How Well Does the New Lung Cancer Staging System Predict for Local/Regional Recurrence After Surgery?

A Comparison of the TNM 6 and 7 Systems

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Introduction: To evaluate how well the tumor, node, metastasis (TNM) 6 and TNM 7 staging systems predict rates of local/regional recurrence (LRR) after surgery alone for non-small cell lung cancer.

Methods: All patients who underwent surgery for non-small cell lung cancer at Duke between 1995 and 2005 were reviewed. Those undergoing sublobar resections, with positive margins or involvement of the chest wall, or those who received any chemotherapy or radiation therapy (RT) were excluded. Disease recurrence at the surgical margin, or within ipsilateral hilar and/or mediastinal lymph nodes, was considered as a LRR. Stage was assigned based on both TNM 6 and TNM 7. Rates of LRR were estimated using the Kaplan-Meier method. A Cox regression analysis evaluated the hazard ratio of LRR by stage within TNM 6 and TNM 7.

Results: A total of 709 patients were eligible for the analysis. Median follow-up was 32 months. For all patients, the 5-year actuarial risk of LRR was 23%. Conversion from TNM 6 to TNM 7 resulted in 21% stage migration (upstaging in 13%; downstaging in 8%). Five-year rates of LRR for stages IA, IB, IIA, IIB, and IIIA disease using TNM 6 were 16%, 26%, 43%, 35%, and 40%, respectively. Using TNM 7, corresponding rates were 16%, 23%, 37%, 39%, and 30%, respectively. The hazard ratios for LRR were statistically different for IA and IB in both TNM 6 and 7 but were also different for IB and IIA in TNM 7.

Conclusions: LRR risk increases monotonically for stages IA to IIB in the new TNM 7 system. This information might be valuable when designing future studies of postoperative RT.

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Despite decreasing prevalence of cigarette use in the United States, lung cancer remains the leading cause of cancer death.[1] Patients with early-stage disease, who represent a minority of patients with lung cancer, are most commonly treated surgically. Recent studies have shown a survival benefit for adjuvant chemotherapy in patients with resected non-small cell lung cancer (NSCLC), namely those with involved regional lymph nodes and possibly with tumors greater than 4 cm.[2,3] Postoperative radiation therapy (RT) is typically recommended for patients with resected N2 disease, given the relatively high risk of local recurrence, with or without chemotherapy.[4–7]

The International Association for the Study of Lung Cancer recently recommended changes to the staging system for NSCLC.[8–12] T and M classification modifications have been proposed based on an analysis of a large international database compiled specifically to review the lung cancer staging system; no changes were made to the N classification. These changes have been validated, both internally and externally, against the Surveillance, Epidemiology, and End Results database and have shown to be prognostic for overall survival.[12] The International Association for the Study of Lung Cancer published their 7th edition of the tumor, node, metastasis (TNM) classification for lung cancer in 2009,[13] which was developed in collaboration with the American Joint Committee on Cancer and the Union Internationale Contre le Cancer.

Although it has been shown that the latest TNM staging system is predictive for overall survival, it is unclear whether the new system is also predictive for local/regional recurrence (LRR). Given the controversies regarding the use of adjuvant therapies, particularly postoperative RT, for patients with resected NSCLC, predictive tools to better define those at increased risk for LRR would be beneficial. For most malignancies, increasing stage is generally associated with a higher risk of disease recurrence. Data for LRR rates in operable patients with NSCLC are limited. We have previously de-

scribed our patterns of failure in a large patient cohort.[14] The goal of this study is to directly compare the new lung staging system (TNM 7) with the previous edition of the TNM staging classification using a large single-institution cancer center database.

