Lung Cancer: A Combined Modality Approach to Staging and Therapy

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To develop treatment strategies for lung cancer, one must know the histology as well as the extent of the disease. This paper emphasizes the importance of the histological diagnosis, the value of careful clinical and pathological staging, and the development of treatment strategies based on this knowledge. The signs and symptoms of lung cancer, the radiographic findings, and the means of obtaining a tissue diagnosis are well-known to all practicing physicians and will only be mentioned as they pertain to the development of treatment strategies.

Histology

Although lung cancers include a wide spectrum of neoplasms that may be of entodermal, mesodermal, or possibly neuroectodermal derivation, carcinomas contribute 90 to 95 percent of these tumors. The four major cell types include epidermoid (squamous cell) carcinoma, small cell (oat cell) carcinoma, adenocarcinoma, and large cell (anaplastic) carcinoma. Approximately two to four percent of lung tumors are composed of a combination of glandular and squamous epithelium (adenosquamous cell carcinoma); carcinoids contribute up to five percent of surgically excised lung tumors. This discussion will deal with the four main types, which are found in the following percentage of lung cancer cases: epidermoid—40 percent; adenocarcinoma—20 percent; large cell carcinoma—10 percent; and small cell carcinoma—20 percent. We usually divide the four groups into small cell and non-small cell (epidermoid, adenocarcinoma, large cell). Electron microscopy has recently shown that the large cell category can be equally divided into the squamous cell category when desmosomes are present, or the adenocarcinoma category when microvilli are present.

The importance of differentiating small cell carcinoma from the other three types is twofold. First, small cell carcinoma is usually widespread, and thus usually not resectable on presentation. However, it is the most amenable, initially, to radiotherapy and chemotherapy.

The histologic type of tumor in itself affects survival. Squamous cell carcinoma has a 25 percent five-year survival rate, while that for both large cell carcinoma and adenocarcinoma is 15 percent, and

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for small cell carcinoma, one percent. But when one considers both the histology and the extent or stage of the disease, a more accurate prognosis can be established, and therefore it is important to the clinician treating the patient with lung cancer to assess the extent of disease; the simple diagnosis of lung cancer by itself is inadequate and incomplete.

Staging: TNM Classification

The TNM staging system for carcinoma of the lung, formulated by the task force on carcinoma of the lung of the American Joint Committee for Staging and End Result Reporting, is a particularly useful and broadly accepted method of systematically determining the extent of disease.\(^5\) It affords precise communication among physicians and other members of the oncology team regarding the extent of disease in a particular patient. It aids in the selection of a treatment plan for a given patient and gives the physician and patient a reasonable basis on which to determine prognosis. It allows comparison of therapeutic results among various institutions and provides a method of evaluating cancer control efforts over a period of time in one institution.

A staging worksheet is particularly helpful in evaluating patients with lung cancer. The worksheet has three columns that are used for the classification of the primary tumor (T), regional lymph nodes (N), and distant metastases (M) (Table 1A). The columns are labeled, from left to right, as clinical value, surgical value, post-surgical treatment value. The clinical value is determined by the clinical examination, chest x-ray and scintigraphic scans, with the Gallium 67 total body scan being most useful. The clinical evaluation can be supported by a tissue diagnosis obtained by bronchoscopy, mediastinoscopy, parasternal mediastinal exploration, or biopsy of a distant organ metastasis. When disease localized to the chest has been removed by a therapeutic pulmonary resection and the surgical specimen is analyzed, the classification is entered under the postsurgical treatment value column. As information concerning the classification of the primary tumor, nodal metastasis and distant organ metastasis is entered from left to right, the classification becomes more definite and the resultant stage more precise. The overall stage of disease is determined by obtaining the sum of the values for each classification and assignment of stage according to Table 1B.

Primary Tumor Size and Extent (T)

The classification of the primary tumor is signified by the letter T with a subscript of \(x\), \(1\), \(2\), or \(3\). \(T_x\) indicates the presence of malignant cells in the sputum but no tumor mass visualized on the chest x-ray or on bronchoscopic exam.

