Location as an important predictor of lymph node involvement for pulmonary adenocarcinoma

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Background: Increasing data implicate histologic grade and radiographic appearance along with tumor size as key prognostic indicators for pulmonary adenocarcinoma. The impact of tumor location on prognosis has not been examined.

Methods: The records of 530 consecutive patients with pulmonary adenocarcinoma pathologically staged between June 1979 and July 2002 were reviewed. All patients had a preoperative computed tomographic scan of the chest and underwent surgical staging by mediastinoscopy, lymph node sampling, or lymph node dissection. Patients with bronchioalveolar cell carcinoma were excluded. Peripheral tumors were compared with central tumors with regard to stage and survival. A tumor was considered to be central if visualized within the inner third of the lung field or seen bronchoscopically. Patients with T1 cancers were further analyzed on the basis of tumor size. Survival was determined by the Kaplan-Meier analysis and comparisons were made by the log-rank method.

Results: Central tumors were more advanced and demonstrated a significantly ($P < .0001$) poorer survival than peripheral tumors (median 18 vs 39 months). Sixty percent of patients with central tumors had stage III or stage IV disease compared with 25% of those with peripheral tumors. Central T1 tumors, however, demonstrated a 50% incidence of lymph node involvement. Although the incidence of lymph node metastases increased incrementally with the size of peripheral T1 tumors, it remained 50% for central T1 tumors irrespective of size.

Conclusion: Tumor location for pulmonary adenocarcinoma should be considered when planning therapy. Central tumors have a high incidence of lymph node metastases (regardless of size) and a poorer prognosis.

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Tumor staging is important in determining the optimal pathway for the treatment of operable non–small cell lung cancer (NSCLC). For patients with stage I NSCLC, lobectomy is the gold standard of therapy on the basis of the results of the Lung Cancer Study Group's landmark study, which compared lobectomy and sublobar resection.[1] Lesser resection has been associated with increased local failure and is used in most centers for the high-risk patient.[2] Recently there has been increased interest in limited resection,[2-4] with the realization that certain prognostic factors separate from the TNM staging scheme may better predict favorable lesions that can be appropriately treated with less than lobectomy resection.

The current TNM system does not address issues such as histologic features, small tumor size, and radiographic appearance. All of these factors have been the subject of recent discussion. For instance, tumors that have a predominately ground-glass appearance on computed tomographic scan are more likely to have favorable clinical behavior.[5] Adenocarcinomas and squamous cancers appear to have a different propensity for lymph node metastasis. In one series comparing the behavior

Abbreviations and Acronyms
NSCLC = non–small cell lung cancer

of adenocarcinoma and squamous cancers, the authors concluded that although limited resection was feasible for squamous cancers 2 cm or less, these operations should not be performed in adenocarcinomas over 1 cm because of an increased incidence of lymph node metastasis.[6]

The poor correlation between clinical and pathologic staging in stage I NSCLC that has been demonstrated in several studies makes it difficult to select an appropriate operation, particularly in the compromised patient. Several studies have reported that the propensity for lymph node involvement varies significantly by the lobar location and side of the tumor.[7,8] Other studies have demonstrated the adverse effect of moderate-to-poor differentiation.[9] Central or peripheral location of tumor, which can be determined by computed tomography, however, has not been examined as a possible factor affecting survival independent of stage. In earlier reports, we[10] noted a significantly higher liklihood of false negative staging of mediastinal lymph nodes for central versus peripheral tumors, particularly for adenocarcinoma. We also showed a 2-fold difference (20% vs 45%) in survival after resection and adjuvant chemo-radiotherapy between these patients, although the difference was not significant. Although lung cancers usually present with more advanced disease, important differences in survival may exist between central and peripheral tumors independent of stage that may be helpful in selecting therapy, particularly for compromised patients or patients with clinical stage I disease.

