The Persistent Problem of Local/Regional Failure After Surgical Intervention for Early-Stage Lung Cancer

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Background. **The goal of the present study was to estimate the rate of local/regional failure (LRF) after definitive surgical intervention for early-stage non-small cell lung cancer (NSCLC), without postoperative radiotherapy, in the era of contemporary imaging and minimally invasive surgical techniques.**

Methods. **Medical records of patients with early-stage NSCLC (pathologic T1-4, N0-1) who underwent lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy, with or without adjuvant chemotherapy, between 2007 and 2015, were retrospectively reviewed. LRF was defined as recurrence at the ipsilateral lung, bronchial stump, mediastinum, chest wall, or supraclavicular region. The Kaplan-Meier method was used to estimate time to LRF, with patients censored at death, and log-rank tests were used for comparisons. A two-sided p value of less than 0.05 was considered significant.**

Results. **Included were 217 patients (median age, 65 years). Preoperative staging with positron emission tomography/computed tomography was performed in 89% of patients, mediastinoscopy was performed in 42%, and video-assisted thoracoscopic surgery was performed in 51%. At a median follow-up of 36 months (range, 1 to 120 months), the 5-year estimated LRF was 26% (95% confidence interval, 20% to 35%). LRF rates were not significantly different in those with and without staging positron emission tomography/computed tomography (hazard ratio, 1.52; $p = 0.43$) and those with video-assisted thoracoscopic surgery versus open thoracotomy (hazard ratio, 1.00; $p = 0.99$).**

Conclusions. **Despite contemporary staging procedures and surgical techniques for early-stage NSCLC, LRF occurs in approximately 1 of 4 patients. The observed rates of LRF are similar to those reported more than a decade ago, suggesting that local/regional control remains a persistent problem. The use of additional local treatments, such as radiotherapy, should be reevaluated to further improve outcomes.**

The most accepted approach for early-stage non-small cell lung cancer (NSCLC) is surgical resection, with or without adjuvant chemotherapy. Significant improvements in surgical technique in the last 20 years, including anatomic lung resections (eg, lobectomy and segmentectomy) and increased use of minimally invasive surgical techniques (eg, video-assisted thoracoscopic surgery [VATS]), have improved short-term surgical outcomes (ie, postoperative complications) [1]. In addition, improvements in preoperative imaging with positron emission tomography (PET) and computed tomography (CT) may have allowed for better selection of patients more likely to have true early-stage disease.

With both improvements, one might therefore presume that oncologic outcomes will improve as well. Better preoperative visualization of the anatomic tumor location could potentially allow for more a accurate operation and pathologic assessments (eg, margin status), and perhaps thoracoscopic approaches might potentially provide better intraoperative visualization of tumor extent (eg, less intraoperative bleeding, less physiologic stress enabling longer procedure times, and magnified views of the operative site). In multiple studies of patients resected for early-stage disease from 1966 to 2006, crude rates of local/regional failure (LRF) were reported in the range of 6% to 28% for N0 disease [2–13] and 18% to 49% for N1 disease [6, 12, 14–19].

In a previous study of patients undergoing resection between 1996 and 2006 at our institution, similar rates of LRF (5-year LRF of 24%) were noted [20]. The goal of the

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present study was to reassess this question in the present era (2007 to 2015) of contemporary imaging with PET/CT and minimally invasive surgical techniques with VATS.

Material and Methods

Study Design and Patients

This was a single-institution retrospective analysis of patients who underwent initial resection for primary NSCLC at the University of North Carolina, Chapel Hill, North Carolina, from January 2007 through December 2015. The University of North Carolina Institutional Review Board approved this study (16-0096).

Only patients with early-stage NSCLC (pathologic T1-4, N0-1, 7th edition American Joint Committee on Cancer staging [21]) who underwent anatomic resection (eg, lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy), with or without adjuvant chemotherapy, were included. Excluded from our analysis were patients who underwent less than an anatomic complete resection (eg, wedge resection), whose mediastinal lymph nodes were not sampled at preresection mediastinoscopy or at the time of the operation, had advanced disease (eg, N2/N3 nodes, M1 disease), positive surgical margins, histologies other than adenocarcinoma, squamous cell carcinoma, or large cell carcinoma (eg, small cell, carcinoid, sarcomas, or metastases), treated with neoadjuvant chemotherapy, radiotherapy (RT), or both, treated with postoperative RT (with or without chemotherapy), had less than 1 month of follow-up, or whose failure status was unknown. A Consolidated Standards of Reporting Trials diagram is shown in Figure 1.