\(T_1\) indicates a primary lung tumor that is \(3.0\) cm or less in greatest diameter, surrounded by visceral pleura, and without evidence of extension proximal to a lobar bronchus at bronchoscopy. Since the resolution of shadows on chest x-ray is approximately one cm, a small \(T_1\) tumor may require tomography to clarify its presence, as shown in Fig. 1. This lesion was resected, and the specimen showed a small \(1.5\) cm squamous cell carcinoma in the middle of the right upper lobe. A primary tumor of this size is usually asymptomatic and is most commonly diagnosed on a routine chest x-ray obtained for other reasons.

\(T_2\) indicates a primary tumor that is greater than \(3.0\) cm in greatest diameter or a tumor of any size invading only visceral pleura or causing associated atelectasis or obstructive pneumonitis, limited to less than an entire lung. At bronchoscopy the proximal extent of demonstrable tumor must be within a lobar bronchus or at least \(2.0\) cm distal to the carina. The chest x-ray shown in Fig. 2 is an example of a \(T_2\) lesion. This tumor was removed by a right upper lobectomy and the surgical specimen showed a squamous cell carcinoma \(6 \times 5 \times 5\) cm.
### TABLE 1A
WORKSHEET FOR STAGING LUNG CANCER*
Value Evaluation

| Classification       | Clinical Value | Surgical Evaluative Value | Post-Surgical Treatment Value |
|----------------------|----------------|---------------------------|------------------------------|
| Primary Tumor        |                |                           |                              |
| \( T_X \)            | 0              | 0                         | 0                            |
| \( T_1 \)            | 1              | 1                         | 1                            |
| \( T_2 \)            | 2              | 2                         | 2                            |
| \( T_3 \)            | 4              | 4                         | 4                            |
| Regional Lymph Nodes |                |                           |                              |
| \( N_0 \)            | 0              | 0                         | 0                            |
| \( N_1 \)            | 1              | 1                         | 1                            |
| \( N_2 \)            | 4              | 4                         | 4                            |
| Distant Metastases   |                |                           |                              |
| \( M_0 \)            | 0              | 0                         | 0                            |
| \( M_1 \)            | 4              | 4                         | 4                            |

Total Value †

*Modified from the worksheet of the American Joint Committee for Cancer Staging and End Results\(^2\).
†Total value is different for every patient and equals the sum of each column.

### TABLE 1B
WORKSHEET FOR STAGING LUNG CANCER*
Stage Evaluation

| Stage | Value  | Classification                        |
|-------|--------|---------------------------------------|
| I     | 1 or 2 | \( T_1N_0, T_1N_1, T_2N_0 \)          |
| II    | 3      | \( T_2N_1 \)                          |
| III** | 4 or more | \( T_3 \) with any N or M \( N_2 \) with any T or M \( M_1 \) with any T or N |

*Modified from the worksheet of the American Joint Committee for Cancer Staging and End Results\(^2\)
**Subcategories of Stage III
1. Disease confined to the thorax = III \( M_0 \)
2. Metastatic disease = III \( M_1 \)
Fig. 1 Chest radiograph (a) and tomogram (b) showing a T2 lesion in the right upper lobe.

Fig. 2 Chest radiograph showing a T2 lesion in the right upper lobe.

Fig. 3 is a chest x-ray of a large T3 tumor that extends into the chest wall. Fig. 4 is a chest x-ray of a small T3 tumor that appears to extend into the left superior mediastinum, causing widening of the superior mediastinum and giving the appearance of a double aortic notch. At thoracotomy this tumor did extend into the superior mediastinum and surrounded the left subclavian artery. Tumors in the apex of the lung, as shown in Fig. 5, are often T3 tumors because of their invasion into the first rib, superior cervical ganglion, and brachial plexus, producing the so-called Pancoast syndrome, which is characterized by severe pain, and the Horner's syndrome. Tumors that cause total atelectasis of one lung as shown in Fig. 6, or have an associated pleural effusion as in Fig. 7, can be classified as T3 on the basis of the chest x-ray abnormality alone.
Normally, pleural fluid is constantly excreted and absorbed by the parietal and visceral pleura. Absorption through visceral pleura occurs via pulmonary lymphatics that pass through the hilum, while absorption through the parietal pleura occurs via the inferior mediastinal lymphatics. Lymph from both areas passes through the superior mediastinum to reach the venous system via the thoracic duct. When the lymphatics are blocked because of tumor metastases in the mediastinal nodes, the resulting obstruction causes decreased absorption and accumulation of pleural fluid within the chest. Therefore, any primary tumor that has an associated pleural effusion in the absence of congestive failure, regardless of whether the fluid contains malignant cells, is considered a T₃ tumor.