MATERIALS AND METHODS

This institutional review board-approved study included patients who underwent surgery for N0-N2 NSCLC at Duke University between 1995 and 2005. Various subsets of patients were excluded given the purpose of the present analysis. As sublobar resections were associated with a higher risk of local recurrence in the Lung Cancer Study Group randomized trial,[15] 204 patients who underwent a wedge resection or segmentectomy were excluded. Similarly, 23 patients with a positive bronchial, vascular, or parenchymal surgical margin after lobectomy or pneumonectomy were excluded. Patients who received chemotherapy ($n = 64$) or RT ($n = 10$) as part of their initial management were also removed from the analysis as both decrease the risk of local recurrence.[16,17] Finally, patients were excluded if they presented with superior sulcus tumors ($n = 30$) or with chest wall involvement ($n = 48$). Some patients within the cohort were excluded for more than one reason. Therefore, the evaluation was performed with a patient population who underwent optimal surgery without adjuvant therapy.

Medical records and pertinent radiographs were reviewed to obtain patient demographics, review surgical reports and pathology, and to determine patterns of failure after surgery. Each patient was staged using both the TNM 6th edition (TNM 6)[18] and 7th edition (TNM 7).[19]

Patterns of failure were determined by postsurgical imaging studies and data obtained from invasive procedures, such as bronchoscopy, mediastinoscopy, or computed tomography-guided biopsies. LRR was defined as disease recurrence at the surgical margin, ipsilateral hilum, and/or mediastinum. Radiographic hilar and mediastinal lymph node recurrences were defined as enlarging lymphadenopathy measuring $\geq$1 cm on the short axis by computed tomography and/or hypermetabolic lymph nodes on positron emission tomography, which in the patient's subsequent history was consistent with a local recurrence. Thus, a borderline enlarged lymph node, increased thickening at the resection margin, or equivocal findings on positron emission tomography were not scored as a LRR. Disease recurrence in the contralateral hilum, supraclavicular fossae, ipsilateral lung parenchyma, or elsewhere was defined as a distant recurrence. A second primary tumor was scored when a patient presented with a new histology or the same histology but a clinical presentation that was consistent with a new primary tumor. All cases of suspected LRR, distant recurrence, and development of second primary lung malignancies were reviewed by three authors (J.M.P., J.B., and C.R.K.), to reach a consensus opinion and improve accuracy.

Statistical Analysis

The Kaplan-Meier method was used to estimate 5-year LRR probabilities and 95% confidence intervals. Time to LRR was calculated from date of surgery to the date of local treatment failure for all patients. Patients who developed a second primary tumor were censored on the date the second primary tumor was diagnosed. Time to distant metastases was also evaluated and calculated in a similar manner. All statistical tests were two sided, and a p value of less than 0.05 was considered statistically significant. Analysis was performed using SAS 9.1 software (SAS Institute, Cary, NC).

In addition, a Cox regression analysis was performed whereby the hazard ratio of LRR of one stage was compared with the succeeding stage (i.e., IA–IB, IB–IIA, and IIA–IIB). This was done independently for TNM 6 and TNM 7 to further evaluate whether the newer staging system better partitions the risk of LRR after surgery between each stage group. Similar findings were obtained when pairwise comparisons were evaluated using a log-rank (Mantel-Cox) test.

RESULTS

Of 1088 patients who underwent surgery during the time interval, 709 patients were eligible for the present analysis. Median follow-up was 32 months (range: 1–174). A total of 576 patients (81%) were pathologic N0 (pN0), 110 (16%) were pN1, and 23 (3%) were pN2. Patient, surgical, and pathological characteristics are reported in Table 1. Stage distribution for both TNM 6 and TNM 7 is listed in Table 2.

Local disease recurrence was identified in 100 patients. This was confirmed pathologically in 46%. The 5-year actuarial risk of LRR for the entire patient cohort was 23% (95% confidence interval: 19–26%).

Conversion from TNM 6 to TNM 7 resulted in stage migration in 21% of patients (13% upstaging and 8% downstaging) (Figure 1). Most upstaging involved TNM 6 stage IB, where 22% and 8% of cases migrated to TNM 7 stage IIA and stage IIB, respectively. In other words, patients with larger primary tumors ($\geq$5 cm) without regional lymph node involvement migrated to stage II in TNM 7. Most downstaging involved TNM 6 stage IIB, where 77% of cases migrated to TNM 7 stage IIA. Thus, patients with hilar lymph node involvement, but with smaller primary tumors between 3 and 5 cm, were downstaged in TNM 7.

