Patterns of Failure in Patients with Resected Stage I and II Non–Small-cell Carcinoma of the Lung

THE LUDWIG LUNG CANCER STUDY GROUP

The pattern of failure was studied in 1012 patients with resected Stage I or II non–small-cell carcinoma of the lung. Initial intrathoracic failure (41%) was more common than initial extrathoracic failure (34%) even though a complete resection was the intent in all patients. The most frequent sites of initial failure were the bronchial resection line (16%) and the central nervous system (CNS) (15%). The site distribution of initial failure does not appear to depend on TNM stage or pattern of nodal involvement. Patients with poorly differentiated disease had a greater rate of initial extrathoracic failure ($p < 0.01$), predominantly bone or CNS. Implications for therapy and future research are discussed.

THE 5-YEAR SURVIVAL RATE for patients with bronchogenic carcinoma, including all stages and all treatment modalities, varies between 5% and 15%, and there has been no substantial change in the last 3 decades. For curvative treatment, surgical resection remains the most effective therapy. However, of the apparently resectable patients with Stage I or II disease, less than 60% survive 5 years. Despite the intended complete removal of the primary tumor, there is a large number of patients with locoregional incomplete resection or microdisseminations at the time of operation.[1]

The search for effective adjuvant therapy in lung cancer has been underway for more than 20 years. To date, however, no significant improvement in survival has been seen from preoperative or postoperative radiotherapy, chemotherapy, or immunotherapy for non–small-cell bronchogenic carcinoma.

After a number of small studies that suggested a promising role for adjuvant immunotherapy, the Ludwig Lung Cancer Study Group was formed in 1977 to conduct large-scale randomized clinical studies in resectable non–small-cell lung cancer to provide definitive evaluation of this modality of adjuvant treatment. Two large clinical studies were begun that compared intrapleural *Corynebacterium parvum versus* placebo and intrapleural plus repeated intravenous *C. parvum versus* bacillus Calmette-Guerin (BCG) *versus* placebo. Intrapleural *C. parvum* was detrimental with respect to survival ($p = 0.06$) and BCG was associated with a decrease in disease-free interval ($p = 0.04$) (see references 2 and 3 for detailed reports of the therapeutic aspects of these studies). This paper reports an analysis of the patterns of failure in patients of these two clinical studies.

From the participants of the Ludwig Lung Cancer Study Group

The study of patterns of failure is important for a number of reasons. Foremost, it gives an evaluation of the weaknesses of current primary therapy. All too often current clinical research simply focuses on whether or not a given approach works; it is as important, if not more so, to determine how something works or fails to work. A progressive approach to therapy development, analyzing the failures and then adjusting treatment to counteract the failures, has proved beneficial in a number of diseases, such as Hodgkin's disease.

A second reason for investigating the patterns of failure deals with defining subgroups of patients who perhaps should be treated differently because of a different natural history. Care must be taken, however, when defining subgroups of patients to receive different primary therapy based on patterns of failure alone. For example, if a particular patient group metastasized earlier than another group after surgery, this would not necessarily imply that surgery does not significantly prolong the survival of this subgroup and should not be given. Other reasons for the study of patterns of failure include the nature and timing of ancillary treatment, supportive care, and understanding of the disease progression.

There are, however, severe limitations to the data on patterns of failure that arise from clinical studies. The reported pattern of relapse will depend on the frequency

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TABLE 1. *Patient and Disease Characteristics*

Characteristic	Percentage of Patients
Age	
<50 years	16%
50–59 years	43%
60–70 years	41%
Sex	
Male	86%
Female	14%
Surgical stage	
pT1N0	36%
pT2N0	39%
pT1N1	8%
pT2N1	17%
Type of resection	
Pneumonectomy	27%
Lobectomy	59%
Bilobectomy	6%
Other	7%
Nodal involvement	
No positive nodes	75%
Intrapulmonary only	21%
Lung hilar nodes	5%
Histologic type*	
Squamous cell	63%
Adenocarcinoma	26%
Large cell	11%
Degree of histologic differentiation*	
Well differentiated	25%
Moderately differentiated	39%
Poorly differentiated	35%

* Participant diagnosis.

and thoroughness of clinical evaluation. The detection of asymptomatic failure depends solely on whether the appropriate clinical study is done at the appropriate time. Perhaps more serious is the delay in time between relapse at some sites and the time when this relapse is clinically detectable. The true pattern of failure could be significantly different from the observed pattern of failure. Despite these limitations, however, identification of the site of first observed failure clearly points out a weakness in current therapy and provides a rational basis for developing more effective treatment.