Data Extraction

The medical records, pertinent radiologic imaging, operative notes, and pathology reports were reviewed to

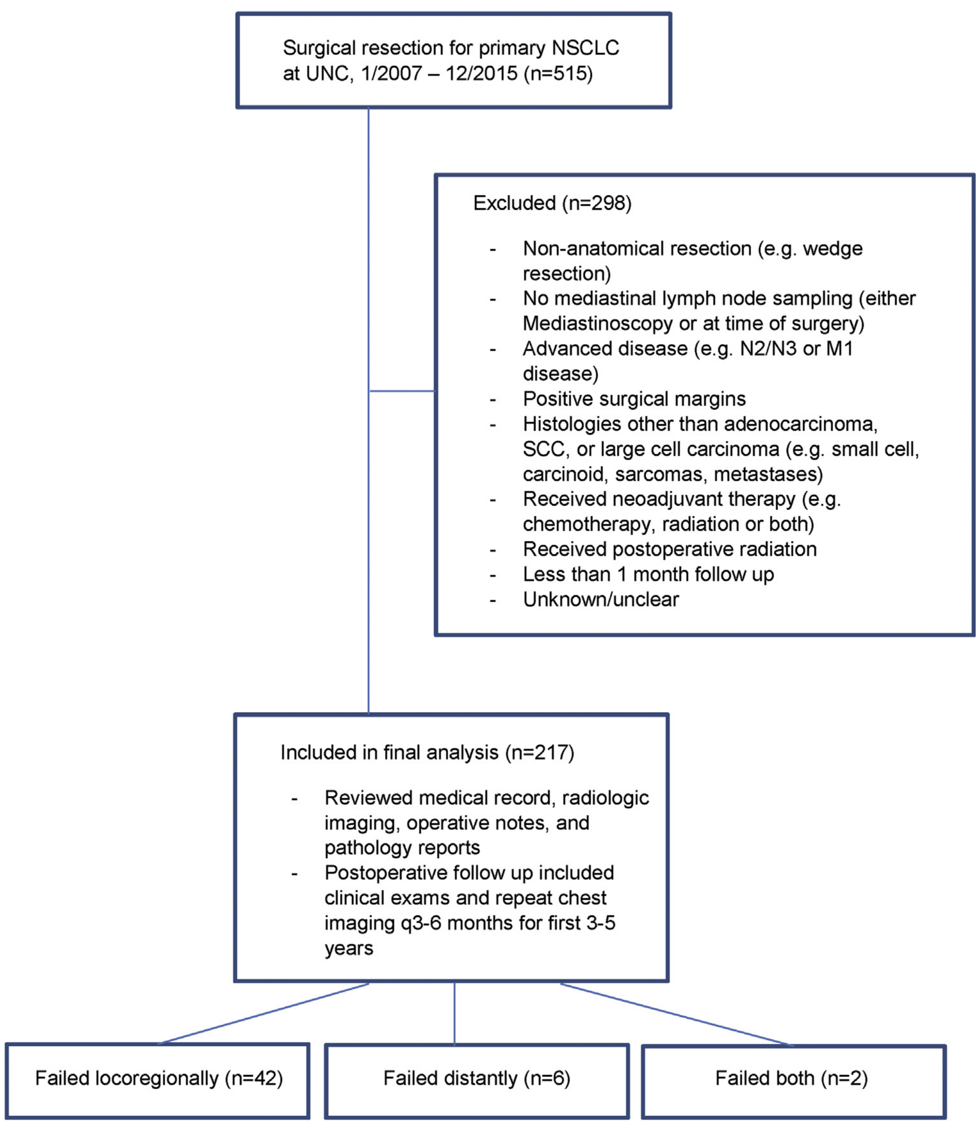

Fig 1. Consolidated Standards of Reporting Trials diagram. (NSCLC = non-small cell lung carcinoma; SCC = squamous cell carcinoma; UNC = University of North Carolina.)

characterize the patient's clinical and demographic information, review preoperative imaging and staging procedures (including tumor location), acquire surgical and pathologic details (including surgical technique, tumor histology, margins, invasion, and pathologic stage), characterize adjuvant therapy, and classify postoperative patterns of failure. Tumor location was collected and defined as central or peripheral according to the distance from the proximal bronchial tree as measured on preoperative chest CT. Central location was defined as tumor within 2 cm of the proximal bronchial tree, which was defined by Timmerman and colleagues [22] as the distal 2 cm of trachea, carina, and major lobar bronchi.