Methods

The records of 530 consecutive patients with pulmonary adenocarcinoma out of 1275 patients with lung cancer pathologically staged between June 1979 and July 2002 were reviewed in our lung cancer database. The T and N status of all patients was updated to conform to the current international system for staging lung cancer. Survival data were available for all patients. All patients had a preoperative computed tomographic scan of the chest and all patients underwent surgical staging by mediastinoscopy, lymph node sampling, or lymph node dissection. The central and peripheral location of each tumor had been recorded prospectively by a single thoracic surgeon (B.D.). Patients with bronchioalveolar cell carcinoma were not included. Eleven patients had a synchronous tumor of other histologic type, either in the same lobe or a different lobe, and were excluded from further analysis. Tumor location could not be verified in 5 additional patients and these were excluded. A total of 514 patients were available for review. A tumor was considered to be central if it was visualized within the inner third of the lung field or seen bronchoscopically. Stage at presentation between peripheral and central tumors was compared by the Fisher exact test. Survival was determined by the Kaplan-Meier analysis for overall and stage-based comparisons using the log-rank method. Survival for patients with stage I tumors was further analyzed according to age, sex, tumor size, and the presence/absence of pleural involvement. Factors demonstrating a significant survival difference at .10 were then compared by a multivariable Cox regression forward analysis. Statistics were performed with SSPS statistical software version 10.1 (SPSS Inc, Chicago, Ill). The nodal status of 291 patients with clinical T1 cancers (tumors 3 cm in size or less) was further analyzed on the basis of size.

TABLE 1. Frequencies of central and peripheral tumors stratified by stage

Stage	Central (n = 111)	Peripheral (n = 403)
I	26 (23%)	243 (60%)*
II	18 (16%)	61 (15%)
III	49 (44%)	72 (18%)
IV	18 (16%)	27 (7%)

*P = .001 for comparison of stage I versus higher stage in central versus peripheral groups (the Fisher exact test).

Results

A total of 403 patients had peripheral tumors and 111 patients had central tumors. Central tumors were more advanced. Sixty percent (67/111) of these patients presented with stage III or stage IV disease and 75% (304/403) of patients with peripheral tumors presented with stage I or stage II disease (Table 1). Fifty patients with central tumors underwent a lobectomy, 20 patients a pneumonectomy, 1 patient a segmentectomy, and 1 patient a wedge resection. Six patients had unresectable tumors at operation and 33 patients did not come to surgery. Conversely, 305 patients with peripheral tumors underwent a lobectomy, only 4 underwent a pneumonectomy, 11 a segmentectomy, and 51 a wedge resection. All except 8 patients undergoing wedge resection had lymph node evaluation. Ten had unresectable tumors at operation and only 4 did not come to surgery. Sixty-six patients with central tumors received radiation. In 23 it was in the neoadjuvant setting and in 35 in the adjuvant setting. Twenty-seven patients with peripheral tumors received neoadjuvant radiation and 87 received adjuvant radiotherapy. Twenty-five patients with central tumors received neoadjuvant chemotherapy and 15 received postoperative adjuvant chemotherapy. A total of 156 patients with peripheral tumors received chemotherapy. In 20 patients it was given in the neoadjuvant setting and in 31 it was given as adjuvant treatment. These factors were not considered in the analysis of survival.

Survival was significantly poorer ($P < .0001$) in patients with central tumors than in those with peripheral tumors (median 18 months vs 39 months, Figure 1). When adjusted for stage, however, only stage I tumors demonstrated a significant survival difference based on location (P =

