per low-nicotine cigarette).*



—Trends since 1950 in lung cancer mortality in U.S. males at young ages; recent decreases are shown for the age groups 30-34, 35-39, 40-44, and 45-49 years.

Figures 6 and 7, Reference 4

CHEMICALS

A number of chemicals, inhaled during occupational exposure, have been implicated as causative of lung cancer. These include: (4,5,16)

(1) Polycyclic aromatic hydrocarbons

(2) Some metals or their compounds (chromium, nickel, arsenic, cadmium)

(3) Simple organic compounds (e.g., mustard gas, chloromethyl ethers, vinyl chloride, acrylonitrile)

These compounds generally have dose-response relationships and long latent periods. (5,16)

Occupational modifications appear to be providing a reduction in the incidence of lung cancer from these exposures. (4,5)

Paradoxically, with some of these chemicals, the relative risk of lung cancer appears greater in non-smokers than smokers. (5)

IONIZING RADIATION

Inhalation of radionuclides in an occupational setting has been associated with an increased risk of lung cancer (e.g. uranium miners, fluorospar miners). (5)

There is a cumulative dose-response relationship. In uranium miners, smoking increases the relative risk in both a synergistic, and perhaps tumor promoting fashion. Heavy smokers with high exposure have an approximately 67 fold greater risk than non-smokers with a low exposure history. (5,17)

There appears to be a selectively greater increase in small cell carcinoma in uranium miners. (5,17)

Polonium 210 (an alpha particle emitter) in cigarette smoke (perhaps as a decay product of less soluble lead - 210) has been suggested as a major carcinogen in tobacco smokers. Filters may not effect this potential carcinogen. (18,19)

There was some increase in non-small cell lung cancer in atomic bomb survivors but of a lesser magnitude than with inhaled radioactivity. (5)

ASBESTOS

The risk of lung cancer in asbestos workers is up to 14 fold greater than control populations. (5,20)

The type of asbestos fiber modifies the risk, chrysotile being less dangerous than amphiboles. (5,20)

The type of exposure effects the risk. In decreasing levels of risk this includes insulation work, manufacturing, mining. (5,20)

There is a clear linear dose-response relationship. (5,21)

Asbestos workers who smoke have a much higher risk whereas non-smoking asbestos workers have only a minimally increased risk. This has suggested a carcinogen promoter role for asbestos instead of a primary carcinogen. (22)

SURGICAL MANAGEMENT

DISEASE STATUS AT PRESENTATION

The relative distribution of apparent (clinical) extent of disease at the time of diagnosis has not changed in several decades and is quite different for non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). (2) Table 2.

The treatment of choice for NSCLC is surgical resection and is the primary curative modality. The proportion of patients potentially curable by resection also remains stable. (23) Table 3.

CLINICAL EXTENT AT PRESENTATION

Extent	NSCLC (%)	SCLC (%)
Local Only	25	< 1
Regional	30	30
Distant Metastases	45	70

Table 2

POTENTIAL FOR SURGICAL Rx AND OUTCOME

	% of Patients
Operable	43
"Curative" Resection	33
5 yr survival	10
10 yr survival	5

Table 3

A number of disease related factors and host factors determine operability for potential curative resection at diagnosis. (23) Table 4.

Distant metastases exclude curative resection. Mediastinal lymph node metastases determined radiologically or by mediastinoscopy is a relative contraindication to curative resection. Contiguous involvement of certain structures (chest wall, parietal pleura, recurrent laryngeal nerve, major vessels, heart, etc.) precludes a curative resection. (23)

Cell type diagnosis is a necessity. SCLC almost never is cured by surgical resection.

FACTORS DETERMINING OPERABILITY

Anatomic Extent

Distant Metastases

Mediastinal Lymph Node Metastases

Involvement of Contiguous Structures

Cell Type

Physiologic Status

Age

Table 4

Definitions of T, N, and M Categories for Carcinoma of the Lung[a,b]

T Primary Tumors	
T0	No evidence of primary tumor
TX	Tumor proven by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically, or any tumor that cannot be assessed
TIS	Carcinoma in situ
T1	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
T2	A tumor more than 3.0 cm in greatest diameter, or a tumor of any size which invades the visceral pleura or, which has associated atelectasis or obstructive pneumonitis, extending to the hilar region; at bronchoscopy the proximal extent of demonstrable tumor must be within a lobar bronchus or 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
T3	A tumor of any size with direct extension into an adjacent structure such as the parietal pleura or chest wall, the diaphragm, or the mediastinum and its contents; or demonstrable bronchoscopically to involve a main bronchus less than 2.0 cm distal to the carina; any tumor associated with atelectasis or obstructive pneumonitis of an entire lung or pleural effusion
N Regional Lymph Nodes	
N0	No demonstrable metastasis to regional lymph nodes
N1	Metastasis to lymph nodes in the peribronchial or ipsilateral hilar region or both, including direct extension
N2	Metastasis to lymph nodes in the mediastinum
M Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis such as in scalene, supraclavicular, cervical, or contralateral hilar lymph nodes, contralateral lung, brain, bones, liver, etc

[a]From the American Joint Committee for Cancer Staging and End Results Reporting: Clinical staging system for carcinoma of the lung. Chicago, 1973 (revision in press, 1977)

[b]Each case must be assigned the highest category of T, N, and M which describes the full extent of disease in that case

Table 5, Reference 24

Physiologic status such as cardiac, pulmonary, renal and other organ functions may preclude curative resection. (23)

Chronologic age, by itself is not an absolute contra-indication to attempted curative resection. (129)

DETERMINANTS OF OUTCOME OF "CURATIVE" RESECTION

Stage of Disease: The AJC system of staging the patient is utilized both pre-operatively and post-surgically to assess operability and outcome. Tables 5 and 6.

