MEDICAL GRAND ROUNDS

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Role of Surgery, Radiation Therapy, and Early Diagnosis in the Treatment of Bronchogenic Carcinoma

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INTRODUCTION

Sixty years ago carcinoma of the lung was such a rarity that it appeared in the pathological literature as a reportable case. Since the early 1930's many series have documented the absolute increase in bronchogenic carcinoma as a fatal neoplastic process (1-4). The epidemic increase in deaths per 100,000 population secondary to

Incidence of Lung Cancer Deaths Compared to
Cigarette Consumption

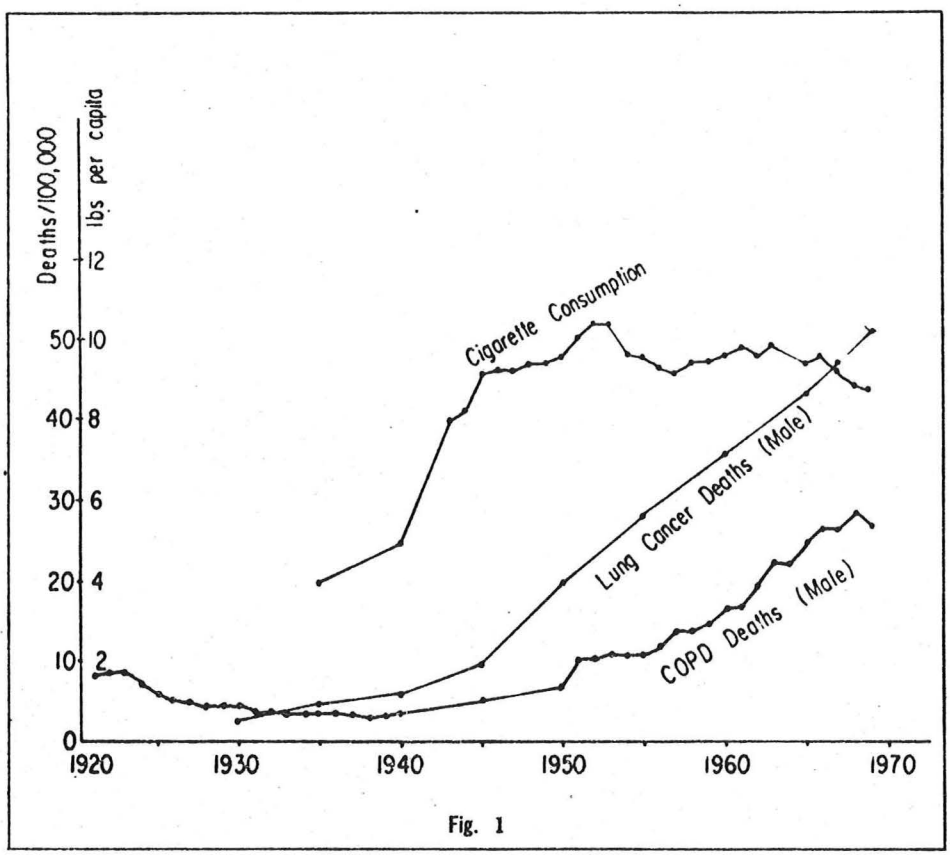


Fig. 1

bronchogenic carcinoma is graphically associated with increasing cigarette consumption as seen in Figure 1 (5).

Studies have shown conclusively that smoking is strongly linked to deaths from squamous cell and anaplastic carcinoma, but not to adenocarcinoma or alveolar cell carcinoma of the lung (4,5).

The American Cancer Society has estimated that 81,000 deaths from bronchogenic carcinoma will occur in 1975 (4). Two prospective studies conducted on over three million individuals in the United States emphasize that risk of developing lung cancer is also related to the number of cigarettes consumed per day.

