A Prognostic Model of Recurrence and Death in Stage I Non-Small Cell Lung Cancer Utilizing Presentation, Histopathology, and Oncoprotein Expression

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ABSTRACT

In order to construct a multivariate model for predicting early recurrence and cancer death for patients with stage I non-small cell lung cancer, 271 consecutive patients (mean age, 63 ± 8 years) who were diagnosed, treated, and followed at one institution were studied. All patients were clinical stage I with head and chest/abdominal computed tomograms and radionuclide bone scans without evidence of metastatic disease. Pathological material after resection was reviewed to verify histological staging. Follow-up documented the time and location of any recurrence, was a median 56 months in duration, and was complete in all cases.

Data recorded included age, sex, smoking history, presenting symptoms, pathological description, and oncoprotein staining for erbB-2 (HER-2/neu), p53, and Ki-67 proliferation protein. Immunohistochemistry of oncoprotein expression was performed on two separate archived paraffin tumor blocks for each patient, with normal lung as control. All analyses were blinded and included Kaplan-Meier survival estimates with Cox proportional hazards regression modeling.

Data, including immunohistochemistry, were complete for all 271 patients. Actual 5-year survival was 63% and actuarial 10-year survival was 58%. Significant univariate predictors (P < 0.05) of early recurrence and cancer-death were: male sex; the presence of symptoms; chest pain; type of cough; hemoptysis; tumor size > 3 cm diameter (T2); poor differentiation; vascular invasion; erbB-2 expression; p53 expression; and a higher Ki-67 proliferation index (>5%). An additive oncogene expression curve demonstrated a 5-year survival of 72% for 136 patients without p53 or erbB-2, 58% for 108 patients who expressed either oncogene, and 38% for 27 who expressed both (P < 0.001). Multivariate independent predictors of early recurrence and cancer death (P < 0.05) were symptomatic presentation, erbB-2 expression, T2 size, vascular invasion, p53 expression, and poor differentiation.

These data allowed the creation of a multivariate model which quantified the risk of recurrence and cancer death for patients with stage I non-small cell lung cancer. This model, based on complete data from 271 patients, represents the largest analysis of its type in the literature and can form the basis for multi-institutional randomized adjuvant trials for "high risk" patients.

INTRODUCTION

Although bronchogenic carcinoma is the leading cause of cancer deaths in women and men in the United States with an estimated 180,000 cases in 1994, few advances in treatment have occurred in the last 2 decades. Additionally, prospective screening trials of high risk populations in the 1970s and 1980s were unable to define a decrease in lung cancer mortality for sputum cytology and chest radiography in the early diagnosis of lung cancer. These data also confirmed that most patients (>60%) present to their physician in the late phases of their disease (1). In order to impact on survival, either earlier diagnosis or improved treatment protocols must be found.

Recent advances in molecular biology and genetics have created new diagnostic and treatment possibilities for clinical oncology. If one could define the genetically "more aggressive" primary bronchogenic carcinomas early in the disease state, adjuvant therapy could be instituted before systemic spread was overwhelming, thereby curing more patients. To put this in perspective, 25–30% of patients with NSCLC3 have pathological stage I disease after operation (35,000–45,000 patients annually). Previous studies have reported a relapse rate in stage I NSCLC of 35–50% by 5 years (2–4); thus, even a modest response to early adjuvant therapy could save many thousands of lives.

PURPOSE

The aim of this project was to define pathological and molecular biological markers for early recurrence and death in localized NSCLC from a cohort of patients with pathological stage I disease. Stage I patients were chosen to eliminate the confounding survival influence of distant metastases or positive mediastinal or hilar lymph nodes. These data make up the largest series of its type and utilize a standard method of diagnosis and treatment. Such data can be used to create a multivariate model predicting the risk of recurrence and cancer death as a function of the presenting clinical data, pathological descriptions, and oncoprotein staining.