Patients and Methods

Patients were considered for entry into the studies if they met the following criteria: less than 70 years of age; no previous history of malignancy or previous treatment by irradiation, cytotoxic drugs, or immunosuppressants; no signs of regional or distant metastases; no pleural exudate; and histologically confirmed squamous cell carcinoma, adenocarcinoma, or large-cell carcinoma classified after operation as pT1N0M0, pT2N0M0, pT1N1M0, or pT2N1M0 and considered radically resected macroscopically and microscopically.

Patients were entered centrally and were randomly assigned after operation to either placebo or intrapleural *C. parvum* for the first study or to either placebo, intrapleural BCG, or intrapleural and intravenous *C. parvum* for the second study. The patients were followed-up every third month during the first 3 years and then every 6 months for the following 2 years, or until death. Before operation and during the follow-up periods the following parameters were recorded: history and clinical examination, lung x-ray (p.a. and lateral), performance status, blood differential counts, liver enzymes, laparoscopy and/or liver scintigram and/or ultrasound when serum enzymes and/or clinical findings led to suspicion of liver metastasis, and pulmonary function tests. All data were reviewed centrally.

For patients with recurrence of disease, the time of first recurrence is the date of definitive diagnosis. Intrathoracic failure was defined as failure in the intersegmental and/or lobar hilar area, lymph nodes, and/or lung tissue. Extrathoracic failure was defined as failure in the lung hilar, mediastinal, paraesophageal area or subaortic nodes, and/or tissue, including thoracic wall and/or any distant site.

Results

From July 1977–January 1983, 1128 patients were entered onto one of the two studies. Of the 1128 patients, 1012 satisfied the entry criteria and were evaluable. As of August 1985, the mean follow-up time for the evaluable patients was approximately 5.5 years; 571 patients (56%) have failed and 510 patients (50%) have died. Autopsies were performed in approximately one quarter of the deaths. The distribution of patients according to selected patient characteristics is given in Table 1.

The site of initial failure was determined for the 571 patients who have failed. Initial failure was classified as either intrathoracic, extrathoracic, or death with no objective clinical evidence of failure. Table 2 lists the pattern of initial failure by treatment and various patient and disease characteristics. The type of surgical resection correlated with the site of first failure, but the difference was not statistically significant. Patients with a pneumonectomy had fewer initial intrathoracic failures, as would be expected. Patients with a histologic diagnosis of poorly differentiated disease had a greater rate of initial extrathoracic failure ($p < 0.01$).

The site of initial failure for the 426 patients with objective evidence of failure is given in Table 3. The most frequent sites of initial failure were the bronchial resection line (16%), central nervous system (CNS) (15%), ipsilateral extrapulmonary tissues (13%), contralateral lung (12%), bone (11%), and ipsilateral lung (11%).

Patients with a diagnosis of poorly differentiated disease failed most often in the CNS (20%) and bone (17%). CNS was the first site of failure for 9% of patients with squamous cell carcinoma, 19% of patients with adenocarcinoma, and 18% of patients with large-cell carcinoma.