The size and extent of the primary tumor itself, without consideration of the extent of lymphatic or hematogenous metastasis, has an effect on survival. A T₁ tumor has a 43 percent, a T₂ tumor a 20 percent and a T₃ tumor a seven percent five year survival.

**Differentiation of Benign and Malignant Primary Neoplasms**

One of the problems in evaluating a patient with a single lung lesion is determining whether the lesion is benign or not. If malignant, is it a primary lung
cancer or a metastatic lesion from a primary elsewhere in the body? The Gallium 67 scan is a noninvasive means of helping the clinician make this differentiation. The principle is that if a single lesion on chest x-ray is gallium positive, there is a 91 percent probability that the lesion is a primary lung carcinoma. If the lesion is gallium negative there is a 76 percent probability that the lesion is not a primary lung carcinoma but a metastatic lesion from another primary or from a nonmalignant disease.

For example, Fig. 8 shows a Gallium 67 scan of the thorax, from the patient whose x-ray is seen in Fig. 2. The gallium scan shows that the lesion seen on x-ray takes up gallium, which strongly suggests that the lesion is a primary neoplasm of the lung. At thoracotomy the lesion was a resectable squamous cell carcinoma of the lung.

Fig. 9 shows a similar lesion on chest x-ray and a gallium scan of the thorax with no uptake of gallium in the area of the lesion. This suggested that the lesion was either a metastasis to the lung from another primary or a benign abnormality. At thoracotomy the lesion was an area of localized bronchiectasis with an associated chronic inflammatory reaction.

Fig. 10 shows a chest x-ray of a 52 year old smoker with an abnormal density along the right superior mediastinal border. Tomogram (Fig. 10b) confirms this to be a mass lesion, but the gallium scan (Fig. 10c) is normal, indicating that the lesion is probably not a primary lung neoplasm. Mediastinoscopy was performed and a lymphoid cyst was found, decompressed and removed.

Fig. 11a is a chest x-ray of a 52 year old male who was a heavy smoker. There is a large mass in the left lower lobe that does not take up gallium (Fig. 11b), suggesting a metastatic lesion. An upper and lower gastrointestinal barium study, IVP, proctoscopy and pelvic exam were normal. An ultrasound exam of the abdomen suggested a lesion in the pancreas. A post mortem exam showed the lung mass to be a metastatic adenocarcinoma secondary to a pancreatic primary.
Gallium scanning to evaluate lung lesions requires that patients with acute pneumonia, sarcoidosis, or lymphoid neoplasms such as Hodgkin's disease and lymphoma be excluded on the initial clinical evaluation; the scan is used to further assess patients who are suspected on clinical evaluation to have a malignant lesion of the lung. A positive scan carries a 91 percent probability that the lesion is a primary lung neoplasm. When the scan is negative, there is still a 24 percent possibility of a primary lung cancer—it does not, therefore, rule out lung cancer but greatly reduces the probability and raises other diagnostic possibilities, particularly that of a pulmonary metastasis from a primary located elsewhere.

There are three clinical situations where a gallium scan is of little help in the evaluation of a primary lung carcinoma. First, small lesions less than 2.0 cm in diameter cannot be evaluated with gallium, due to the limits of resolution in scanning technology. Second, an associated pleural effusion can surround the tumor and prevent its detection. Third, chronic atelectasis that fails to clear due to tumor obstruction of the bronchus will often give a negative scan.