Postoperative follow-up typically included clinical examinations and repeat chest imaging (mostly CT scan) every 3 to 6 months for the first 3 to 5 years. Adjuvant chemotherapy was included in the analysis and typically administered to patients with stage IB or higher disease and an acceptable performance status.

Disease Failure

The presence and site of a failure was obtained from the medical records. LRF was classified as the ipsilateral lung, stump, mediastinum, chest wall, or supraclavicular region. Nodal failure was defined as a new or enlarging lymph node 1 cm or larger on short-axis CT or hypermetabolic on PET and was consistent with disease failure on subsequent follow-up appointments. Treatment failure was defined as local/regional, distant, or both. The date of failure, date of death (if applicable), and whether the recurrence was proven by a biopsy specimen was also collected.

Statistical Methods

Descriptive statistics were used to describe the patient characteristics, surgical details, and pathologic details. The primary outcome of interest was the time to LRF measured from the date of the operation. Patients who did not experience LRF were censored at the last follow-up or death. The Kaplan-Meier method was used to estimate the cumulative incidence rate, and the log-rank test was used to compare cumulative incidence curves. A two-sided p value of less than 0.05 was considered significant. The Cox regression model was used to estimate the hazard ratio (HR). A sensitivity analysis treating death as a competing risk was explored using the Fine and Gray method; however, due to few deaths, results were similar. SAS 9.4 software (SAS Institute Inc, Cary, NC) was used for all analyses.

Results

During the study period, 515 patients underwent an initial operation for a primary diagnosis of NSCLC, of which 217 met inclusion criteria and were included in the final analysis. The median follow-up from the operation was 36 months (range, 1 to 120 months). Patients were a median age of 65 years (range, 42–90 years), 75% were male, 71% were white, and 87% had a tobacco history greater than 10 pack-years.

Preoperative staging with chest CT was performed in 25 patients (11%) and with PET/CT in 192 (89%). Mediastinoscopy was performed in 90 patients (41%): 34 preoperatively and 56 during resection. The surgical procedure was VATS in 51% of patients, and 92% underwent a lobectomy. The pathologic stage was I in 74% of patients, and 80% of patients did not receive adjuvant chemotherapy. Most tumors were peripherally located (74%), and the mean distance to the closest positive margin was 2.2 cm (median, 1.9 cm; range, 0.1 to 9.0 cm). The margin distance was less than the maximum tumor diameter in 56% of cases. Additional patient, surgical, and pathologic details are presented in Table 1.

The 5-year estimated LRF for the entire cohort was 26% (95% confidence interval, 20% to 35%; Fig 2). Local failures occurred in 42 patients (19%), with 74% confirmed by biopsy specimen, and the rest were confirmed with CT (18%) or PET/CT (9%). Distant failures occurred in 6 patients, all of which were proven by a biopsy specimen. The 5-year estimated LRF for patients with pathological stage T1 N0 and T2 N0 are 18% and 26%, respectively (the other subgroups were not large enough to perform the calculation). For the T1 N0 subgroup, local failures occurred in 13 patients (31%), with 92% confirmed by biopsy specimen. For the T2 N0 subgroup, local failures occurred in 14 patients (33%), with 79% confirmed by biopsy specimen. Most of the local failures occurred in the ipsilateral lung (7% for both T1/T2 N0) and mediastinum (7% T1 N0, 5% T2 N0), followed by the contralateral lung (2% T1 N0, 5% T2 N0), staple line (5% T1 N0, 2% T2 N0), stump (2% for both T1/T2 N0), chest wall (0% T1 N0, 2% T2 N0), and multiple sites (5% T1 N0, 10% T2 N0).