TABLE 2. *Pattern of Initial Failure*

Characteristic	Percentage of Patients: Intra-thoracic	Extra-thoracic	Death and No Objective Evidence of Recurrence or Metastases	Total No. of Failures
Treatment				
Placebo	40%	36%	24%	260
C. parvum (IP)*	42%	32%	26%	127
BCG	38%	33%	28%	120
C. parvum (IP + IV)†	44%	31%	25%	64
Age				
<50 years	40%	42%	18%	88
50–59 years	43%	36%	21%	226
60–70 years	39%	30%	31%	256
Sex				
Male	39%	34%	27%	503
Female	50%	38%	12%	68
Surgical Stage				
pT1N0	39%	36%	25%	181
pT2N0	38%	32%	31%	220
pT1N1	53%	29%	18%	45
pT2N1	43%	38%	19%	125
Type of Resection				
Pneumonectomy	31%	37%	32%	165
Lobectomy	45%	35%	21%	322
Bilobectomy	32%	34%	34%	44
Nodal Involvement				
No involvement	38%	34%	28%	401
Intrapulmonary only	47%	33%	20%	131
Lung hilar nodes	41%	44%	15%	39
Histologic Type				
Squamous cell	49%	31%	29%	330
Adenocarcinoma	39%	37%	24%	150
Large cell	48%	36%	17%	59
Histologic differentiation				
Well differentiated	49%	28%	23%	100
Moderately differentiated	44%	25%	32%	139
Poorly differentiated	33%	41%	26%	131
Total	41%	34%	25%	571

* IP = intrapleurally.
† IP + IV = intrapleurally + intravenously.

The relationship between first and second sites of failure was also studied. There were tendencies for the patients who failed in the ipsilateral lung to fail next in the contralateral lung (11 of 47 patients), the patients who failed in the ipsilateral extrapulmonary tissues to fail next in the contralateral extrapulmonary tissues (9 of 57 patients) or nodes (9 of 57 patients), and the patients who had bone metastases to fail next in the liver (6 of 48 patients), or CNS (6 of 48 patients). It was also noted that patients with CNS metastases tended to fail next in the ipsilateral extrapulmonary tissues (5 of 63 patients). However, the true pattern of failure may have been in the opposite direction, with different rates of time until clinical detection being responsible for the observed pattern.

Figure 1 gives a schematic diagram of the pattern of failure for these patients. This figure gives the pattern of failure as a percentage of patients as they move from study entry to death. Estimates of this distribution pattern were obtained from the patients who had recurrence or who had died; patients who were alive and disease-free were considered censored.

TABLE 3. *Site of Initial Failure for Patients with Objective Evidence of Failure*

	No. of Patients	Percentage of Patients
Intrathoracic		
Bronchial resection line	66	16%
Ipsilateral intrapulmonary	47	11%
Ipsilateral extrapulmonary	57	13%
Contralateral intrapulmonary	50	12%
Contralateral extrapulmonary	6	1%
Intrathoracic, site unspecified	5	1%
Extrathoracic		
Ipsi- or contralateral supraclavicular, scalene or cervical nodes	14	3%
Other nodes	2	1%
Bone	48	11%
Liver	24	6%
CNS	63	15%
Other	20	5%
Second cancer	24	6%
Total	426	100%

Discussion

The three principle conclusions of this study are that for patients with Stage I and II radically resected non-small-cell carcinoma of the lung: (1) control of intrathoracic disease is still a main problem; (2) the lack of control in the intrathoracic area was especially pronounced at the bronchial resection line; and (3) a significant number of patients have disease progression in the CNS.

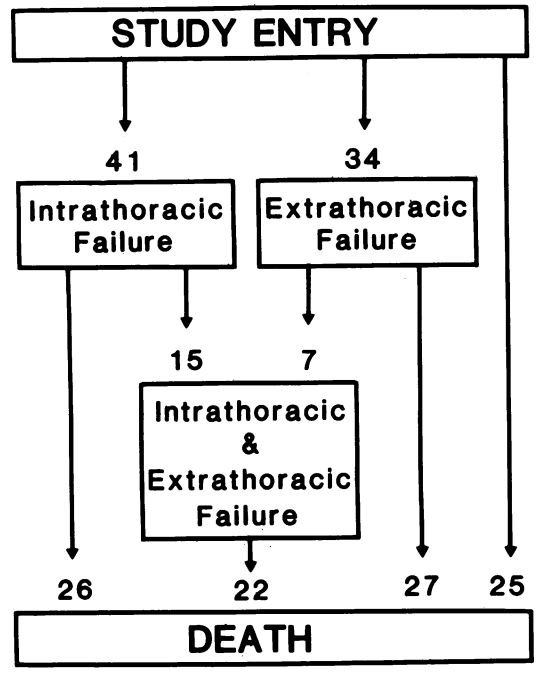

FIG. 1. Pattern of initial and subsequent failure (percentage of patients).