Fig. 8 Gallium-67 scan of patient shown in Fig. 2 showing uptake of Ga-67 by a primary squamous cell carcinoma of the lung. There is no uptake in the mediastinum. The mediastinal lymph nodes were free of tumor at resection.

Fig. 9 Chest radiograph (a) showing a T1 perihilar lesion in the right lung. Gallium-67 scan (b) showing no uptake of Ga-67 by the lesion. At resection, a localized area of bronchiectasis with chronic inflammation was found.
Fig. 11 Chest radiograph (a) showing a large T3 lesion of the left lower lobe. Gallium-67 scan (b) showing lack of uptake by the mass. At autopsy, the lung mass was discovered to be a metastasis from a primary carcinoma of the pancreas.

The various cell types of lung cancer all have a 98 to 100 percent incidence of positive gallium scans, with the exception of adenocarcinoma, which has an 88 percent incidence and probably reflects the accidental inclusion of some unrecognized metastatic lesions. We feel that if a biopsy of a single peripheral
lesion shows an adenocarcinoma and the gallium scan is negative, strong consideration should be given to the possibility that the lesion is a metastatic carcinoma. The most commonly overlooked primary source for an adenocarcinoma metastatic to the lung is a carcinoma of the pancreas.

Lymphatic Spread (N)
The classification of the extent of lymphatic spread of a primary lung tumor is signified by the letter N with a subscript of 0, 1, or 2. N₀ indicates no demonstrable metastasis to regional lymph nodes. N₁ represents metastasis to lymph nodes in the peribronchial and/or ipsilateral hilar region. N₂ indicates metastasis to lymph nodes in the mediastinum, contralateral hilum or cervical region. For purposes of clinical differentiation between ipsilateral hilar and mediastinal lymph nodes, any node that can be removed or biopsied with a mediastinal scope is considered a mediastinal node.

The extent of lymphatic spread in itself, without consideration of the size of the primary tumor or the presence of hematogenous metastasis, has a marked effect on survival. Patients classified as N₀ have a 30 percent five-year survival rate; for those designated as N₁ and N₂, 12 percent and three percent, respectively. At present, the only accurate clinical method of determining mediastinal lymph node metastases is mediastinoscopy; there is no means of determining contralateral hilar lymph node metastases other than exploratory mediastinotomy or thoracotomy. Recently gallium scanning has been shown to be a noninvasive way of determining the presence of mediastinal or contralateral hilar lymph node metastasis and serves to increase the yield of positive biopsies on mediastinoscopy by directing attention to areas of gallium uptake. The principle is that if the primary chest tumor is gallium positive and the mediastinum and/or hilar area are positive there is a 90 percent probability that the mediastinal or contralateral hilar lymph nodes contain tumor. If the primary tumor is gallium positive and the mediastinum and/or contralateral hilar areas are negative, there is a 67 percent probability that the mediastinal or contralateral hilar lymph nodes do not contain tumor. In the 33 percent with negative gallium scan of the mediastinum and mediastinal node...
metastasis on mediastinoscopy, the metastases are usually adjacent to the primary tumor or microscopic in size and below the resolution of the scanning equipment. Figs. 12a and b show a chest radiograph and gallium scan of a patient with a T2 primary lung carcinoma that takes up gallium. The mediastinum is free of localized gallium uptake, suggesting the absence of disease in the mediastinal lymph nodes; this was subsequently proven to be so at thoracotomy. Fig. 13 shows a chest film and gallium scan obtained in a patient with a lesion in the right middle lobe. The scan shows gallium uptake in a middle lobe tumor.
with distinct areas of gallium uptake in the mediastinal and cervical area, representing lymph node metastasis. When the mediastinal area is evaluated with gallium scanning, it is helpful, as in this patient, if the primary tumor is peripheral in location. This is because it is difficult to separate uptake of the primary tumor from mediastinal uptake when the tumor mass overlies the mediastinum.