Clinically (pre-operatively) approximately 30% of patients appear to be stage I.

Post-surgically, approximately one-third of clinical stage I patients are actually stage II or III.

Results of resection correlate with the post-surgical A&C staging system. (25-32) Table 7.

Stage Grouping in Carcinoma of the Lung[a]

Type	Definition
Occult carcinoma	
TX N0 M0	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
Stage I	
TIS N0 M0	Carcinoma in situ
T1 N0 M0 T1 N1 M0 T2 N0 M0	A tumor that can be classified T1 without any metastasis or with metastasis to the lymph nodes in the ipsilateral hilar region only, or a tumor that can be classified T2 without any metastasis to nodes or distant metastasis
	Note: TX N1 M0 and T0 N1 M0 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	
T2 N1 M0	A tumor classified as T2 with metastasis to the lymph nodes in the ipsilateral hilar region only
Stage III T3 with any N or M N2 with any T or M M1 with any T or N	Any tumor more extensive than T2, or any tumor with metastasis to the lymph nodes in the mediastinum, or with distant metastasis

[a]From the American Joint Committee for Cancer Staging and End Results Reporting: Clinical staging system for carcinoma of the lung. Chicago, 1973 (revision in press, 1977)

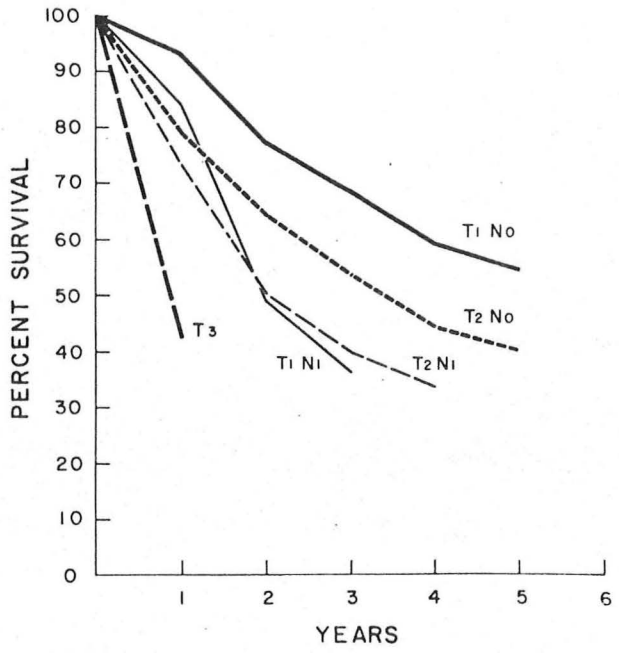
Table 6, Reference 24

RESULTS OF "CURATIVE" RESECTION BY POST-SURGICAL STAGE

Stage	% of Resections	5 Year Surv (%)
I	42	53 - 70
II	13	24
III	45	16

Table 7

Subgroups of post-surgical stage I patients (by TN factors) have significantly different prognoses. (28-32) Figure 8.



Postrandomization survival curves for patients assigned to the revised T, N, and M categories.

Figure 8, Reference 31

Stage III patients have significantly different prognoses dependent upon TNM determined subsets. (26,23-40) Table 8.

SURVIVAL FACTORS STAGE III

Factor	% 5 yr Survival
T_3N_o (resectable)	16 - 32
N_2 (resectable)	0 - 10
M_1	0

Table 8

T_3N_o patients in whom resection of disease can be accomplished have a finite cure rate. Particularly where T_3 is due to chest wall invasion. (33,34)

N_2 patients may occasionally be cured by resection. (26,35,36). This is dependent on sampling of mediastinal nodes and the number of mediastinal sites involved (37,38). The metastatic pattern pathologically has prognostic significance (39,40). Patients who were clinically not stage III have a better chance for surgical cure. (37)

Cell Type: In patients with lymph node metastases, long term survival is also cell type dependent, squamous cell tumor patients having a better chance of cure. (27,35-37)

Extent of Resection: Patients undergoing pneumonectomy have a worse prognosis than those requiring lesser resections. It is not clear whether this is an independent variable. (26,27,29)

CAUSES OF FAILURE OF SURGICAL RESECTION

Operative Mortality: The operative mortality (deaths within 30 days of attempted resection) ranges from 2 - 10%. Extent of resection and individual institutions or surgeons are significant variables (selection criteria for surgery and technical expertise) (26,27,41,42).

Disease Related Deaths Versus Non-Tumor Causes: During the first two post-surgical years, tumor recurrence is the primary cause of death. Subsequently non-tumor related causes become predominant or second lung cancers occur. (26,27,38,41,42). Table 9. Life table analysis of survival does not discrimate according to cause of death.

CAUSES OF DEATH IN PATIENTS RESECTED FOR CURE

Cause	Time Post Resection: < 2 yrs (%)	Time Post Resection: ≥ 5 yrs (%)
Primary Tumor	85	14
Second Lung Cancer	{ 15	12
Other Causes		62
Unknown	-	12

Table 9

The frequency of surgical failure is dependant upon the initial stage of disease as well as the cell type. The latter is most prominent in patients with nodal metastases. (38) Table 10.