MATERIALS AND METHODS

Population. From January 1, 1980 until December 31, 1988, 1928 consecutive patients with documented NSCLC were seen at the Comprehensive Cancer Center of the Duke University Medical Center. Of these, 308 patients had T1N0M0 disease, which was reviewed by a pathologist to ensure pathological stage I NSCLC (all hilar and mediastinal nodes were proven uninvolved with cancer). For inclusion, the cell type had to be adenocarcinoma (either papillary or acinar), alveolar cell carcinoma, large cell undifferentiated carcinoma, or squamous cell carcinoma. Nineteen patients were excluded from analysis because of unclear or mixed histology (e.g., adenosquamous), and 18 additional patients were excluded for the lack of adequate paraffin-embedded tumor blocks. Therefore, the population of this study consisted of the remaining 271 patients (mean age, 63 ± 8 years; range, 34–82 years) with complete follow-up data through December 31, 1993. All patients were clinically diagnosed, resected, and followed for at least 60 months at the Duke University Medical Center. All of the patients were preoperative clinical stage I, having no evidence of metastases on head and chest/abdominal computed tomograms and radionuclide bone scans. No mediastinal adenopathy was visualized greater than 1 cm on computed tomography. If enlarged nodes were present, operative sampling was performed at resection, verifying stage I. The Karnofsky performance status was 90% or greater in all patients. Tumor size was classified as T1 for tumors ≤ 3 cm diameter and T2 for tumors > 3 cm diameter. Using standard pathological criteria, differentiation was graded as well, moderate, poor, or undifferentiated (5), and the primary lesion was carefully examined for the presence of vascular invasion of pulmonary arteries or veins.

The abbreviation used is: NSCLC, non-small cell lung cancer.
Complete follow-up was obtained, including the time and location of any recurrent disease. Patient demographics are demonstrated in Table 1.

Before beginning the study, statistical estimation of the size of a patient population needed for an adequate multivariate evaluation of stage I NSCLC was obtained. Preliminary sample size estimates indicated that if the proportion of patients who failed (recurrence or cancer death in stage I NSCLC) were approximately 40%, a minimum of 250 patients would be needed to observe a sufficient number of failures to satisfy the statistical power considerations. Specifically, assuming a dichotomous covariate where the number of failures were in a 4:1 ratio, a total of 100 failures would be needed to detect a doubling of the hazards ratio associated with the covariable with 85% power. When the number of failures for a dichotomous covariable was in a 1:1 ratio and a total of 100 failures observed, a doubling of the hazards ratio was detectable with 93% power. There were 105 failures in our population of 271 patients; therefore, the multivariate predictive power of the results would be greater than 93% (6–7).

**Immunohistochemistry.** Two paraffin blocks of tumor were obtained for each case and were given a code which would be used throughout the study. Immunohistochemical analyses were performed on paraffin blocks of resected lung tissue obtained via an approved Human Subjects Review Committee protocol. Three different types of oncoproteins were chosen for this analysis: erbB-2 (HER-2/neu), a dominant oncogene; p53, a tumor suppressor gene; and KI-67 (8–10), a marker of active nuclear proliferation. The techniques utilized have been proven to be accurate and reproducible by the authors in an experience with breast cancer (8–15). The methodology is simple, inexpensive, and could be performed at most hospitals, making it useful for future broad application.

**Tissue Preparation.** The staining procedure has been described in detail (8–15), and briefly as follows: (a) paraffin microtome sectioning (4–6 μm) and slide labeling; (b) deparaffinization with xylene and ethanol; (c) antigen retrieval with 5 min of microwave and PBS wash; (d) incubation with the primary mAb or control antibody [p53: mouse mAb (Pab 1801; Oncogene Science, Mineola, NY), erbB-2: rabbit polyclonal Ab to p185pp (PAB2; Triton Biosciences, Alameda, CA), or KI-67: mouse mAb to M, 67,000 nuclear proliferation antigen (Dakopatts, Glostrup, Denmark)]; (e) incubation with secondary antibody (either goat anti-mouse IgG or goat anti-rabbit IgG); (f) developing with Elite Universal kit (Vector Labs, Burlingame, CA) and diaminobenzidine-H2O2; and (g) counterstaining with methyl green.