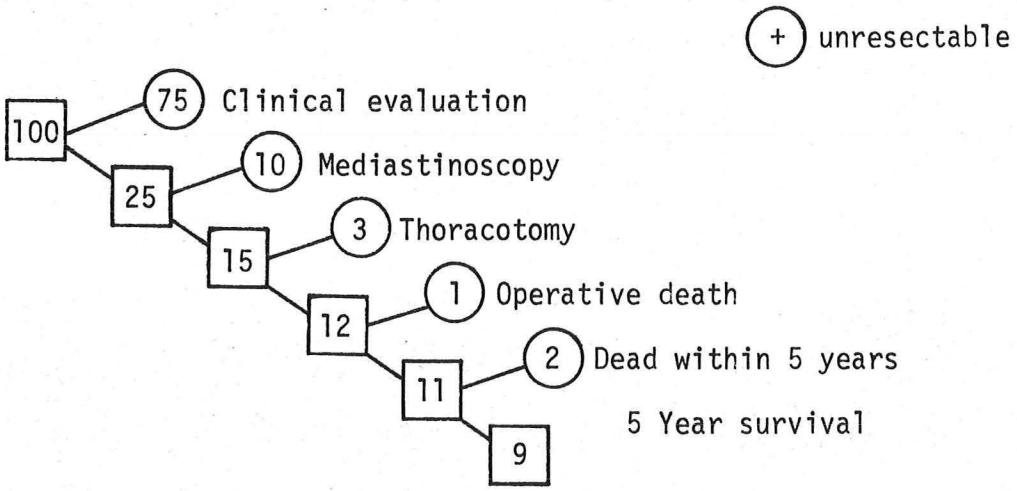
Table I

Risk of Death from Lung Cancer as a Function of Cigarette Consumption

		Mortality Ratio			
Cigs/day	0	1-9	10-19	20-39	40
Kahn	1.0	5.49	9.91	17.41	23.93
Hammond	1.0	4.60	7.48	13.14	16.61

Since the per capita consumption of cigarettes is not decreasing, the assumption can be made that the recommendation for detection and therapy of this entity will become an increasing problem for the internist as well as the surgeon.

Resectability on presentation is still the most significant factor in ultimate prognosis. A composite of statistics taken from several large series is represented by the outcome of 100 average patients who come to diagnosis by all routes (8-11). Figure 2.



Seventy-five out of every 100 patients are unresectable on presentation, 13 have undetected mediastinal involvement and are unresectable at operation. There is a 1% operative mortality, two will die from metastases and nine will survive five years.

This can be compared with a 1% five year survival of untreated patients prior to surgical availability (12).

Of these tumors 60% arise in the pheriphery and 95% are radiographically evident six months prior to diagnosis. However 10% are radiographically apparent 36 months prior to diagnosis and 4% may be present for as long as five years (12-14).

It is this highly variable natural history that makes this neoplastic process very difficult to evaluate from a therapeutic standpoint.

Surgery, Cell Type and Staging

Although surgical resectability is still the most significant factor in a favorable prognosis, the overall five year survival of 9% remains dismally low.

Certain factors when present can markedly alter this statistic either favorably or unfavorably. It is my purpose to examine these variables so that a rational recommendation can be made to individual patients.

A combination of cell type and the anatomic and clinical stage of disease have now been shown to effect resectability as well as response to other forms of therapy (15-17).

The World Health Organization attempted to standardize the histologic reporting of bronchogenic carcinoma in 1967 with subsequent modification into six main categories (18). Table II.

The incidence of each cell type varies among the large series but there is definitely a preponderance of squamous cell carcinoma, being from 40-50% of all bronchogenic carcinomas. These lesions are most often central in origin and visible at bronchoscopy (19).

Table II

Histologic Classification of Bronchogenic Carcinoma

WHO Classification	Synonym
Well-Differentiated Epidermoid Poorly-Differentiated Epidermoid	Squamous cell
Well-Differentiated Adenocarcinoma Poorly-Differentiated Adenocarcinoma	Glandular including alveolar cell
Small Cell Undifferentiated	Oat cell
Large Cell Undifferentiated	Anaplastic

Adenocarcinoma represents about 20% of all lesions and tends to be more pheripheral, of smaller total diameter and having a propenisity to occur in females (20).

Small cell undifferentiated carcinoma comprises about 15-20% of reported incidences and may be either central or pheripheral in location and is most often associated with early distant metastases (20).

The incidence of large cell undifferentiate or anaplastic carcinomas is the lowest of all bronchogenic carcinomas in the range of 10-15%. The lesions tend to be pheripheral and greater than 4 cm in diameter with a tendency to early metastases (21).

Using cell type alone as a criteria for prediction of five year survival, the average of many large series would indicate that squamous cell and adenocarcinoma following resection, have a five year survival in the range of 20-30% (20, 22-29).

Table III is a composite of these series and emphasizes the variability which may in part be due to difficulty with histologic classification. It does indicate quite clearly that cell type alone is a poor prognostic indicator.