When analyzed by stage, the 5-year actuarial risks of LRR for stages IA, IB, IIA, IIB, and IIIA were 16%, 26%, 43%, 35%, and 40%, respectively, using TNM 6 (Figure 2). According to TNM 7, the 5-year LRR rates were 16%, 23%, 37%, 39%, and 30%, respectively (Figure 3).

With TNM 6, the HR for LRR was statistically different for stage IA compared with IB ($p < 0.001$). Nevertheless, there was no statistical difference between the other stages using a Cox regression analysis. With TNM 7, the HR for LRR was statistically different for IA and IB ($p = 0.009$) as well as IB and IIA ($p = 0.006$). There was no difference between IIA and IIB ($p = 0.792$) or IIB and IIIA ($p = 0.589$).

We also evaluated the risk of developing distant metastases according to TNM 6 and TNM 7. When analyzed by stage, the 5-year actuarial risks of developing distant metastases for stages IA, IB, IIA, IIB, and IIIA were 16%, 36%, 64%, 49%, and 85%, respectively, using TNM 6. According to TNM 7, the corresponding 5-year rates were 16%, 28%, 56%, 53%, and 65%, respectively.

TABLE 1. Patient and Treatment Characteristics ($N = 709$)

Characteristics	No.	Value	Percentage
Age (yr)			
Median		67	
Range		20–92	
Gender			
Male	393		55
Female	316		45
Race			
White	598		84
Black	91		13
Other	20		3
Surgical procedure			
Lobectomy (or bilobectomy)	625		88
Sleeve resection	24		3
Pneumonectomy	60		8
Surgical approach			
Open	474		67
VATS	235		33
Hilar lymph node sampling			
Yes	651		92
No	58		8
Mediastinal lymph node sampling			
Yes	642		91
No	67		9
Size (cm)			
Median		2.9	
Range		0.3–13	
Histology			
Adenocarcinoma	317		45
Squamous cell[a]	264		37
Large cell	34		5
Bronchioloalveolar	22		3
NSCLC NOS	68		10
Histologic differentiation			
Well	55		8
Moderate	317		45
Poor	199		28
NS	138		19
Lymphovascular space invasion			
Yes	143		20
No/NS	566		80
Visceral pleural invasion			
Yes	129		18
No/NS	580		82

[a]Including adenosquamous ($n = 4$).

VATS, video-assisted thoracoscopic surgery; NOS, not otherwise specified; NS, not stated; NSCLC, non-small cell lung cancer.

TABLE 2. Stage Distribution (TNM 6 and TNM 7)

TNM 6	No.	TNM 7	No.
T1 N0	307	T1a N0	181
		T1b N0	126
T2 N0	269	T2a N0	182
		T2b N0	59
T3 N0	N/A	T3 N0	28
T1 N1	33	T1a N1	15
		T1b N1	18
T2 N1	77	T2a N1	59
		T2b N1	12
T3 N1	N/A	T3 N1	6
T1 N2	11	T1a N2	4
		T1b N2	7
T2 N2	12	T2a N2	7
		T2b N2	3
T3 N2	N/A	T3 N2	2

TNM, tumor, node, metastasis; NA, not applicable.