**Slide Evaluation.** We have developed and validated these immunohistochemical methods in breast and ovarian cancer. In each case, blocks of normal lung served as negative controls. Slides were read immediately by two independent observers and classified as either positive or negative for erbB-2 or p53. Both blocks had to be graded positive (widespread staining with an vascular invasion. Immunohistochemical variables included presence of immunostaining for erbB-2, p53 and KI-67 proliferative index score (16). The log-rank test was used to compare these subgroups with respect to cancer-specific survival (17). With the use of Cox’s proportional hazards model and spline transformations of the covariables, the linear and nonlinear effects of age and KI-67 were examined individually (18–19).

The joint effect of covariables, which were significant at the 0.25 level in univariate analysis, were examined using the stepwise Cox regression. The 0.10 level of significance was the significance level used for entering or removing a covariable from this model.

Overall cancer-specific survival was defined as from the date of operation to the date of cancer death. An observation was censored at the last follow-up if the patient was alive or the patient had died from a cause other than NSCLC. Cancer-free survival or the risk of recurrence was defined from the date of operation to the date of recurrence or last follow-up.

**RESULTS**

The population included 97 women (36%) and a range of smoking histories such that 218 (80%) had smoked more than 20 pack-years. Most patients had no symptoms attributable to the cancer [n = 179, 56% (Table 1)].

The majority of the patients underwent a lobectomy with hilar and mediastinal lymph node sampling [n = 181, 67% (Table 1)]. All patients who underwent a stapled wedge resection had a thorough search for enlarged hilar or mediastinal lymph nodes and at least a 2-cm margin of normal lung tissue around the tumor proven by frozen section. There were no inoperative deaths; however, 1 patient died of a myocardial infarction 3 days after operation, 1 patient died of a

<p>| Table 1 Factors for decreased overall cancer-specific survival (% (5-year and 10-year) |
|---------------------|---------------------|---------------------|---------------------|</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Subset</th>
<th>Actual P value</th>
<th>Actuarial P value</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
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</tr>
<tr>
<td></td>
<td>Male</td>
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<td>Age (years)</td>
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<td></td>
<td>40-69</td>
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<td>0.38</td>
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<tr>
<td></td>
<td>&gt;69</td>
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<td>0.38</td>
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<tr>
<td>Smoking history (pack-years)</td>
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<tr>
<td></td>
<td>&lt;50</td>
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<tr>
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<td></td>
<td>Large cell</td>
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<td>Tumor Size (cm)</td>
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<td>Vascular Invasion</td>
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<tr>
<td></td>
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<tr>
<td>p53</td>
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<td></td>
<td>Present</td>
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<td>KI-67 Index</td>
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</tr>
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<td></td>
<td>6–10%</td>
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<td></td>
<td>&gt;10%</td>
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pulmonary embolus 7 days after operation, and 1 patient died at home on postoperative day 21 for an overall 30-day mortality of 3 of 271 (1%).

Median follow-up was 56 months (range, 0.2-161 months). At last follow-up, 124 patients were alive and free of cancer, 42 patients died of other causes without evidence of cancer, 5 patients were alive with recurrent cancer, and 100 patients had died of cancer. The median time to recurrence was 13 months; the recurrence rate was 105 of 271 (38%), and the location of recurrence was initially located at a distant site in 52 (19%) or within the ipsilateral hemi-thorax in 53 (19%). With 5-year follow-up on all patients, actual 5-year survival was 63%, while actuarial 10-year survival was 58% (Fig. 1). Table 1 demonstrates the univariate predictors of decreased overall cancer-specific survival. All factors which were significant predictors of decreased overall cancer-specific survival were also predictors of early recurrence. Therefore, significantly increased risk of early recurrence and significantly decreased overall survival ($P < 0.05$) were noted for male sex, the presence of symptoms (Fig. 2A), type of cough, hemoptysis, and chest pain. Significant pathological variables included tumor size $>3$ cm (Fig. 2B), the presence of vascular invasion, and poor differentiation (Fig. 2C). For demonstration in Fig. 2C, patients with undifferentiated large cell histological type of NSCLC ($n = 39$) were removed so the remaining non-large cell patients could be stratified as well, moderate, or poor. However, for both univariate and multivariate analyses, all levels of differentiation were included.