Anatomic staging of tumors of all cell types was standardized in 1968 by the International Union Against Cancer. The TNM system was devised by this group wherein T denotes the primary tumor, N the regional lymph nodes, and M the distant metastases. The application

Table III

Reported Five Year Survivals after Resection for Bronchial Carcinoma

Author	Adeno-carcinoma (%)	Squamous Carcinoma (%)	Oat-cell Car-cinoma (%)	Undifferen-tiated (Anaplas-tic Carcinoma (%)	Total Resec-tions
Bignall and Moon, 1955	41	36	--	26	453
Kirklin et al, 1955	54	20	9	25	844
Paulson, 1957	22	17	0	0	44
Collins, 1958	9	21	0	4	33
Clagett, 1960	28	33	15	27	584
Spjut et al, 1961	18	24			225
Siddons, 1962	41	36	--	31	250
Taylor, 1960	13	25	13	7	465
Feinstein, 1974	21	28	9	8	160
Average	27	26	7.6	16	3758

of the TNM system to lung cancer has been carefully described and then categorized into stages as outlined in Table IV (30).

Table IV

Anatomic Staging of Bronchogenic Carcinoma

Stage		Description
Localized	0	Occult carcinoma: malignant cells in sputum, no evidence of primary or metastases.
	1	Tumor < 3 cm in diameter with ipsilateral nodes, or tumor > 3 cm without nodes.
Regional	2	Tumor > 3 cm with ipsilateral
Distant	3	Tumor larger than Stage 2, or any tumor with mediastinal or distant metastases.

Anatomic staging was designed to determine surgical resectability and the system has been examined by many different series with the following average five year survival rates (31,32).

Table V

Five Year Survival by Anatomic Stage

I	II	III	Total
Localized	Regional	Distant	
35/216	8/180	2/280	45/678
16%	4%	1%	7%

When you include all cell types only localized carcinoma has a minimally increased five year survival and then only if small nodes are all resectable with the speciman. The 4% survival with regional metastases is no better than that achieved with other forms of therapy. For this reason surgery should only be recommended to patients assessed as anatomic Stage I.

Small cell carcinoma has been shown by several groups to defy anatomic staging in terms of survival post resection (31). For this reason most centers now consider a histologic tissue diagnosis of small cell carcinoma as evidence of non resectability (32). In the older literature, however, the evidence for this is less clear and there has been great variability in post-operative survivors as illustrated in Table II. This variability may be partially explained by the problem of histologic classification.

Bronchoscopy and mediastinoscopy have been used to make a histologic diagnosis as well as to access the anatomic stage of disease.

Mediastinoscopy and left second interspace exploration allow the surgeon direct visualization of the mediastinal nodes. The value of these procedures in staging appears directly related to the surgeon's expertise. There is no doubt that examination of mediastinum has precluded thoracotomy in some patients. The false-negative rate is highly variable but nevertheless most important in evaluating the procedure as an adjunct to thoracotomy (33-35). It is most likely to be falsely negative in those patients who have no evidence of adenopathy on plain chest x-ray or mediastinal tomography. It is these patients who are subjected to two surgical procedures when thoracotomy would suffice. The procedure has proven most useful in establishing a diagnosis and assessing inoperability if the P-A chest film clearly suggests mediastinal adenopathy.

Bronchoscopy has for years been used to establish a histologic diagnosis of bronchogenic carcinoma. The flexible fiberoptic bronchoscope may have now become important in determining resectability. In a retrospective study of 1,038 patients Stoloff has shown a clear gradation in survival rate for those patients with involvement of the stem bronchus to those whose lesion arose more pheripherally (36).

Table VI

% Survivors by Endobronchial Location

Years Post Op	1	2	3	4	5
Stem	12	4	3.4	2	1.7
Pheripheral	32	22	18	14	13

Patients were included in the study irrespective of cell type or attempt at anatomic staging.

Of those patients with stem bronchial cancer 65% were declared inoperable at thoracotomy and only 10% were thought to have a curative resection. Although this study has not been repeated, experience with resection of solitary pulmonary nodules would seem to be comparable.

Solitary pulmonary nodules up to 4 cm in size have a considerably better prognosis than endobronchial lesion again almost independent of cell type. Jackman and Good in predominately asymptomatic patients reported a three year survival of 53.5% in a group of patients who had an unrevealing bronchoscopy (37).

These patients would be similar to those reported by Stoloff and confirm that thoracotomy for endobronchial lesions defined as stem bronchus is contraindicated in light of the results of radiotherapy.

Even in early series on survival following resection, it was noted that cell type plus anatomic staging was not the ultimate prognosticator

and many patients with well differentiated cell types classified as Stage I did poorly (38). It was further noted that particularly in patients with solitary pulmonary nodules those that were asymptomatic consistantly had the highest survival rate (39,40).