FREQUENCY OF FAILURE DURING FIRST TWO POST-RESECTION YEARS

	Frequency by Cell Type	
Post Surgical Stage	Squamous Cell	Adeno & Large Cell
I	18	24
II	36	50
III	48	70

Table 10, Reference 38

PATTERNS OF FAILURE AFTER SURGICAL RESECTION

Local Recurrence Versus Distant Metastases: Distant metastases are more common than local recurrence. The presence or absence of nodal involvement may effect this pattern. (43-45)

Residual Tumor at Autopsy in Operative Deaths: Autopsies of patients undergoing what was felt to be a "curative" resection demonstrate a high frequency of residual disease. The pattern correlates with recurrence patterns but also with cell type (47), Table 11. In patients with distant metastatic deposits, the abdominal region predominated. Table 12.

Brain Recurrence: Clinically, brain relapse is often the only recognized site of first failure. (46)

RESIDUAL AND METASTATIC TUMOR AT AUTOPSY
IN PATIENTS DYING WITHIN 30 DAYS OF CURATIVE RESECTION

Cell Type	# Patients	Persistent Disease (%)	Local/Regional Only (%)	Distant Metastases (%)
Squamous	131	33	50	50
Adenocarcinoma	30	43	8	92
Large Cell	22	14	0	100
Total	183	33	13	87

Table 11, Reference 47

SITES OF DISTANT METASTASES AT AUTOPSY
WITHIN 30 DAYS OF CURATIVE RESECTION

Site	% of Patients with Metastases
Adrenal	38
Abdominal Nodes	30
Liver	24
Kidney	19
Brain	19
Opposite Lung	13
Vertebrae	11

Table 12, Reference 47

DETECTION OF DISTANT METASTASES

Based on the frequency of occult metastatic disease noted at autopsy in patients dying within 30 days of apparent complete resection, adequate techniques for identifying those metastases should significantly reduce the number of patients subjected to thoractomies who are destined to fail because of the already existent dissemination. (47)

In the autopsy study, 60% of the residual local-regional or metastatic deposits were single foci.

Methods of detection and reliability vary depending on the organ system being evaluated. The results discussed are data from patients otherwise considered candidates for potential "curative" resection.

LIVER

The frequency of liver metastases, as detected by varying methods, in operable patients, as compared to the early autopsy data are shown in table 13.

DETECTION OF LIVER METASTASES IN OPERABLE PATIENTS

Method of Detection	Approximate % True Positive
Autopsy After Early Death	24
Exploratory Laparotomy	10
Transdiaphragmatic Exploration	9
Radionuclide Liver Scan	6
Liver Biopsy with Laparoscopy	3

Table 13, Reference 48-56

Radionuclide Liver Scan (51-56)

Approximately 10% are positive in operable patients but 25-40% of these are false positive.

Approximately 10% of scans are false negative (15-20% based on early autopsy data).

Specificity increases with multiple abnormal liver function tests or enlarged liver (80-90%).

Summary and Recommendations

Detection of occult liver metastases is suboptimal with present methods.

Radionuclide scanning should be reserved for patients with clinically suspected liver metastases by LFT or size.

Biopsy via peritoneoscopy should be considered if scan is positive, especially in Stage I and squamous cell carcinoma.

ABDOMINAL LYMPH NODES AND ADRENAL GLAND

30-40% have involvement of these sites at autopsy after early death. (47)

Lymphangiogram will not detect adrenal or high abdominal nodes.

No data exists for sonography or C.T. scanning of the abdomen in NSCLC although C.T. scanning has been useful in SCLC for detecting lymph node and adrenal metastases at diagnosis. (57)

BRAIN

5-10% of all NSCLC patients, including clinically operable, have detectable brain metatastases at presentation. (58)

$\sim$ 20% of all NSC patients resected for cure have brain metastases at autopsy within 30 days of resection. (47)

5-10% of clinically operable NSCLC patients have positive radionuclide brain scans. Approximately 20% of the positive scans are associated with normal neurologic examinations. (54-56)

False positive brain scans approach 0%.

Recommendations. CT or radionuclide brain scans are indicated in patients who have abnormal findings on a careful mental status and neurologic examination.

BONE

10-15% of NSCLC operable patients have demonstrable bone metastases at presentation or at autopsy following early death. (47,52,53)

The specificity of radionuclide bone scans is dependent upon interpretation and radiologic correlation for other causes of a positive scan. (54-56)

False negative rate of bone scans are unknown but autopsy data indicates up to 25%, especially in vertebrae. (40)

The specificity is enhanced when bone pain and/or an increased alkaline phosphatase are present.

Recommendation. Radionuclide bone scans are indicated in the presence of bone pain or an unexplained elevation of the alkaline phosphatase. They must be correlated by site of abnormality and with radiographs of abnormal areas. (54-56, 60)

A summary of the use of routine radionuclide organ scans in potentially resectable NSCLC patients is shown in table 14. (54-56,60)

ROUTINE RADIONUCLIDE SCANS IN POTENTIALLY OPERABLE PATIENTS

Site	Possible Frequency of Metastases (%)	True Positive (%)	False Positive (%)	False Negative (%)
Liver	20 - 25	5 - 10	25 - 40	10 - 20
Brain	15 - 20	5 - 10	Rare	10 - 15
Bone	10 - 15	5 - 10	Variable	? 25
Adrenal and Abdominal Nodes	30 - 40	-	-	-

Table 14

Routine multiple scans will identify clinically occult metastases in approximately 2% of patients. Therefore much less than 1% of all scans are true positive.

Approximately 4% of patients will have clinically suspected and proven metastases with negative scans.

Approximately 85% of positive scans in the presence of suspected metastases are accurate.

Perhaps 80% of positive scans in the absence of suspected metastases are false positive.

MASS SCREENING OF HIGH RISK PERSONS FOR EARLY DETECTION OF LUNG CANCER

Lung cancer cure is dependent primarily upon diagnosis at an early AJC stage to allow curative resection.