Fig. 14a is a chest x-ray of a patient with a primary carcinoma of the lung in the right lower lobe. There is no finding on the x-ray to indicate mediastinal or contralateral hilar lymph node involvement. Fig. 14b shows the gallium scan of the thorax in the same patient, with uptake in the lesion and contralateral hilum. Gallium scan in this patient indicated the need for mediastinoscopy via a left parasternal incision to biopsy the left hilar nodes.
Distant Metastasis (M)

The classification of the presence of distant metastasis from the primary tumor is signified by the letter M with the subscripts of 0 and 1. M_0 represents no distant metastasis, while M_1 indicates distant metastasis in such organs as the contralateral lung, brain, liver, bones, kidney, adrenal, and so on. The presence of metastatic disease has a profound effect on survival, regardless of the size of the primary tumor or extent of lymphatic spread. Patients with the classification of M_0 have a five percent five year survival vs. one percent for patients classified as M_1.

One of the problems in accurate staging of lung cancer patients is that many distant metastases are clinically occult. Matthews et al reported in 1973 on 202 patients with carcinoma of the lung in whom a pulmonary resection was performed for cure and who succumbed within one month of the operation. Twenty-four percent of these patients had undetected distant metastatic disease, making resection of the primary tumor alone a futile attempt for cure. It is critically important that some means be developed to detect occult metastases. We believe that total body gallium scanning is of some help in this regard. If the primary tumor is positive on gallium scan there is a 90 percent probability that any extrathoracic site of gallium uptake represents a metastatic lesion and should be biopsied. When gallium is used as a screening test for the presence of extrathoracic disease, 30 percent of the metastatic lesions detected will be clinically occult.

Fig. 15a is a chest film of a patient with a resectable T_1 tumor. Fig. 15b shows a gallium scan of the head with an area of gallium uptake in the skull. A biopsy of this area showed a distant, occult metastatic squamous cell carcinoma.

Fig. 16a is a chest x-ray of a patient with a T_3 right lower lobe tumor. Fig. 16b is a total body tomographic gallium scan that shows, in addition to uptake of gallium in the chest, an abnormal uptake of gallium behind and below the left diaphragm. A biopsy of this area (Fig. 16c) showed metastatic squamous cell carcinoma to the kidney.

Fig. 17a is a chest x-ray of a patient with a left upper lobe T_2 tumor. Fig. 17b is a gallium scan showing uptake of gallium in the tumor and an area of localized uptake in the brain. A CAT scan of...
TABLE 2
UNIVERSITY OF CHICAGO
CHEST ONCOLOGY SEQUENTIAL STAGING PROGRAM

Symptoms And Chest
X-Ray Suggestive
of Lung Cancer

No Symptoms
Of Metastatic
Disease

Gallium-67
Scan

Uptake by
Chest Lesion
(Positive Scan)

No Uptake by
Chest Lesion
(Negative Scan)

Evaluate for
Other Primary
(Pancreas)

No Other
Primary
Found

Other Primary
Found

Rx as Primary
Lung Cancer
or Benign Disease

Rx as Indicated

Evaluation of Primary
Tumor Histology and
Mediastinal Node Metastasis

Uptake in
Mediastinum or
Contralateral Hilum

Mediastinoscopy
Only if Histology of
Primary Tumor Unknown

Mediastinal
Node Metastasis

Stage III M₁

Mediastinoscopy

No Mediastinal
Metastasis

Stage I or II
or Benign Disease

No Uptake
Outside
Thorax

Stage III M₂

Specific
X-Ray, Scan
or Biopsy of
Site to
Confirm
Metastatic
Lesion &
Tumor Histology

Mediastinum
or
Contralateral Hilum

Uptake
Outside
Thorax

Specific
X-Ray, Scan
or Biopsy of
Site to
Confirm
Metastatic
Lesion &
Tumor Histology