Although these isolated reports suggested a prognostic importance for the symptoms of lung cancer, the concept of using the symptoms of lung cancer to classify patients for prognostic and therapeutic purposes has been examined primarily by Feinstein.

He introduced the concept in 1964 that "a disease (or pathological) lesion either does or does not produce symptoms in its human host, and the symptomatic host either reacts or does not react to the symptoms by seeking medical attention." This was the basis for classifying the type of symptom in which the patient comes to medical attention (41). This classification is illustrated in Table VII.

Table VII

Definition of Symptomatic Groups in Lung Cancer

Asymptomatic	No symptoms attributable to cancer.
Long Primary	One primary pulmonary symptom (hemoptysis, cough) present for > 6 months.
Short Primary	One primary pulmonary symptom present for < 6 months.
Systemic	With or without primary symptoms (anorexia, weight loss).
Metastatic	With or without primary or systemic symptoms (bone pain, neurologic symptoms)

Applying only these symptomatic criteria he examined the five year survival of a group of 678 patients with lung cancer treated by all modes of therapy and found a clear survival gradient (42). Table VIII summarizes the results.

Table VIII

Five Year Survival of Various Symptomatic Categories

Symptomatic Category	Five Year Survival	
Asymptomatic	8/44	(18%)
Long primary	13/81	(16%)
Short primary	9/102	(9%)
Systemic	15/232	(6%)
Metastatic	0/219	(0%)
	45/678	(7%)

He then investigated the relationship between the symptomatic and the anatomic method of staging lung cancer. For statistical purposes he combined the asymptomatic and long primary (Stage I) and the short primary and systemic (Stage II). The results regardless of therapy are summarized in Table IX (43).

Table IX

Per Cent Five Year Survival

Symptomic Stage	Anatomic Stage			
	I	II	III	Totals
I	24	10	4	17
II	15	5	1	7
III	0	0	0	0
Totals	16	4	1	7

These results have been validated in another series of 646 patients with an even more striking five year survival gradient (44). Using clinical stage alone they report a 32% five-survival for the asymptomatic group and a 2% for the metastatic group. When they correlated those patients in anatomic Stage I with the three modified clinical stages the results were 40% Stage I, 19% Stage II, and 1% Stage III.

Summary

When cell type, anatomic and clinical stage of disease is considered as an entirety, several surgical recommendations can be made.

Cell type should not influence surgery with the exception of small cell carcinoma which precludes resection.

Well differentiated cell types are most often associated with asymptomatic localized disease and have a better prognosis.

Surgery with anatomic Stage I is rarely curative unless the lesion is clearly pheripheral and asymptomatic. In that circumstance the five year survival approaches 40% and is a clear cut indication for expedient resection.

Surgery is contraindicated even in anatomic Stage I if the patient is symptomatically Stage III or IV.

Radiotherapy

Radiation therapy has been employed alone and in conjunction with surgery in the treatment of bronchogenic carcinoma. Evaluation of the place of radiation therapy is more complex than determining five year survival rates.

Palliation of symptoms and prolongation of short term survival as well as potential role as a curative procedure must be evaluated.

Dose and Methods of Administration

Bloedorn in 1961 carried out a program of preoperative irradiation followed by lobectomy or pneumonectomy. The tumor dose was 6,000 rads to the primary site and mediastinum. In 26 surgical specimens 54%

showed no recognizable tumor at the primary site and 92% had sterile mediastinal nodes (45).

In 1968 Holsti reported on 67 patients with inoperable lung cancer who had varying dosage from 2,000-6,250 rads. In 18 cases, all of whom received 4,800-6,250 rads, there was no microscopic evidence of carcinoma in the primary treatment area, though all died from metastatic disease. In 26 cases showing visible carcinoma in the treatment area, therapy had been discontinued at 2,000-3,000 rads (46).

A clinical study by Brizel would tend to confirm these observations. Of 264 inoperable patients there was a 13% one year survival when 3,000-4,000 rads were administered and a 30% one year survival when 5,000-6,000 rads were given (47).

All of these studies commented on the increased morbidity of esophagitis and nausea but the symptoms were rarely a reason to discontinue therapy and resolved spontaneously within two to three weeks. None of the authors discontinued therapy for symptoms of radiation pneumonitis.

These data indicate that any increase in survival rates following radiotherapy would encompass a total dosage of 5,000-6,000 rads.