Identification is presently accomplished routinely only by radiologic or cytologic means. AJC stage I or stage 0 (radiologically occult) tumors represent a minority of patients at the time of diagnosis.

Older mass screening studies were poorly designed and showed no impact on the clinical stage at diagnosis.

An NCI sponsored study of mass screening of high risk patients was initiated in 1974 with enrollment completed in 1978 at three participating institutions. (61-66) Preliminary results of parts of these studies are summarized in table 15.

IMPACT OF MASS SCREENING OF POPULATIONS AT
HIGH RISK FOR DEVELOPING LUNG CANCER

	General Population	MLCP-1	MLCP-2	J.H.
# Studied	-	4618	4593	10387
# Incidence Cases	-	135	104	200
Annual Incidence/1000	-	4.4	3.0	4.7
% Resectable	33	66	28	45
% X-Ray Occult	0.5	13	0	-
% Post Surg Stage 0-I	20	60	21	41
Probability 5 yr Surv (%)	10	45	19	-
% NSCLC	80	74	67	-
Estimate 5 yr Surv (%) for NSCLC	15	60	28	-

Table 15

J.H. Johns Hopkins - Randomized annual CXR or annual CXR plus every 4 months sputum cytology (groups combined).
MCLP Mayo Clinic MCLP-1 Every 4 mos CXR and sputum cytology.
MCLP-2 Recommend seeing own MD annually. Annual questionnaire of status.

In addition, early stage identification of NSCLC is increasing with years in progress. (71)

Disease free survival of resectable stage I patients may be better in screened group than general population. (71)

Conclusions: Intensive continuous screening of high risk population for lung cancer improves cure rate. Cost effectiveness remains major drawback.

ROLE OF RADIATION THERAPY IN NSCLC

RADIATION RESPONSIVENESS

Potential for tumor eradication in a radiation field has been demonstrated by operative evaluation and autopsy studies in up to 30% of patients. (67-69)

Dose related tumor regression occurs in 40-70% of patients with tumor doses of $\geq$5000 rads (>1600 rets) including approximately 25-50% complete radiological regressions. (70-74)

POTENTIAL UTILITY OF RADIATION THERAPY

Palliation of Symptoms

Prolongation of Symptom Free State

Prolongation of Survival

Long Term Survival - "Cure"

Operable - resectable patients

Inoperable or unresectable patients

Palliation of Symptoms: Clearly attainable in some patients.
Results are dependent on symptom, location and size of lesion, e.g. - with SVC compression, bronchial obstruction and pain success is often seen. With recurrent laryngeal nerve paralysis there is generally a poor effect.

Prolongation of Symptom Free State (Early "Palliative" Treatment):
Very little data exists. This is the most controversial area in lung cancer radiotherapy. (75,76)
No controlled studies of early versus late R.T. are available.
A retrospective analysis of 80 patients with inoperable disease and no distant metastases suggests the potential feasibility of this commonly utilized approach. (75) Table 16. The rationale is based on the radiation therapy principle that for a given tumor dose, local control will be accomplished more effectively the smaller the tumor mass being irradiated.

SYMPTOM STATUS AFTER RADIATION THERAPY AT DIAGNOSIS

		2 mos (%)		6 mos (%)		
Initial Symptom Status	#	Stable	Improved	Stable	Improved	Worse
None or mild	19	100	0	91	0	9
Moderate	37	30	70	28	68	4
Severe	24	0	92	0	88	12

61% of patients with severe local symptoms at Dx had minimal symptoms at 6 months.

Table 16, Reference 75

Prolongation of Survival:
Early data including randomized studies indicated no effect of R.T. on survival (76-80). These historical studies utilized orthovoltage equipment and lower doses of radiation than are presently accomplished.

Early studies indicated a 5-6% 5 yr survival in inoperable patients without distant metastases treated by 'radical' radiotherapy. (78-80)

The natural history of inoperable patients who are not treated was demonstrated by the VALG studies. (77)

Results of more recent studies indicate a probable effect of radiotherapy on survival using better equipment, higher doses and improved techniques. (71-74, 81) Table 17

SURVIVAL OF INOPERABLE PATIENTS WITH LOCAL/REGIONAL DISEASE TREATED WITH "RADICAL" RADIOTHERAPY

Study	Median Survival (wks)	% Surviving 1 yr	2 yr	3 yr	5 yr
VALG (1968)*	22	18	-	-	-
VALG (1981)	33 - 56	18-56	15-25	-	-
RTOG (1982)	45	45	25	-	-
Victoria (1980)	55	57	31	18	10
Galveston (1981)	52	50	29	-	-

* The VALG 1968 data are the untreated patients for historical natural history comparison.

Table 17, Reference 71-74, 81

Table 18 lists those variables which tend to predict the likelihood for a long-term survival outcome with radiation therapy. (71-74,82)

PROGNOSTIC VARIABLES IN RELATION TO SURVIVAL IN PATIENTS TREATED WITH "RADICAL" RADIOTHERAPY

Variable	Optimal Status	Potential for 5 yr Survival Without Optimal Status
Tumor Size	3 cm or less	Yes
Performance Status	No Symptoms	Yes
Weight Loss	Less than 5%	Yes
Cell Type	Squamous	Yes
Supraclavicular L.N.	None	No
Response	"Complete"	No
Pleural Effusion	None	No