**Immunohistochemistry.** Immunohistochemical staining for p53, erbB-2, and KI-67 was complete for all 271 patients. All pathological types of NSCLC had expression of erbB-2 and p53, for an overall incidence of 21 and 38%, respectively (Table 2). A significant increase in the rate of recurrence and a decrease in overall survival was observed in the 58 patients who were erbB-2 positive ($P < 0.001$ (Fig. 3A)). Similarly, early recurrence and cancer death were significantly associated with p53-positive tumors ($n = 104; P < 0.02$ (Fig. 3B)). If a survival curve was created with respect to the number of expressed oncogenes by the patients, the survival was worse for patients who expressed both erbB-2 and p53 compared to expression of only one oncogene. Additionally, the 136 patients who did not express either erbB-2 or p53 had an actual 5-year survival of 72% (Fig. 3C). Analysis of the measured proliferation index (median, 5.3%; range, 0.1-71% nuclear staining) demonstrated a continuous effect of the variable which predicted recurrence and subsequent death at all levels of KI-67 staining [i.e., the higher the proliferation index, the more likely recurrence and death occurred; $P < 0.02$ (Fig. 4)].

Correlation between variables was assessed. No association was observed for any variable with respect to age or date of enrollment. A significant association ($P < 0.02$) was observed between KI-67 proliferation index and p53 status. Also, an association was found between KI-67 and differentiation ($P < 0.05$). No significant association was noted for erbB-2 and p53 expression. All recorded variables with univariate significance ($P < 0.25$) were placed into a Cox proportional hazards regression model in order to define independent risk factors for early recurrence and overall survival. Many of the univariate predictors of early recurrence and cancer death were eliminated with the multivariate model (Table 3). Variables which maintained independent predictive value for overall survival were (from most to least significant): symptoms at presentation; erbB-2 status; tumor size $>3$ cm ($T_2$); vascular invasion; and p53 status. Poor differentiation was marginally significant. Variables which maintained independent
significance for early recurrence included (from most to least significant): symptoms at presentation; erbB-2 status; vascular invasion; tumor size >3 cm (T2); poor differentiation; and p53 status. Given that a significant association between p53 and KI-67 was observed, the stepwise model was refit with KI-67 replacing p53 status. The fit of the model with p53 was better than that with KI-67.

DISCUSSION

The purpose of this study was to create a model which would predict recurrence and death in a large population of patients with stage I NSCLC. The current model of 271 consecutive patients can be used to stratify high risk future populations for adjuvant therapy. Our population numbers have a predicted statistical power greater than 93% in a multivariate analysis for recurrence and cancer death.

Previously published retrospective series of all stages of NSCLC have documented a decrease in overall cancer-specific survival for several presenting symptoms, each of which suggests systemic spread of the tumor, such as weight loss, neurological symptoms, generalized weakness, and bone pain. The performance status in this population of localized stage I NSCLC was good, with no symptoms present which limited daily activities. None of the patients in our cohort had systemic symptoms and only 34% had any symptoms which could be attributed to their lung cancer. Therefore, survival analysis by the performance status was limited. Uniquely, these data documented increased risk of recurrence and cancer death for the presence of any symptom, including the presence of chest pain, hemoptysis, and type of cough. There was a spectrum of cancer risk for the type of cough at presentation such that no cough was better than a nonproductive cough, which was better than a productive cough (Fig. 2C). Due to the covariance of these symptom variables, specific symptoms were not significant independent predictors in the multivariate model.

There are several retrospective series in the literature which detail the results of resection for limited stage NSCLC; however, many are older series which did not have modern radiographic staging available (head and chest/abdominal computed tomography, radionuclide bone scan) to rule out distant disease at patient presentation. This may explain the improved overall survival of this series (63% at 5 years) compared to those published in the literature (20–27). Additionally, there are few series available which used multivariate analysis of presenting symptoms and complete pathological descriptions to stratify stage I patients into high and low risk groups. There are three large series in the literature which enrolled patients after 1970 and were analyzed with both univariate and multivariate techniques. Pairolero et al. (4) observed an overall survival of 65% at 5 years for 328 stage I NSCLC patients. The only independent predictor of decreased survival was tumor size (T2 or T3) (4). Ichinose et al. (27) observed a significant decrease in survival for poor differentiation and aneuploidy using multivariate analysis on 151 patients, and Macchiarini et
al. (28) observed that the presence of vascular invasion and mitotic count (≥13/high powered field) were independent negative indicators of survival in 95 T1 stage I NSCLC patients. Our study is the first to combine patient history and symptoms, pathological description, and oncoprotein staining to form a model of recurrence and cancer death.