The preferred method of administration of the therapeutic dosage has also been investigated.

Holsti has reported on a group of 208 patients randomized to continuous versus split course therapy. The continuous therapy was

5,000-6,000 rads given six days per week for 5-6 weeks. The split course patients were given 5-10% more total dose with a 16-17 day rest interval. The results are shown in Table X (48).

Table X

Survival Rates after Split and Continuous Dose Radiotherapy

(per cent)

Technique	No. Cases	1 yr.	2 yr.
Split	118	42	15
Continuous	90	39	12

Other investigators (49,50) have confirmed the fact that there seems to be no significant difference in survival between the two groups and have taken this as evidence that split dose therapy is preferred because of patient tolerance. In spite of similar disease, a higher percentage of split therapy patients were able to complete therapy (48).

The incidence and severity of radiation pneumonitis in 74 patients treated by split dose and in 33 patients treated by continuous dose has been compared. Dose levels were slightly higher in the split course group being up to 7,000 rads in some patients. The incidence of radiologic signs of pneumonitis and later fiberosis was high in

both groups being greater than 98% of patients treated. However both symptoms and signs of the reaction occurred about two months later in the split group and were unquestionably milder. Dysphagia disappeared during the rest interval and there was earlier relief of symptoms because of higher initial doses (51).

Abramson in a unconfirmed series of 84 consecutive patients showed an increase in one year survival for split dose therapy patients (43%) over continuous therapy (14%) (52).

The evidence all seems to indicate that at present split dose therapy is preferable due to patient toleration and the possibility of prolonging one year survival.

Palliation of Symptoms

Palliation of symptoms has always been one of the goals of radiation therapy. Numerous studies have addressed this question either directly or as an ancillary benefit in debilitated patients.

A composite of many series indicated that approximately 75% of patients experience some type of symptomatic relief (53-56).

Few series have quantified this symptomatic improvement but of 67 patients treated by Garland and Sessons 75% noted marked to moderate decrease in hemoptysis, 60% marked decrease in cough and localized pain and 50% marked to moderate relief of mediastinal obstruction (55).

This compares favorably with the review by Schulz who collected several large series and attempted to combine the per cent of palliation expected by symptom (57-58). These results are given in Table XI.

Table XI

Palliation with Radiotherapy

Symptom	Per Cent Relief of Symptom
1. Hemoptysis	75
2. Cough	50
3. Local Pain (excluding nerve root)	80
4. Bronchial Obstruction	45-50
5. Dyspnea (excluding lymphangetic metastases)	50
6. Dysphagia (excluding invasion of esophagus)	20
7. Superior Vena Caval Syndrome	75
8. Pain-Distant Metastases	90-95

Intrepretation of these data indicates that radiation therapy should be given to all symptomatic patients with expectation of significant palliation regardless of cell type.

Treatment of Asymptomatic Lesions with Radiotherapy

Review of the natural history of untreated, inoperable, bronchogenic carcinoma is useful in assessing the benefits of radiation in prolonging life. The largest series in the literature is that of Ariel and Pack collected from six clinics. The study encompassed a total of 4,814 patients, 2,792 of whom were explored, with 1,155 proving unresectable at operation. None of these patients received treatment and none survived five years (59). Other studies have confirmed a 0-1% five year survival in untreated patients (12).

The use of radiotherapy in the treatment of patients with anatomically inoperable lesions or with severe concurrent medical illness has been debated.

Objective criteria which have been investigated include mean survival from time of diagnosis in unselected patients, overall five year survival and short term survival.

Mean survival time and overall five year survival in unselected patients has not been shown to be increased after treatment with varying doses of radiation (60-61). All of these series included large groups of patients with disseminated disease.

Short term survival in patients with localized disease has been significantly altered.

Table XII compares a group of 678 control patients with localized disease who received no treatment with a collected total of 1,756

patients who received "curative" doses of radiation therapy (47,52, 60-68).

Table XII

Results of Radiotherapy with Localized Disease

Series	No. Pts	Anatomic Stage	Rads	Mode of Administration	Percent Survivors by Months			
					12	24	36	60
Controls	678	localized	0	--	12.5	3.9		0
Smithers	171	localized	5-7,000	cont	37	13	9	4
Morrison	83	localized	4,500	cont	30	14	6	6
Hazra	75	localized	4,500	split	94	43	--	--
Caldwell	255	localized	6,500	cont	30	20	9	6
Guttman	150	unselected	5-6,000	cont	40	13	7	--
Guttman	103	localized	5-6,000	split	60	30	17	9
Brizel	101	unselected	3-4,000	cont	13	--	--	--
Brizel	88	localized	5-6,000	cont	30	--	--	--
Abramson	271	some with reg. nodes	4,000	split	38	13	7	--
Holsti	118	not given	5,500	split	42	18	--	--
Eastridge	341	localized extension	6,000	cont	23	--	--	3.5
Treated	1,756				42	21	9	5.7

The series of Guttman and Brizel are particularly interesting in that they have compared their results in selected and unselected patients and each showed a marked increase in one year survival in the localized group.