Table 18, Reference 71-74, 82

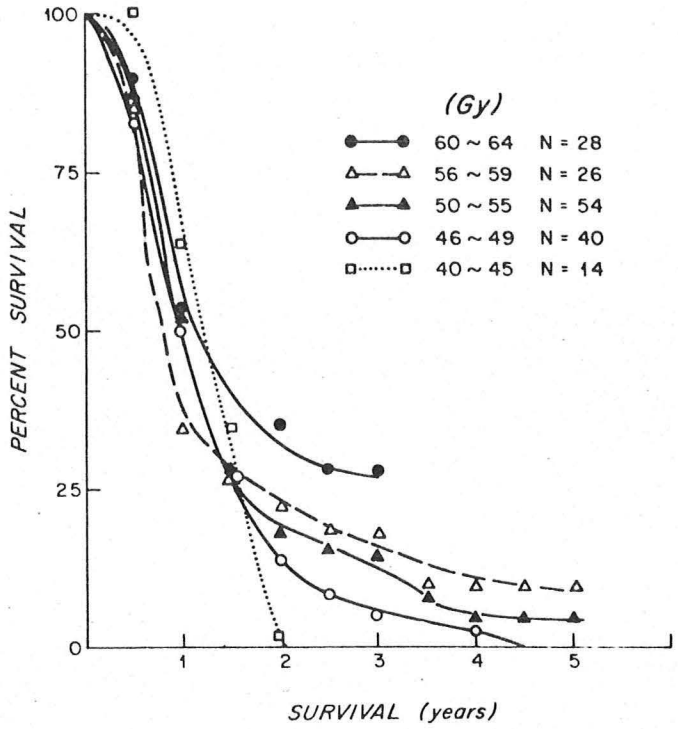
Long Term Survival - "Cure"

Up to 20% of candidates for curative resection may be cured by radiation therapy. (83,84)

10-20% of inoperable patients with good performance status (asymptomatic or minimal symptoms) and disease limited to the intrathoracic region and no pleural effusion achieve 5 yr survival with present standard techniques of R.T. (43,85,86)

New technical advances hold potential for higher cure rate for the inoperable patient: (87) Figure 9. These include:

- Higher energy equipment
- Changing fields during the radiotherapy course
- Utilizing oblique fields
- Utilizing simulators and improved blocking techniques
- Utilizing optimal time-dose relationships



Actuarial survival curves of the patients who had been treated with different radiation doses and target volumes with minimum follow-up of 2 years (See Table 3).

Figure 9, Reference 87

PATTERNS OF FAILURE AFTER RADICAL RADIOTHERAPY

Table 19 shows the patterns of tumor recurrence after attempted curative radiotherapy in two large cooperative group trials. (88,89)

PATTERNS OF FAILURE AFTER RADICAL RADIOTHERAPY

	% of Failures by Site		
Cell Type	Local Only	Local & Distant	Distant Only
Squamous	42 - 57	17 - 21	26 - 37
Adeno & Large Cell	23 - 25	21 - 22	53 - 56

Table 19, Reference 88,89

Improved local control is the primary objective in squamous cell carcinoma. (87-89). 50% die without experiencing distant metastases.

Distant metastases are the predominant cause of failure in non-squamous - NSCLC and are a target for systemic treatment in an adjuvant setting. (87-89). 60% die with continued control of local regional disease.

The brain is the single most common first distant site of failure in the non-squamous-NSCLC groups. (87,89) This raises the possibility of prophylactic cranial irradiation as is done in SCLC. (90)

Majority of local failure occurs by 18 months and the majority of distant failures by 24 months. (91)

ROLE OF CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER

To date, no study has convincingly demonstrated a significant impact of chemotherapy on the survival of patients with non-small cell lung cancer. (92)

A number of problems exist in the interpretation of published chemotherapy results which cloud the frequent conclusions that chemotherapy is beneficial to some patients. (Table 20)

PROBLEMS IN INTERPRETATION OF CHEMOTHERAPY TRIALS

- Prognostic Factors
  - Physical Status (Performance Status)
  - Prior Physical Status (Weight Loss)
  - Disease Status (Extent of Disease)
  - Prior Treatment
  - Histology
- Evaluation of Response
- Evaluation of Survival

Table 20

PROGNOSTIC FACTORS

Evaluation of over 5,000 patients with inoperable lung cancer from VALG protocols indicates a major variability in survival likelihood by non-treatment parameters. Other studies confirm these patterns. (93,94)

Multivariate analysis indicates that three major factors (of 77 evaluated) best predict for survival with the median likelihood ranging from 6 weeks to 72 weeks.

Current Physical Status (Performance Status):

Evaluation is carried out by one of two standard functional performance scales. (Tables 21,22)

This is the single most important predictor of survival likelihood (Table 23,Figure 10) with a range of 3 - 34 weeks median survival by this parameter alone. Grouping of these subsets will blunt their impact.

"PERFORMANCE STATUS" (KARNOFSKY SCALE)

Criteria of Performance Status (PS)		
Able to carry on normal activity; no special care is needed	100	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; a varying amount of assistance is needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance but is able to care for most of his needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospitalization is indicated although death not imminent
	20	Very sick; hospitalization necessary; active supportive treatment is necessary
	10	Moribund, fatal processes progressing rapidly
	0	Dead

PERFORMANCE SCALE (PS) (ECOG)

GRADE

0 — Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100)

1 — Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80)

2 — Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60)

3 — Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40)

4 — Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20)

Table 21

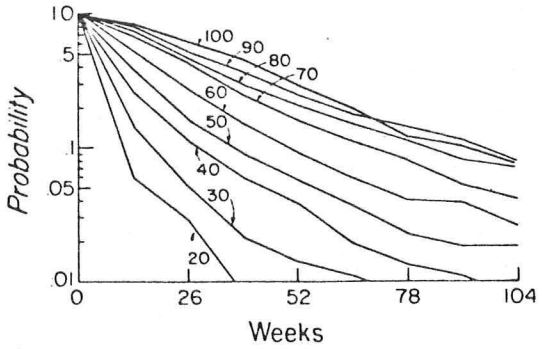
ECOG/ Zubrod scale	Karnofsky scale (%)
0	90-100
1	70-80
2	50-60
3	30-40
4	10-20