Other
Primary
Found

Stage III M₁
### TABLE 3
**FINAL STAGE IN 115 PATIENTS DIVIDED BY HISTOLOGY**
(University of Chicago, 1976-77)

| Histology                  | No. of pts. | I | II | III M₀ | III M₁ |
|----------------------------|-------------|---|----|--------|--------|
| Squamous cell carcinoma    | 49          | 4 | 2  | 19     | 24     |
| Adenocarcinoma             | 37          | 4 | 4  | 13     | 16     |
| Large Cell Carcinoma       | 8           | 2 | 0  | 4      | 2      |
| Small Cell Carcinoma       | 21          | 1 | 0  | 9      | 11     |

### TABLE 4
**C.A.M.P. REGIMEN FOR NON-OAT CELL CARCINOMA OF THE LUNG**
(University of Chicago)

| Drug            | Dosage | Date of Administration and Route |
|-----------------|--------|----------------------------------|
| Cyclophosphamide| 300 mg/m² | 1,8, I.V.                       |
| Adriamycin      | 20 mg/m²  | 1,8, I.V.                       |
| Methotrexate    | 15 mg/m²  | 1,8, I.V.                       |
| Procarbazine    | 100 mg/m² | 1-10, p.o.                      |
this area, done with contrast infusion, showed a metastatic lesion in the cerebellum. This was one of the few asymptomatic brain metastases we have detected, but obviously they do occur.

These examples emphasize how gallium scanning, particularly the tomographic scan, can be helpful in detecting metastatic disease. A gallium scan and careful clinical exam, with emphasis on the detection of bone pain, mild neurological abnormalities and liver nodularity, coupled with careful reading of the chest film for the presence of bone erosion plus contralateral pulmonary metastasis will uncover 70 percent of distant metastases. The remaining 30 percent of metastatic lesions detected by gallium will be clinically occult. In this situation the gallium scan identifies areas to be evaluated by more specific radiographic technique or a surgical biopsy.

**Sequential Staging**

As a result of the usefulness of Gallium 67 scanning in the detection of bronchogenic carcinomas, we have established a sequential staging program at our institution (Table 2). Patients receive a history and physical examination, routine chest x-ray, and routine laboratory blood counts and chemistries. The extent of disease after these evaluations is called the initial stage (IS). Patients then undergo gallium scanning to assess the extent of disease both in the chest and extra-thoracically. The extent of disease after the gallium scan and any other tests ordered to confirm or refute the findings on gallium scan is called the clinical stage (CS). Subsequently, if necessary, biopsies may be performed to establish the validity of the scans, or thoracotomy if no distant disease is present. The extent of disease after the operative procedures is called the final stage (FS), which is equivalent to the postsurgical treatment stage.

In a recently completed study from our chest oncology program Mintz, et al. reviewed the sequential staging on 115 consecutive, previously untreated patients seen during an 18 month period in 1976 and 1977. After IS, only 18 percent were III M1, but after CS, 29 additional patients were moved to III M1 for a total of 43 percent. After final staging, three of 10 CS I patients were upgraded (one to FS II and two to FS III M0), seven of 11 CS II patients were changed (four were downgraded to FS I and three upgraded to FS III M0). Only four of 44 CS III M0 patients were changed (one was downgraded to FS II and three upgraded to FS III M1). Thus, only three more patients were advanced to metastatic disease after FS. Clinical staging seems to be very important in assessing the extent of lung cancer.

**Therapy**

Patients can be classified by histology and final stage (Table 3). Knowledge of the histology of a bronchogenic carcinoma and the extent of the disease in a given patient can help us to formulate a treatment plan for each patient. Treatments that have been found to be effective include surgery, radiotherapy, combination chemotherapy, and immunotherapy.

It can be seen from Table 3 that most patients with small cell carcinoma have FS III M0 or III M1 disease; only a rare patient has true stage I disease. In contrast, 16 of 94 patients with non-small cell carcinoma have localized (FS I or II) disease. We will address the approach to non-small cell carcinoma first.