From these data it would seem that in patients with localized disease the significant increase in short term survival would warrant an attempt at radiotherapy with "curative doses" except in those patients with severe respiratory insufficiency.

This seems further justified by the observation that there is also a small but significant increase in five year survival.

There is one series in the literature that is poorly reported but nevertheless addresses the question of radiotherapy as a curative procedure and is worthy of further investigation (69).

In 1960 Hilton reported on thirty-eight patients who were diagnosed by biopsy or sputa cytology. Histologic types included: 24 squamous cell, 9 anaplastic, 1 adenocarcinoma and 4 undifferentiated. There was no clinical or radiologic evidence of local or distant secondary tumor and all were considered operable. Tumor dose of radiation was not given but survival was 71% at one year, 47% at two, and 21% at five years. This study has never been repeated but is suggestive that radiotherapy has a curative potential with the selection of the most favorable patients.

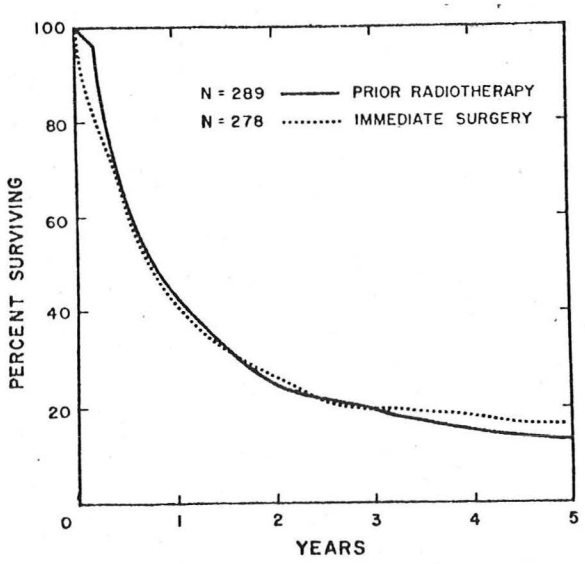
The therapy of small cell or oat cell carcinoma presents a particularly difficult problem. It has long been appreciated that anatomic staging of oat cell carcinoma followed by surgical resection did not correlate with five year survival. This has been recently confirmed by the Medical Research Council in England where they reported on a 10 year study on 144 patients randomized to a surgical versus radiation therapy group. None of the patients had evidence of local or distant metastases. The survival was essentially the same at one year but at five years the only three survivors were in the radiation treated group (70). A follow-up study on a very small number of patients would indicate that radiotherapy followed by surgery in this type of tumor has somewhat better prognosis but is still ineffective and that these patients would best benefit from some combination of chemotherapy or perhaps immunotherapy (71).

Pre-Operative Radiation

The role of pre-operative irradiation has been argued for many years and the finding of sterile lesions at thoracotomy or autopsy directed interest in this area (Bloedorn). Recent evidence in a cooperative study from 17 different centers seems to have settled the question. Pre-operative radiotherapy will allow resection of some previously unresectable tumors and up to 27% will have no tumor

at surgery (72). However, the yearly survival rates for the two groups remain completely unchanged (73). Figure 3.

Survivors Following Pre-Operative Radiotherapy



The conclusion can be made that general use of pre-operative irradiation is unwarranted.

The one exception seems to be in those tumors classified as superior sulcus tumors. These tumors are predominately squamous cell in histologic type and involve the brachial plexuses causing severe radicular pain. In those patients with localized disease a pre-operative course of 3,000 rads followed by radical surgery in 4-5 weeks has yielded a five year survival of 35% (74).

Post-Operative Radiation

Attempt to improve survival rates by the use of post-operative radiation has also received some attention in the past. Current evidence would again indicate that such therapy is unwarranted (75, 76).

A prospective study of patients undergoing pneumonectomy and then randomization to "no further therapy" or treatment with 4,500 rads was instituted.