Table 22

—*Survival statistics by initial performance status*

Karnofsky performance status	No. of patients	Median survival, wk	Significance of each level relative to next lower level
100	88	34.1	$P=0.5956$
90	635	27.1	$P=0.0199$
80	948	24.0	$P=0.0003$
70	1,117	20.9	$P<0.0001$
60	892	13.8	$P<0.0001$
50	626	9.1	$P=0.0002$
40	479	6.7	$P<0.0001$
30	202	4.6	$P=0.0140$
20	35	3.2	—

Table 23, Reference 93



—Survival by initial performance status

Figure 10, Reference 93

Current Disease Status (Extent of Disease):

A simple division of disease status clinically is the second most predictive parameter of survival. These are usually defined as:

Limited Disease: Evident disease limited to one hemithorax and the mediastinum.

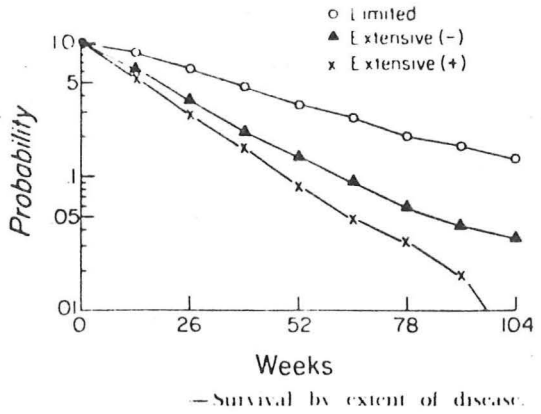
Extensive Disease: Distant metastatic disease including the opposite hemithorax.

Involvement of ipsilateral supraclavicular or scalene lymph nodes modifies the survival likelihood of both subsets, most especially those with extensive disease.

This parameter alone predicts median survivals with a range of 13-30 weeks. (93) Figure 11.

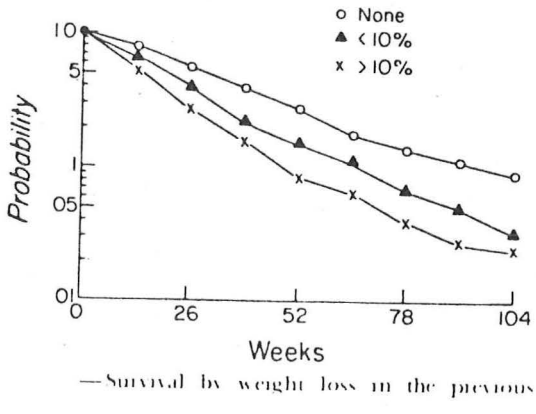
Prior Physical Status (Weight Loss):

The degree of weight loss over the six months preceding evaluation is the third most important prognostic variable. Alone it predicts a median survival likelihood ranging from 11-28 weeks using no weight loss, <10% body weight and >10% body weight as the categories. (93) Figure 12.



—Survival by extent of disease.

Figure 11, Reference 93



—Survival by weight loss in the previous 6 mo

Figure 12, Reference 93

These three factors, when utilized together, predict a potential survival likelihood of a wide range independent of treatment variables. (Table 24)

—*Additive prognostic factor model*

Median survival = 14 wk
+ Performance status
  90, 100 → +12 wk
  70, 80 → +8 wk
  30, 40, 50 → −7 wk
+ If limited disease
  Weight loss < 10% → +20 wk
  Weight loss > 10% → +2 wk
+ If extensive disease
  No weight loss, no scalene or supraclavicular nodal involvement → +8 wk
  Weight loss, scalene or supraclavicular nodal involvement → −4 wk

Table 24, Reference 93

Prior Treatment:

Prior radiation therapy was a variable with significant survival prediction in the VALG studies. Overall however, it did not add further predictive information to the above three. In recent chemotherapy studies, it appears that patients who received prior radiotherapy or chemotherapy may have a lesser likelihood of tumor response. (93)

Histology:

To date, no consistent correlation between cell type of NSCLC and chemotherapy response has been shown and histology does not add additional prognostic data to other criteria in multivariate analysis. (93,95)

EVALUATION OF RESPONSE

Standard response criteria are utilized in cancer chemotherapy trials:

Complete Response: Disappearance of all signs of disease.

Partial Response: Greater than 50% reduction in the product of the perpendicular diameters of measurable lesions without appearance of new lesions.

Minor Response: Tumor reduction less than partial response without appearance of new lesions.

Stable Disease: No significant regression or progression of disease and no new lesions.

Progression: Greater than 25% increase in the product of the perpendicular diameters of any measurable lesion or the appearance of new lesions.

In general, response is said to have occurred if a complete or partial response is noted. In NSCLC, lesions are often not measurable in the above terms and anything less than a complete response may be difficult to evaluate. (92,96)

A true complete response should have objective evidence that all previously identified disease is absent on re-evaluation.

Response criteria in many NSCLC chemotherapy trials are variable and not completely defined.