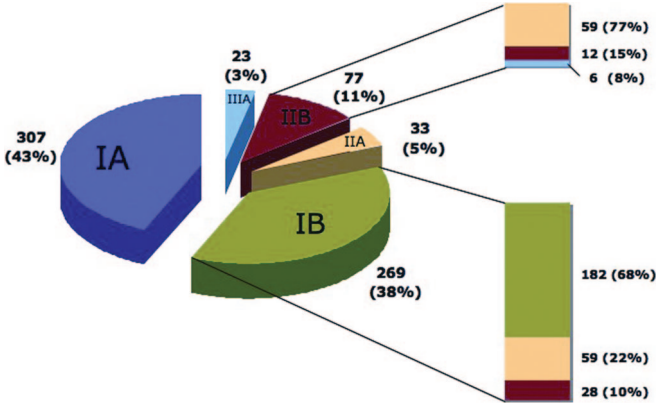

FIGURE 1. Stage migration from TNM 6 to TNM 7 is illustrated. The pie chart indicates distribution by stage within TNM 6. The bars indicate redistribution within TNM 7. Note: all patients with TNM 6 stages IA, IIA, and IIIA remained within the same stage group in TNM 7; all stage migration occurred within TNM 6 stages IB and IIB.

DISCUSSION

For healthy patients with early-stage NSCLC, the preferred treatment is initial surgical resection, with or without adjuvant chemotherapy and/or RT. Recent randomized trials have demonstrated that adjuvant cisplatin-based chemotherapy improves overall survival in stages II to IIIA NSCLC.[17,20,21] The role of adjuvant RT remains controversial. Because of the findings of the postoperative RT (PORT) meta-analysis, which showed a survival detriment in N0 and N1 disease, adjuvant RT is not routinely recommended for patients without lymph node involvement or when disease has spread to hilar lymph nodes.[16] Adjuvant RT is generally recommended for patients with resected IIIA (N2) disease given the high risk of local disease recurrence with surgery alone when mediastinal lymph nodes are involved. Nevertheless, our group and others have demonstrated that the risk of local recurrence is relatively high in subsets of patients with N0 to N1 disease.[14,22] The purpose of this study was to determine whether the revised staging system for lung cancer was a better predictor of local recurrence after surgery for NSCLC.

Our study demonstrates that LRR increases monotonically for stage I and stage II lung cancer using the new American Joint Committee on Cancer staging system (Fig-

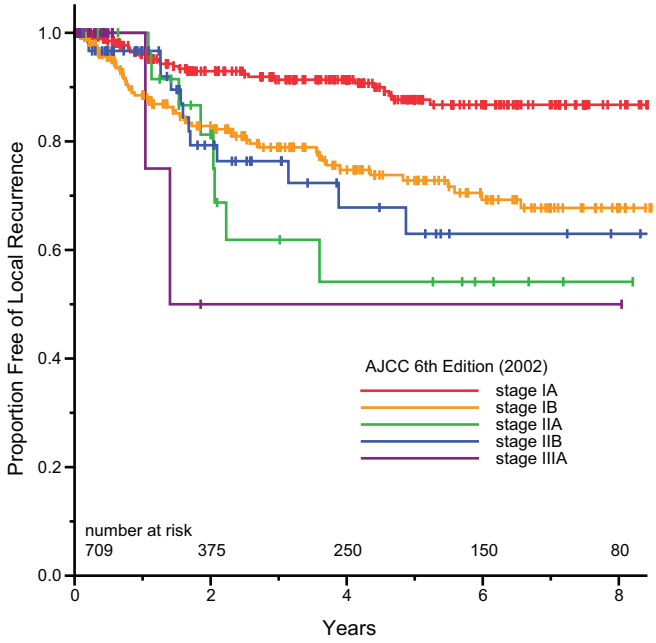

FIGURE 2. Kaplan-Meier curve of time to local/regional recurrence based on stage, TNM 6.