The three year survival rates in the two groups were comparable being in the range of 35%. Patients who received pre-op irradiation had a 43% incidence of distant metastases verses a 28% incidence in those receiving no further treatment. This led the authors to the conclusion that post-operative radiation is probably contraindicated (77).

Early Diagnosis

The unsatisfactory results of treatment of bronchogenic carcinoma has led to the assumption that control of the disease in the absence of smoking cessation rests in early diagnosis and treatment.

The pattern of development of primary lung cancer has been compared with that of the uterine cervix. In both sites the columnar epithelium slowly undergoes changes to invasive neoplasia. Mass

screening and early diagnosis of cervical carcinoma has almost eliminated Stage IV from modern practice (78).

At least two new developments have led investigators to undertake various screening procedures to facilitate early diagnosis of bronchogenic carcinoma.

These have been the promising results of surgery on the asymptomatic lesion and the ability of the fiberoptic bronchoscope to localize the more pheripheral lesions.

In a retrospective study of 28 surgically resected cases of in-situ bronchogenic carcinoma, 64% had a positive chest x-ray, and 82% a positive sputa cytology. Of these patients there is currently a 76% three year survival and a 60% five year survival. Nine of the 10 patients with negative chest x-rays had positive sputa cytology and the lesions were identified and diagnosed with the fiberoptic bronchoscope (79).

Screening has therefore been directed at cytologic exam of the sputum, routine chest radiographic and a combination of the two procedures followed by bronchoscopy.

Several large prospective studies have been constructed to evaluate these procedures both individually and incombination (80-85).

Cytologic Screening

Mass cytological screening for bronchogenic carcinoma even in a high risk group has an extremely low yield. In the American Cancer Society - Veterans Administration study, 14,607 men were screened with a total of 41,206 cytologic exams. There were 50 cases of carcinoma detected or 0.3% of those screened which is similar to that in most series (80,82).

Further, it has been shown that 3-5 specimens must be submitted to obtain an acceptable accuracy of diagnosis. Collection of more than one specimen has proven difficult even in controlled populations (80).

The specificity of the test is good in most centers with only a 2% incidence of false negative examinations (80). The sensitivity or false positives, however, vary and may be as high as 33% (82).

All of these factors make screening by cytology alone impractical even in high risk groups.

Radiographic Screening

Modeled after screening for tuberculosis, investigators in the United States and England have employed the technique of six monthly chest x-ray examination of smokers over 40 years of age. The results have varied but again have been of extremely low yield.

In a series reported in the British Medical Journal a total of 29,723 men in a test group were screened with bi-yearly chest x-rays and compared with 25,311 in a control group who were screened only at the beginning and end of the study. The groups were followed for three years and 101 cases of carcinoma were diagnosed in the test group. For the detection of these 101 cases 178,338 chest x-rays were taken or 0.05% yield per test (81).

The Philadelphia Neoplasm Project attempted to screen 6,027 individuals with six monthly chest x-rays for a total of 10 years. During this period 121 or 2% of those screened developed lung cancer (84). This would have represented 120,540 exams if compliance had been 100%. Compliance in both series was approximately 60% and obviously effected the results.

The results of the controlled series reported in the British Medical Journal are given in Table XIII.

Table XIII

Results of Radiographic Screening for Early Detection Bronchogenic Carcinoma

		Cases Detected	Per Cent Resected	Overall Five Year Survival
Control	25,044	76	29	6
Test grp.	29,723	101	43	15

Of the 101 cases of carcinoma in the test group only 65 were actually detected by six-monthly chest radiographics. The remainder presumably became symptomatic and sought medical attention.

The overall five year survival of the test group was not statistically different from that of the control group.

From these results it can be concluded that routine radiographic screening for bronchogenic carcinoma is impractical and cannot be expected to prolong survival by early diagnosis.

It has been estimated that the duration of growth before a carcinoma reaches 2 cm in size is 9.1 years for squamous cell and 25.5 for adenocarcinoma (86,87). This is of course highly variable but indicative of the fact that most carcinomas are present for years in a phase not visible radiographically. This would make the routine chest x-ray a very insensitive screening technique.