A review of all ECOG NSCLC trials revealed that the only variable that significantly affected response was performance status (ECOG 0-1 vs. 2-3) $p = 0.027$. Extent of disease, weight loss or cell type were not significant predictors of response, nor was prior radiotherapy. (95)

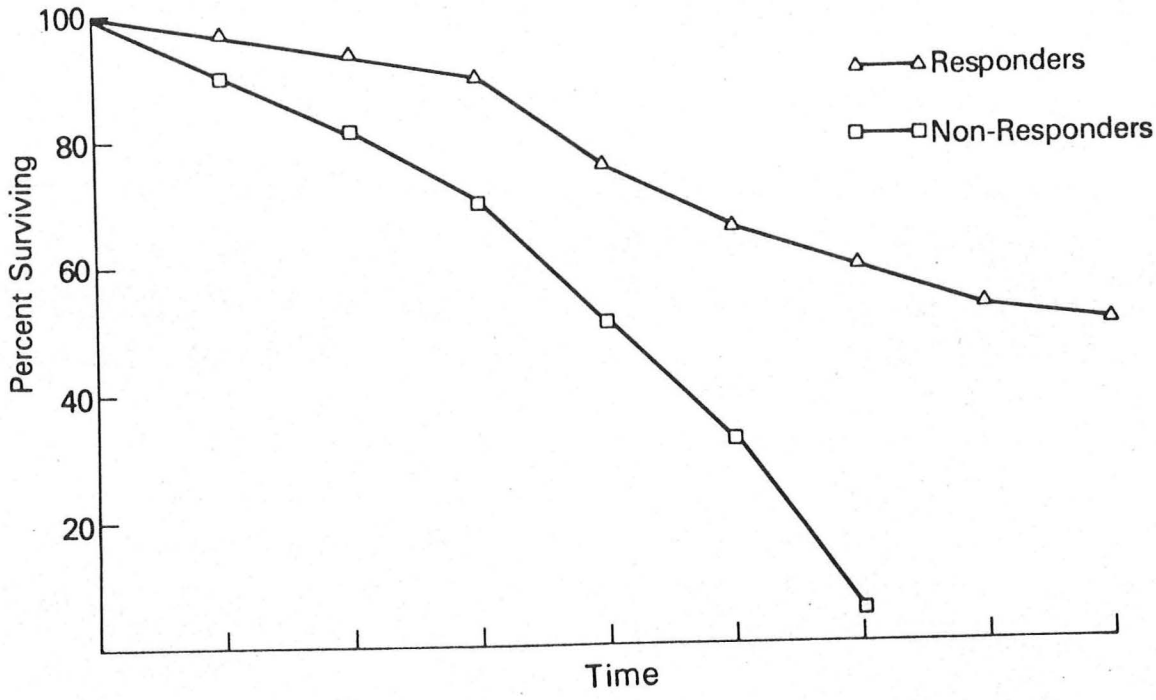
EVALUATION OF SURVIVAL (92)

No recent combination chemotherapy trials employ a simultaneous no treatment or ineffective treatment control group.

Survival has been primarily evaluated by comparing the median survival (time at which 50% of the evaluated group are dead) of those who are "responders" vs. those who are "non-responders". (Figure 13)

The percentage of patients surviving beyond a given time point are generally not reported.

A detailed breakdown of responders and non-responders by prognostic criteria are either not given or the numbers of patients are too few for statistical evaluation by these parameters.



Hypothetic survival curves modeled after many reports showing the effect of response to theoretic combination XYZ on survival in non-small cell carcinoma. This curve shows that the responders do better than the nonresponders, a feature common to most human malignancies. The figure, however, does not take into account the various prognostic factors that determine survival.

Figure 13, Reference 92

Sequential ECOG chemotherapy trials (415 patients) evaluated by multivariate analysis revealed the following variables to have prognostic significance for survival: performance status, extent of disease, weight loss, prior radiotherapy and response to chemotherapy. (95) Median survival of responders versus non-responders was 31.6 weeks versus 15.7 weeks ($p = 0.002$).

Toxicity is not insignificant. In the only two ECOG regimens with a >20% response rate, there were 60% of patients who experienced severe or life-threatening toxicity and 4% drug related deaths. (95)

Results of Selected Recent Trials:

A summary of three popular and frequently employed combinations drug regimens are shown in table 25 as the results were reported in individual trials. (97-107)

Initial series are usually small in numbers of patients and report a 40-50% response rate.

The mix of prognostic factors is widely variable and prior weight loss is almost never reported.

Subsequent trials, with usually more patients, usually demonstrate lower response rates.

Cooperative group studies tend to have lower response rates (though often better prognostic variables) and tend to predict the expected clinical outcome more accurately.

Quality of life is generally not described or effectively assessed.

SUMMARY OF CHEMOTHERAPY DATA

A clear cut effect of chemotherapy on the survival of patients with inoperable non-small cell lung cancer has not been adequately documented.

Randomized trials with newer "effective" regimens do not exist.

The prognostic variables known to effect survival are not well documented, adequately evaluated or the series are too small to draw conclusions.

Responders to chemotherapy do appear to survive slightly longer than non-responders. Whether other biologic factors that affect response also effect survival is unknown, but without randomized trials, this possibility cannot be eliminated.

Approximately 20 - 25% of patients will show tumor regression. Complete responses are rare (probably <5%). Complete responses, with other tumors, are best correlated with a major survival benefit.

Median survival of responders will be near eight months and non-responders near 3-4 months. Actual long term (greater than one or two year) survival rates are uninown relative to untreated patients.