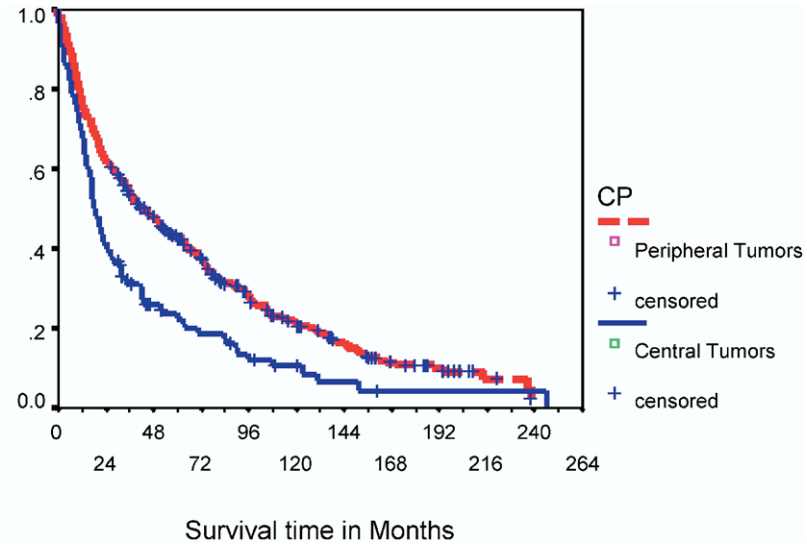

Figure 1. Graph demonstrating Kaplan-Meier survival stratified by adenocarcinoma location for the overall cohort. There is a significant difference between peripheral and central locations ($P < .0001$). *CP*, Central/peripheral.

.0299). Patients with peripheral stage I tumors had a better overall median survival than did those with central tumors (60 months vs 41 months, Figure 2). Univariate analysis demonstrated significance for age, sex, and location. Mutivariable analysis similarly demonstrated significance for age and sex with location approaching significance (Table 2). The nodal status of the subset of patients with clinical T1 tumors is demonstrated in Tables 3 and 4. Fifty percent of patients with central T1 tumors had nodal disease. Peripheral tumors, on the other hand, had a 24% incidence of nodal metastasis (Table 5). Seventeen percent of patients with peripheral tumors 2 cm in size or less had nodal disease.

Discussion

New pulmonary screening programs using computed tomography are identifying increasing numbers of small early-stage lung cancers.[11] These clinical T1 N0 lesions have been targeted as potential candidates for limited resection surgery. The benefits of limited resection surgery include improved residual pulmonary function[12] and decreased operative mortality. Attempts at limited resection surgery in the past as standard therapy, however, have resulted in increased local failure, leaving lobectomy as the current standard for the treatment of lung cancer. The identification of improved prognostic factors in detecting favorable early lesions has sparked renewed interest in limited resection surgery. These new factors outside the standard TNM staging scheme include stratification of size within the T1 classification, histologic features, and radiographic appearance. Tumor location, however, has not been examined as a potential prognostic factor for small T1 N0 lesions.

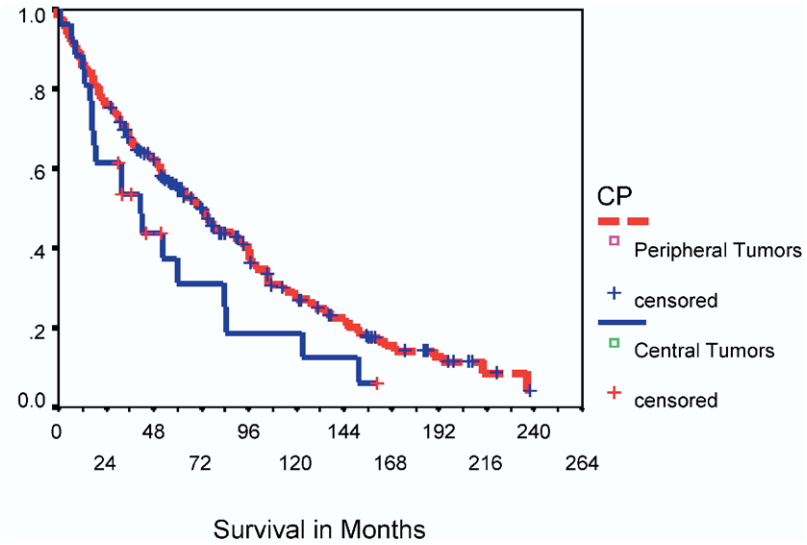

Figure 2. Graph demonstrating Kaplan-Meier survival for stage I adenocarcinomas stratified by central and peripheral locations. There is a significant survival difference between the two locations ($P = .03$). *CP*, Central/peripheral.

TABLE 2. Cox regression multivariable for variables influencing survival in stage I pulmonary adenocarcinoma

	Significance
Age	.013
Sex	.001
Central/peripheral	.070
Visceral pleural involvement	.569

Variables include sex, age, visceral pleural involvement, and location. Statistical significance is achieved by a value less than .05.