The risk of LRF was higher in men than in women (34% vs 17%; HR, 2.10; $p = 0.03$), in those with lymphovascular space invasion (38% vs 25%; HR, 2.33; $p = 0.03$), T3 and T4 disease compared with T1 and T2 (64% vs 23%; HR, 3.35; $p = 0.001$), N1 disease compared with N0 (47% vs 24%; HR, 2.19; $p = 0.03$), and disease stage II and III compared with stage I (42% vs 21%; HR, 2.19; $p = 0.01$; Table 2). A higher risk for LRF was not significantly associated with VATS versus open surgical technique (27% vs 26%; HR, 1.00; $p = 0.99$), preoperative imaging with PET/CT versus no PET/CT (32% vs 26%; HR 1.52, $p = 0.42$), central versus peripheral tumor location (31% vs 24%; HR, 1.41, $p = 0.29$), or margin status of 2 cm or less versus more than 2 cm (30% vs 23%; HR 1.32, $p = 0.40$; Figs 3 and 4, Table 2).

Comment

Resection alone continues to be the most accepted approach for patients with early-stage NSCLC. The main mode of recurrence in these patients has traditionally been thought to be distant because local control rates of 80% or more have been reported [7] and adjuvant chemotherapy has been shown to improve overall survival in select cases [23, 24]. Nevertheless, the estimated 5-year LRF rate in the current series is 26% and is similar to 5-year LFR rate of 24% reported from our

Table 1. Patient and Tumor Characteristics

Characteristic[a]	Result (n = 217)
Age, years	
Mean	64
Median (range)	65 (42–90)
Gender	
Male	124 (57)
Female	93 (43)
Race	
White	153 (71)
African American	55 (25)
Other	9 (4)
Tobacco use	
Never	20 (9)
≤10 pack-years	8 (4)
>10 pack-years	189 (87)
Preoperative imaging	
CT chest	25 (11)
PET/CT	192 (89)
Surgical procedure	
Lobectomy	200 (92)
Bilobectomy	6 (3)
Pneumonectomy	11 (5)
Surgical approach	
VATS	110 (51)
Open	107 (49)
Mediastinoscopy	
Yes	90 (41)
Preoperatively	34 (38)
During resection	56 (62)
No	127 (59)
N1 lymph node sampling	
Yes	215 (99)
No	2 (1)
N2 node stations sampled, No.	
0	5 (2)
1	23 (11)
2	92 (42)
3	59 (27)
4	19 (9)
≥5	19 (9)
Location of tumor	
Right upper lobe	86 (39)
Right middle lobe	10 (4)
Right lower lobe	36 (17)
Right middle, right lower lobe	3 (1)
Right upper, right middle lobe	4 (2)
Left upper lobe	47 (22)
Left lower lobe	30 (14)
Left lower, left upper lobe	1 (1)
Histology[b]	
Adenocarcinoma	134 (62)
Squamous cell carcinoma	75 (35)
Large cell	7 (3)
Pathologic size of lesion, cm	
Mean	3.1
Median (range)	2.5 (0.2–10.3)
Histologic differentiation[b]	
Well	22 (10)
Moderate	140 (65)
Poor	54 (25)
Lymphovascular space invasion[b]	
Yes	24 (11)
No	192 (89)
Perineural invasion[b]	
Yes	4 (2)
No	212 (98)
Visceral pleural invasion[b]	
Yes	32 (15)
No	184 (85)
Distance to closest surgical margin,[b] cm	
Mean	2.2
Median (range)	1.9 (0.1–9.0)
Pathologic stage[b]	
IA	106 (49)
IB	54 (25)
IIA	30 (14)
IIB	21 (10)
IIIA	5 (2)
Adjuvant chemotherapy	
Yes	42 (19)
No	174 (80)
Unknown	1 (1)
Tumor location	
Central	57 (26)
Peripheral	160 (74)

[a] Categoric data are shown as number (%) and continuous data as indicated. [b] No malignancy in 1 specimen.

CT = computed tomography; PET = positron emission tomography; VATS = video assisted thoracoscopic surgery.

institution in previous years (1996 to 2006), as well as other prospective and retrospective studies [6, 14], and suggests that local/regional control remains a persistent challenge.