The analysis of the study population revealed a number of factors which significantly decreased survival. Preoperative variables which had no impact on survival were the amount of smoking, age, environmental exposure, or family history. After resection, evaluation of pathological variables revealed no association for survival and histological types of NSCLC. When the cell types were combined into squamous and non-squamous histology, no difference in survival was noted. Pathological variables which had significant univariate and multivariate impact on early recurrence and cancer death were tumor size >3 cm (T2) and vascular invasion. The impact of tumor size on survival in stage I NSCLC is the most consistent finding in the literature (2–4, 20, 23, 24). In our population of patients, poor differentiation was a significant univariate predictor of early recurrence and cancer death. However, poor differentiation was only marginally significant as an independent predictor of early recurrence and cancer death in the multivariate model. Our finding are similar to those published in the literature in studies using multivariate analysis (27, 28).

Evaluation of survival analyses demonstrates that the results of the current study are similar to those in previously published retrospective series. Therefore, this large cohort of 271 appears to be a good cross-section of patients with stage I NSCLC and would be a good group to analyze for the usefulness of newer molecular biological markers.

At the present time, DNA analysis of genetic aberrations (oncogenes) can be expensive, time consuming, and difficult to accomplish on a small amount of tissue. However, identifying the protein products of these abnormal genes can be done more easily using immunohistochemistry. For use in this study of stage I NSCLC, three different protein products were examined by immunohistochemistry. These three were chosen from a list of oncogene products which have been shown in small, retrospective series to impact on survival. Included was an example of a proto-oncogene (erbB-2), a tumor suppressor gene (p53), and a protein which is expressed in active cellular proliferation (Ki-67).

This study was designed to prove the feasibility of immunohistochemical techniques for survival analyses on a large population of patients. It was performed in a timely manner (12 months), with complete clinical data on all patients. Because the paraffin blocks have been archived, this data set can be used to test other oncogene products which might impact on survival in NSCLC. Tumor angiogenesis or microvessularity measured with factor VIII expression (28–29), K-ras expression in adenocarcinoma (30), tumor expression of the blood group A antigen (31, 32), H/Le/Lex cell surface antigen expression (33), BCL-2 expression (34), and rb gene expression (35) will be examined in the future. Addition of these new factors should increase the predictive value of the overall results.

The overexpression of the erbB-2 (HER-2/neu) gene, which has significant sequence homology with the gene for the epidermal growth factor receptor (erbB-1), was shown by Kerns et al. (36) to be a negative prognostic indicator for 10 of 29 patients with advanced adenocarcinoma of the lung (P < 0.04). In previous studies, we have demonstrated close correlation between detection of high level immunohistochemical reactivity in paraffin sections of breast tumors and the presence of erbB-2 gene amplification (14). In this population of 271 patients with stage I NSCLC, erbB-2 expression was observed in all histological types of NSCLC. This is in contrast to the smaller population studied by Kerns et al. where there were no erbB-2-positive patients with large cell undifferentiated NSCLC. Additionally, we found a significantly increased risk of recurrence and subsequent cancer death for the 58 patients (21%) who expressed erbB-2. Even more important, expression of this dominant oncogene was an independent risk factor for both recurrence and cancer death in the Cox multivariate model. In fact, the erbB-2 status was the second most significant independent predictor of early recurrence and cancer death.