RESULTS OF REPRESENTATIVE CHEMOTHERAPY TRIALS
FOR INOPERABLE OR METASTATIC NSCLC

	Source/#	Rx/Date Pub	% OF PATIENTS WITH Limited Disease	P.S. 0 - 1	CR	CR + PR	Median Survival (wks) ALL	Responders	Non-Responders
				C A P					
INST.	19	1978	0	58	5.2	42	29	28	31
INST.	54	1981	39	?	0	35	33	54	21
GROUP	131	1981	26	77	1.5	27	24	33	20
INST.	50	1981	0	22	0	6	18	32	17
TOTAL	254		22	± 57	1.1	25.6	18-33	28-54	17-31
				C A M P					
INST.	23	1976	0	35	17.4	48	35	54	13
INST.*	54	1978	0	39	9.2	33	36	55	23
INST.	35	1981	34	40	2.9	11	26	35	17
GROUP	76	1981	0	75	6.8	23	20	33	18
TOTAL	165 (studies 2-4)		7	56	6.7	23.6	20-36	33-54	13-23
	* Update of Initial Study on preceding line								
				M A C C					
INST.	68	1979	22	22	4.4	44	31	47	17
GROUP	43	1979	21	67	-	12	15	25	14
GROUP	76	1981	36	53	1.3	21	33	49	24
TOTAL	187		27	45	2.1	27.3	15-33	25-49	14-24

INST = Trial in a single medical center.
GROUP = Trial performed by a cooperative study group.

Table 25

COMBINED MODALITY TREATMENT

The combination of standard treatment modalities to attempt to overcome the causes of failure of traditional approaches has been under investigation in both single institution and cooperative group trials. Selected examples are summarized below.

SURGERY PLUS RADIATION THERAPY

These studies are directed at either increasing resectability of selected intrathoracic presentations or to enhance local control rates by theoretically eradicating residual microscopic disease.

Superior Sulcus (Pancoast) Tumors:

As first described by Pancoast, these are tumors presenting in the extreme apex of the lung associated with one or more of the following manifestations: shoulder pain with radiation, weakness and atrophy of the upper extremity, Horner's syndrome and rib or vertebral invasion. (108)

Paulson first reported favorable outcomes when pre-operative radiation (approximately 3000 rads) is followed by surgical resection. (109,110)

Randomized studies have never been performed to control for the local invasive variables, mediastinal node involvement and resectability.

Many institutions have reported series indicating agreement with this approach. Overall five year survivors approximate 28-35% (110-112). The resectability rate is enhanced. (112)

Patients with node involvement rarely survive 5 years using this approach. Those without have a 40-50% 5 year survival. (110-113)

A recent study utilizing radiation therapy only reported a better than 20% 5 year survival and a 25% 5 year survival in patients with mediastinal lymph node matastases. (114)

Conclusion: In patients who are potentially resectable, without evidence of mediastinal metastases, pre-operative radiation followed by attempted resection provides a significant likelihood of long term survival. Inoperable patients or patients with mediastinal node metastases may occasionally achieve a long survival with intensive radiotherapy alone.

Stage III (N_2M_0):

The results of surgical resection alone are only a 0-10% 5 year survival. (25,35,36)

Utilizing post-operative radiation therapy, three groups report significant long term survivals: 38% at 4 years (115,116) and 18-24% at 5 years (117,118).

These are non-randomized studies and cannot be directly compared to radiation therapy only since many patients had only microscopic evidence of mediastinal nodal involvement.

Patients who were clinically stage I prior to resection had significantly better survival likelihood than those who were clinical stage II or III. (115,116)

Conclusion: A patient who undergoes an attempt at curative resection and is found to have mediastinal metastases may benefit from post-operative radiation therapy especially if the metastases are occult and the pre-operative AJC stage was I.

All Stages Resected for Cure:

A large randomized trial by the EORTC of post-operative radiotherapy in patients with all AJC post-surgical stages indicated no overall effect on survival. Actually, patients with negative nodes had a significantly poorer survival. (119)

Conclusion: Routine post-operative radiotherapy, except possibly in N_2 disease is not proven beneficial.

SURGERY PLUS RADIOTHERAPY + CHEMOTHERAPY

Theoretically, this combined modality approach should attack both the problems of occult distant metastases and residual local-regional disease in patients undergoing resection for cure. (47)

Only one small, non-randomized study with short followup has been published. Twelve patients with N_2 disease were treated with CAP and radiotherapy pre-operatively - 11 were resectable. Eight of 12 were disease free for 9 or more months. (120)

This approach holds promise theoretically but remains investigative.

SURGERY PLUS IMMUNOTHERAPY

Surgical Resection plus Intrapleural BCG:

A well designed, randomized, single institution trial of intrapleural BCG in patients resected for cure demonstrated a statistically significant improvement in disease free survival for post-surgical stage I patients. (121)

The NCI Lung Cancer Study Group repeated this approach in a larger randomized study in stage I patients and demonstrated no effect. (122)

This proved to be an example of a statistical aberration since the control group in the Albany study had an inferior recurrance rate relative to that expected for stage I patients.

SURGERY PLUS CHEMOTHERAPY

Minimal data exists on post-operative adjuvant therapy trials since potentially more effective chemotherapy regimens have been developed.

A retrospective analysis of non-randomized trials in Stage III M_o patients suggested a benefit from post-operative CAP. (123)

A non-randomized trial using historical controls in Stage II patients suggested a benefit from post-operative CAMP. (124)

RADIOTHERAPY PLUS CHEMOTHERAPY

Published attempts at improving upon the established modest benefit of radiotherapy in inoperable limited stage disease by the addition of chemotherapy are also few since more effective chemotherapy regimens have been developed.

Two non-randomized studies have demonstrated a 60-70% objective response rate in Stage III M_o patients. Median survivals have been 9-10 months with responders having superior results. Long term effects are pending. (125,126)

Two randomized studies have been published. Early results in the EORTC study indicated a beneficial effect of chemotherapy. The other demonstrated no benefit in squamous cell carcinoma. (127,128)

This approach shows enough promise to be pursued in a randomized investigational setting.

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