Tumor size affects survival.[13,14] Even within the current TNM staging scheme, those lesions classified as T1 may be further stratified to reflect prognosis. The association of increasing size with nodal involvement may in part explain this. Even with adenocarcinomas 1 cm in size or less, Ohta,[15] Wu,[16] and their colleagues reported a small incidence of micrometastasis, and Ichinose with his group[17] demonstrated lymphatic vessel invasion in 25% of patients with tumors 1 cm or less. Occult nodal involvement within tumors less than 1 cm, previously undetected by standard staining schemes, is now being identified increasingly with the use of immunohistochemical evaluation. Although it is now evident that adenocarcinoma of any size may harbor occult nodal disease, increased lymphatic spread and hematogenous metastases are demonstrated at higher incidence for tumors greater than 2 cm. Finally, Wisnivesky, Yankelevitz, and Henschke[18] identified improved curability with decreasing tumor size for T1 N0 lesions. In our series, the incidence of lymph node metastases and tumor stage increased with tumor size for peripheral tumors (Table 4). However, the incidence of nodal disease was 50% for central T1 tumors of any size. Both central and peripheral tumors, regardless of size, may harbor occult nodal disease. It is clear from our data that central tumors are rarely, if ever, suitable for sublobar resection and that even with peripheral adenocarcinomas, sublobar resection should only be considered after thorough evaluation of the lobar, hilar, and mediastinal lymph nodes. In our series, 17% of peripheral tumors 2 cm in size or less had nodal metastases at the time of resection.

It would be expected that small early-stage lesions devoid of lymphatic invasion, regardless of location, treated by adequate surgical resection should demonstrate similar survival. In our experience when comparing pathologically staged T1 N0 adenocarcinomas of peripheral and central location, there was a statistically significant difference in survival by univariate analysis. However, in a multivariable analysis this significance was diminished ($P = .07$) and the difference could be explained by either sex or age alone (Table 2). The isolated significance for stage I lesions may possibly reflect a higher incidence of occult nodal involvement for centrally located tumors. Almost 50% of all central tumors 3 cm or less demonstrated nodal involvement, whereas comparatively fewer peripheral lesions were lymph node positive. Peripheral lesions also demonstrated decreasing nodal involvement when stratified by size within the T1 classification. An argument can therefore be made that central tumors should warrant more aggressive therapy. Goldstein and colleagues[19] identified characteristics such as increasing nuclear grade and central fibrosis as markers of increased lymphatic invasion, suggesting the addition of adjuvant therapy when identified within smaller lesions.

Overall, central adenocarcinomas present at a later stage. Location does not appear to play a role in prognosis when comparing stage-adjusted advanced lesions. There is, however, a difference in survival between stage I tumors of central and peripheral location. This difference may be attributed to a higher incidence of lymph node involvement for T1 central tumors. This may also explain the overall tendency of central lesions to be more advanced (stages III and IV) at presentation. This difference should be taken into consideration when defining treatment. Early-stage central tumors should be treated aggressively by lobectomy with consideration for adjuvant therapy.

TABLE 3. N staging of central T1 tumors

Tumor size (cm)	N1	N2	N3
0-1.0	1	1	0
1.1-2.0	0	5	0
2.1-3.0	4	3	0

Represents the N stage for patients with T1 central tumors by size.

TABLE 4. N staging of peripheral T1 tumors

Tumor size (cm)	N1	N2	N3
0-1.0	19	2	2
1.1-2.0	8	15	1
2.1-3.0	15	20	1

Represents the N stage for patients with T1 peripheral tumors by size.

TABLE 5. Percentage of patients with N1 and N2 positive lesions stratified by tumor size

	Tumor location	
Tumor size (cm)	Central	Peripheral
0-1.0	50% (1/2)	16% (4/25)
1.1-2.0	50% (7/14)	18% (24/137)
2.1-3.0	50% (4/8)	34% (36/105)

Represents the number of patients with T1 disease for both peripheral and central tumor location. T1 lesions with N1 or N2 disease are also indicated. Almost half of all central T1 lesions demonstrate advanced disease. The percentage is lower for peripheral tumors and is further stratified by size within the T1 classification.

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