Patients who have FS I disease can receive maximum benefit by surgery, which includes either segmental resection, lobectomy or pneumonectomy, depending on the extent of the primary tumor. Recently, McKneally et al have shown additional benefit in patients with FS I disease using intrapleural BCG administration. Both the relapse-free interval and the survival were significantly improved in the BCG treated group as compared to the control group. At the University of Chicago, we are currently randomizing pathological stage I patients (all have negative hilar nodes) between no further treatment and BCG scarification. Twelve patients are in each group;
the only two relapses have been in the control group. Although the relapses are too few to compare statistically, it is important to note that only two of 24 patients have relapsed. Patients with FS II disease are few (five percent). Because of historical five year survival of less than 35 percent, this group might benefit from a combined modality therapy. We treat patients with surgical resection, 3000 rads of radiotherapy to the mediastinum, and at least 12 cycles of combination chemotherapy with cyclophosphamide, adriamycin, methotrexate, and procarbazine (CAMP) (Table 4). Patients with this stage of disease would benefit from participation in a nationwide study to assess the merits of this additional therapy by means of a randomized prospective trial.

Patients with FS III M₀ disease have been treated with radiotherapy of 6000 rads alone. Recently Chan et al used 4000 rads plus bleomycin versus 4000 rads alone in a randomized prospective trial.¹³ Tumor response was greater in the combined-modality group (46 percent) than in radiation-only controls (26 percent); median survival was 13 and six months, respectively. Our program has used 3000 rads followed by CAMP, and we recently reported 39 patients treated in this fashion.¹⁴ The median survival for all patients treated was 9.6 months compared to 6.4 months for historical controls. Patients who responded to the treatment program had a significantly longer survival (median 15.2 months) compared to non-responders and historical controls.

Certain patients with FS III M₀ disease can be considered resectable. Patients undergoing resection for a superior sulcus tumor (Pancoast tumor) have been shown to have, approximately, a 30 percent five year survival. Some patients with large primary lesions that invade the chest wall or come within 2.0 cm of the carina bronchoscopically and without mediastinal lymph node metastases (T₃M₀ or T₃N₁), or patients with a T₁ or T₂ tumor and ipsilateral intranodal mediastinal lymph node metastases, can undergo resection. Because of the low five year survival rate for these patients in the past, we are currently advising preoperative radiotherapy of 3000 rads and at least 12 cycles of CAMP chemotherapy after surgical resection. We need a randomized prospective trial to test this combined modality therapy versus surgery alone.

Patients with FS III M₁ disease have been treated with a variety of combination chemotherapy programs. Besides CAMP, which we have recently shown as giving a 35 percent response rate and stabilizing the disease in another 20 percent,¹⁵,¹⁶ another similar combination called MACC, which substitutes CNU for procarbazine, has elicited a similar response.¹⁷ Responders live longer than non-responders and historical controls. Both of these protocols can be administered on an outpatient basis and require few periods of hospitalization. Other regimens that include four and five drugs have a similar response rate, but the median survival of responders is little improved and the toxicity is such that many patients require hospitalization during therapy.

Patients with small cell carcinoma of the lung require intensive combined-modality therapy. The majority of patients have metastatic disease on presentation. Treatment with drug programs that include both cyclophosphamide and adriamycin is advisable. The use of prophylactic radiation therapy to the brain can decrease subsequent CNS relapses, but does not affect overall survival.¹⁸ Most patients respond to therapy with objective tumor shrinkage, but relapses usually occur within one year. We have recently reported a response rate of 90 percent with a regimen including cyclophosphamide, adriamycin, medium dose methotrexate, and leucovorin rescue.¹⁹ Improved long-term survival awaits the development of effective combinations of chemotherapy that can be used sequentially over extended periods of time. Therapy for patients with FS III M₀ disease has consisted of both local radiotherapy and combination chemotherapy. It is not unusual for patients with this
stage of disease to live two years after the
start of therapy. Because 50 percent of
these patients relapse at the primary site,
some major centers for the study of lung
cancer are reevaluating the role of sur-
urgery in patients with FS III M_0 disease.

Both histology and stage of disease
are important in assessing prognosis in
lung cancer, as well as in determining a
therapy plan. If both are carefully as-
sessed, it will become obvious that there
are various subsets of patients who can
benefit maximally from current therapies,
and that there are other subsets who re-
quire the development of new drugs as
well as new treatment strategies.

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