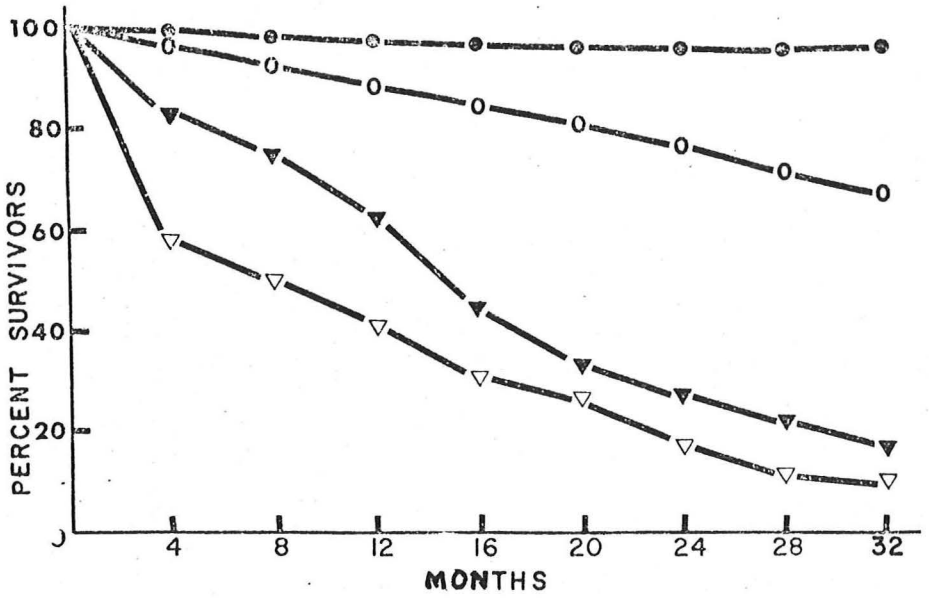
Cytological and Radiographic Screening

When cytology was combined with routine chest x-ray in the combined study of Lilienfield there were 73 newly detected cases out of the 14,607 screened. These authors estimate that the addition of cytology increased the number of lung cancer cases by about 50% over that detected by x-ray screening alone.

The fate of these 73 cases is again disappointing and is represented in Figure 4.

Per Cent Survival of Cases Detected by Screening Procedures

● STUDY POPULATION UNDER 45 YEARS OF AGE
o STUDY POPULATION 75 AND OVER
▼ 73 NEWLY DETECTED CASES OF LUNG CANCER
▽ 26 NEWLY DETECTED OPERATED CASES OF LUNG CANCER



Of the 73 cases, 44 were inoperable, 8 refused surgery and there was a 12% three year survival of those resected.

Other series on fewer numbers of patients confirm these investigators experience (88-90).

Cytology and Bronchoscopy

The localization of radiographic occult bronchogenic carcinoma diagnosed by positive sputa cytology is assumed to be the earliest form of detection of bronchogenic carcinoma. The problem of localization prior to the introduction of the flexible fiberoptic bronchoscope has been well documented and this difficulty has been given as a reason for poor surgical results (90-92).

Following the availability of the fiberoptic bronchoscope, Ikeda and others have shown that irregularity of bronchial mucosa, engorgement of blood vessels and compression or narrowing of bronchi are associated with brush and forceps biopsies that reveal bronchogenic carcinoma (93-95).

The possibility with this technique of detecting and localizing radiographically occult bronchogenic carcinoma led to the establishment of The Mayo Clinic Lung Project in 1972. At that time the investigators estimated they could detect 3-5 cancers per 1,000 men - years of observation (97).

They have screened 4,353 heavy smokers and have detected 33 unsuspected carcinomas for an incidence of 0.8%. Of these 24 were

visualized on chest x-ray and 10 had curative resections which compares favorably with the five year survival of all asymptomic pulmonary nodules. They have also investigated a total of 15 radiographically occult lesions.

Ten of these patients underwent "curative" resection with three deaths from metastatic disease. Those with resection have not been followed a sufficient period of time to offer an estimate of reasonable prognosis (97-99).

The results of this meticulous project again seem to emphasize the very low yield in detecting potentially curable lesions.

Even more disturbing is the fact that of the 15 patients with occult bronchogenic carcinoma three developed multicentric lesions. This is keeping with the work of Auerbach and others who demonstrated microscopically invasive carcinoma in the contralateral lung of patients undergoing resection for bronchogenic carcinoma (100-102).

Various screening procedures have failed to demonstrate that early detection is correlated with an improved prognosis. This seems inconsistant with the retrospective experience of resected in-situ carcinoma and the generally good prognosis of the asymptomatic pulmonary nodules. The explanation must lie in the doubling time of individual tumors. Thus there is "good" cancer and "bad" cancer and the best correlation seems to be with rapidity of development of symptomatology.

Those carcinomas that are detected in an early stage but recur after resection may be those that would have produced the earliest symptomatology if left to their natural history.

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