Although a resection for cure was the intent of surgery, more than half of the initial failures were intrathoracic, and of these failures, 76% were ipsilateral. Twenty-nine per cent of the intrathoracic failures were at the bronchial resection line. This is a clear indication that more emphasis should be given to local control.

Autopsy data on 202 patients with a curative resection for lung cancer who died within 30 days of the operation showed that 35% had persistent disease.[1] Of the 131 patients with epidermoid carcinoma, 44 patients (33%) had persistent disease identified at autopsy; 50% of these patients had disease limited to the bronchial stump or the hilar or the mediastinal lymph nodes. The remainder had distant metastases. Unfortunately, there is little information about the surgical procedures and staging reported in this study.

The sites of recurrence for resected Stage I non–small-cell lung cancer were reported for 390 patients by the North American Lung Cancer Study Group; approximately 39% of the first failures were intrathoracic (26%: involved lung and 13%: contralateral lung).[4] A study of 346 similar patients from the Mayo Clinic showed first recurrence rates of 19%: local recurrence only, 26%: subsequent primary, and 55%: nonregional metastases.[5]

Patterns of failure were studied in Houston in a series of 592 patients with lung cancer with no known disease remaining after resection.[6] Seventy-four per cent of the first failures were distant, 21% were regional, and 5% were both distant and regional simultaneously. The first observed failure was in the ipsilateral hemithorax or primary lung for 31%.

Relapse rates of 41% local recurrence *versus* 59% distant metastases were seen in Chicago in a study of 99 patients with resected Stage I or II disease.[7]

Neither adjuvant radiotherapy nor chemotherapy has improved survival for patients with Stage I and II resected non–small-cell lung cancer. The effect of a more extended surgical procedure is uncertain. Controlled studies to investigate whether better local control is obtained by more radical extended resections that include more extensive margin removal at the point of resection, the more frequent use of pneumonectomies, and the prophylactic removal of ipsilateral and mediastinal nodal systems and noncritical adjacent tissues are not available. However, a median time of disease recurrence of 4 years and a median survival of less than 5 years indicate that concerns about disease control should receive more emphasis.

Fifteen per cent of the initial failures in this study were found in the CNS. This rate is similar to the 21% rate of brain metastases as the first site of relapse in the study reported by the North American Lung Cancer Study Group.[4] The brain was the most frequent single site of first failure (19%) in the Houston Study.[6] Prophylactic cranial irradiation (PCI) is of benefit in reducing the number of CNS relapses in a number of randomized trials in small-cell carcinoma; a combined analysis indicates a reduction in CNS relapses from 22% to 6%.[8] PCI has also been shown in a controlled trial to reduce relapses in the brain in patients with advanced non–small-cell carcinoma from 13% to 6%.[9] However, it must be pointed out that although there was a reduction in CNS relapses in the above-mentioned studies, there was no corresponding increase in median survival rates.

The CNS failure rates for this study were highest for patients with adenocarcinoma (19%) and large-cell carcinoma (18%) compared with squamous cell carcinoma (9%); this pattern has also been seen in a number of other studies of patients with resectable cancer, primarily with Stage I disease.[4] However, the propensity for patients with adenocarcinoma and large-cell carcinoma to have higher rates of distant failure than patients with squamous cell carcinoma, as seen for inoperable patients,[10–12] was not seen in this study. The suggestion has been made to conduct randomized trials of PCI for patients with resectable non–small-cell lung cancer.[4]

There has been little progress in therapy for resected non–small-cell lung cancer in recent years even though a substantial number of studies have been conducted. This may be due in part to the relatively few studies that have looked at the patterns of failure in this disease.

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