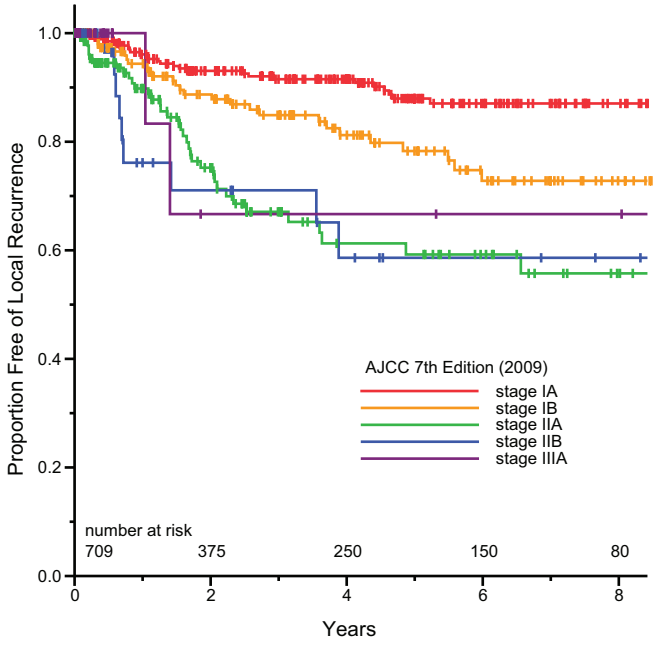

FIGURE 3. Kaplan-Meier curve of time to local/regional recurrence based on stage, TNM 7.

ures 2 and 3). The LRR for stage II disease (based on TNM 7) in our patient cohort approached 40%, which is certainly high enough to warrant further investigation of postoperative RT. There remains a reluctance to use postoperative RT due to findings from the PORT meta-analysis and other retrospective studies.[16,23] Nevertheless, with modern treatment techniques, and smaller, more conformal radiation fields, the potential benefit of modern RT may outweigh the risks when rates of local recurrence are this high. Indeed, two randomized prospective studies published after the PORT meta-analysis suggest that the use of more conformal/limited RT fields may improve outcomes in patients with resected NSCLC.[24,25]

The LRR rates for IIIA disease using TNM 6 and TNM 7 were 40% and 30%, respectively. Nevertheless, we only had a small number of patients with pathologic N2 disease who did not receive any adjuvant therapy. Further, it is not surprising that the overall risk of local recurrence would decrease if more patients with N1 disease are combined with patients with N2 disease. In TNM 7, patients with large (≥7 cm) primary tumors with N1 involvement are now classified as IIIA.

Reported actuarial rates of local failure after surgery for NSCLC vary in the literature. For example, reported local failure rates vary from 6 to 45% in studies examining stage I NSCLC.[15,25–32] These discrepancies are likely multifactorial, including differing definitions of LRR, diligence in which local recurrence is evaluated and scored, and the use of crude rates as opposed to actuarial rates. Additionally, many studies report only first sites of failure. Distant recurrences are easier to assess clinically and radiographically than LRR, and thus, rates of local failures can be underreported. In our study, the overall actuarial LRR rate was 23% in a population of patients who underwent either lobectomy or pneumonectomy and did not receive neoadjuvant or adjuvant therapy.

There are many strengths of this analysis. This is one of the largest studies examining rates of local failure with more than 700 patients examined. This is after excluding many patients with confounding variables: sublobar resections, positive surgical margins, or any RT or chemotherapy. Our definition of local recurrence was tightly defined. Only failures at the surgical stump, ipsilateral hilum, and/or mediastinum were considered as a LRR. Several studies have used broader definitions of LRR, including any failures within the ipsilateral lung. By contrast, our definition only includes sites that are encompassed within a typical postoperative RT field, thus making our data more informative in the design of future studies of adjuvant therapy.

Our analysis has the limitations common to most retrospective studies. First, pathological and clinical data were not collected prospectively, thus increasing the possibility of errors within the database. Second, patients were treated during an 11-year time interval with somewhat variable approaches. Nevertheless, the studied patients were all uniformly treated with surgery alone; patients who received any adjuvant chemotherapy or RT were excluded. Third, not all patients had pathologic confirmation of local disease recurrence. The remaining were confirmed using radiographic studies. Although this may overestimate rates of LRR recurrence, we did our best to verify each case of recurrence by having three physicians review each local failure. Despite this, however, errors may have been made. Finally, some of our subgroups, particularly those with IIIA disease, contained only a modest number of patients. This decreased the power of our analyses.

CONCLUSION

The TNM 7 system seems to be a better predictor for LRR after surgery for NSCLC than TNM 6. This information may prove to be valuable when designing future studies of postoperative RT.

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