Tumor suppressor genes require that both alleles or their normal products be eliminated in some way to initiate transformation. Detectable expression of p53 correlates with point mutations in this tumor suppressor gene because the mutant p53 protein is more stable and resists usual degradation pathways. Nonmutant (wild-type) p53 protein is rapidly degraded and does not reach detectable concentrations. Mutant p53 is associated with many solid tumors and the Li-Fraumeni syndrome, and has been evaluated in several published series which included all stages of lung cancer (37–40). McLaren et al. (37) were unable to define a role for p53 overexpression by immunoperoxidase staining in a small series of patients, while Quilan et al. (38) demonstrated a significant relationship between survival and positive tumor staining for p53 in 49 patients compared to the remaining 65 p53-negative patients. Ebina et al. (39) observed p53 expression in 35% of 71 patients with stages I–II NSCLC, and there was a decreased survival for these patients compared to the rest of the population (P < 0.01). Data from our population of 271 patients revealed p53 expression in 104 patients (38%), which was present in all cell types of NSCLC. More important, p53 expression was a univariate risk factor for early recurrence and cancer death. Additionally, the multivariate Cox model found p53 status was a significant independent predictor of recurrence and cancer death.

An additive effect in a “dose-response” manner was created by analyzing survival and the number of oncogenes expressed for our population of tumors (Fig. 3C). An explanation for this additive effect could be that erbB-2 and p53 act independently in tumorogenesis. This hypothesis is supported by the fact that Cox proportional hazards regression analysis defined an independent risk of early recurrence and cancer death for both p53 and erbB-2 and no significant covariation was observed for p53 and erbB-2 in our population. erbB-2 and p53 data on a population of 230 women with localized breast cancer (stages I and II) revealed a similar additive effect curve for oncogene expression and survival (15).

Retrospective radiographic determinations of tumor-doubling times have demonstrated a decrease survival in cases of lung cancer with shorter doubling intervals. One method to define these more aggressive, rapidly dividing tumors utilizes immunohistochemical preparations of a proliferation-associated nuclear antigen which can estimate the tumor growth capacity (Ki-67). This non-histone protein is expressed in the nucleus of cells which are in active division (cell phases late G1, G2, S, and M) and can be an index of the rate of tumor growth. Pence et al. (10) defined a subpopulation of 19 NSCLC patients who had a poor prognosis compared to the remaining 42 when a proliferation index was more than 5% [P < 0.04 (10)]. Data analysis on 271 patients revealed Ki-67 to be a continuous variable for the risk of recurrence and cancer death (Fig. 4). However, Ki-67 was eliminated from significance in multivariate analysis. Because of this, we tested all of the variables for interrelationships with Ki-67. p53 status and differentiation were significantly associated with the Ki-67 proliferation index (P < 0.02). This explains the elimination of the Ki-67 data from the Cox model and also supports a hypothesis that many of the newly defined biological markers may be measuring similar changes (i.e., Ki-67 and p53 for cell cycle arrest or apoptosis) and
need to be evaluated by multivariate techniques using large datasets.

Data obtained in this study have defined independent risk factors for early recurrence and death in localized NSCLC. Using the Cox proportional hazards regression risk ratios (Table 4), one could estimate the risk of recurrence and cancer death for any patient by multiplying the ratios for all factors present. An example of this would be a calculated recurrence risk 8.3 times the overall population of stage I NSCLC for a symptomatic patient with a $T_2\text{er}B^2$-positive adenocarcinoma (2.74 x 1.81 x 1.67). A treatment protocol could be constructed with stratification by an estimated risk of 5 or more compared to the overall population. These patients with high risk for recurrence and death would receive adjuvant therapy. A study proposed for the Cancer and Leukemia Group B (study # 9333) by Strauss et al. (41) incorporates some of these findings in order to stratify patients for adjuvant chemotherapy. Patients with primary tumor size $\leq$3 cm diameter ($T_2$) are considered at low risk for recurrence, having an overall 5-year survival of 70%, and do not warrant adjuvant treatment at this time. These $T_2$ patients will be observed. In the initial phase of the study, all patients with primary tumors $>$3 cm diameter ($T_2$) will undergo randomization to either observation or cisplatin and vinblastin chemotherapy after resection (41). The correlative science study will record all histopathological descriptors and collect tissue for oncoprotein staining, and will allow a prospective multi-institutional validation of the findings in this cohort of 271 patients. Variables which have been proven as independent predictors of poor survival can be added to future randomized clinical trials.

REFERENCES


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