Direct LRF comparisons between studies are difficult given the variability in the definition of a local failure in the literature. Some studies define ipsilateral mediastinum as a local recurrence but not contralateral mediastinum [24], and others report isolated local failures defined as the ipsilateral lung or mediastinum, or both [3, 7]. In addition, local recurrence may be underreported or missed if it is not the primary end point of a study, is not thoroughly looked for, or is only scored in the absence of a distant recurrence [7].

Surgical techniques have evolved over time, with VATS becoming more common during the last decade. This significant change in technique has led to improvements

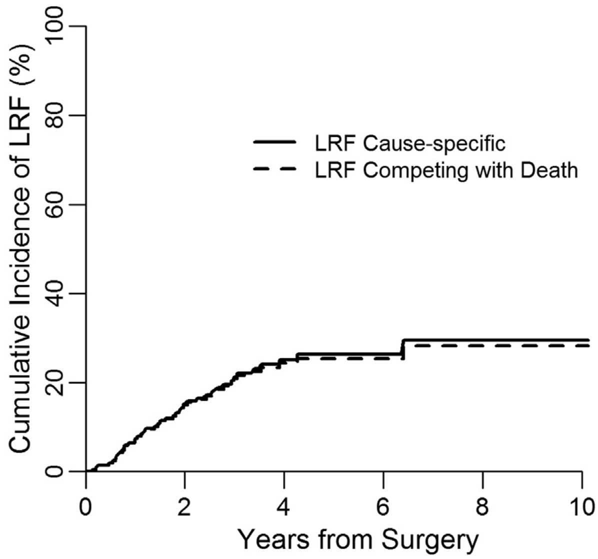

Fig 2. Cumulative incidence curve shows overall time to local/regional failure (LRF): cause-specific rate of 26% at 5 years and competing risk-adjusted rate of 25% at 5 years.

Table 2. Clinical and Pathologic Factors on Risk of Local/Regional Failure

Factor	Univariate Analysis: Hazard Ratio	95% CI	*p* Value
Gender			
Male vs female	2.10	1.08–4.10	0.03
Histology			
Squamous vs nonsquamous	1.63	0.89–2.99	0.11
Surgical technique			
VATS vs open	1.00	0.55–1.84	0.99
Lymphovascular space invasion			
Yes vs no	2.33	1.08–5.05	0.03
Visceral pleural invasion			
Yes vs no	1.20	0.50–2.85	0.68
Margin status			
≤2 cm vs >2 cm	1.32	0.69–2.53	0.40
Margin distance > max tumor diameter			
Yes vs no	0.53	0.23–1.06	0.07
Tumor location			
Central vs peripheral	1.41	0.74–2.70	0.29
T stage			
T3-4 vs T1-2	3.35	1.55–7.25	0.001
N stage			
N1 vs N0	2.19	1.05–4.58	0.03
Stage			
II-III vs I	2.19	1.19–4.03	0.01
Imaging			
PET/CT vs no PET/CT	1.52	0.54–4.26	0.43

CI = confidence interval; PET/CT = positron emission tomography/computed tomography; VATS = video-assisted thoracoscopic surgery.

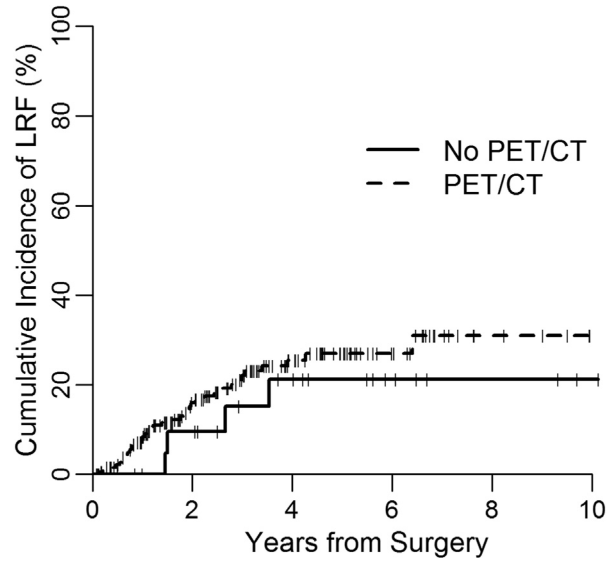

Fig 3. Cumulative incidence curve shows time to local/regional failure (LRF) in patients who had a preoperative staging with positron emission tomography/computed tomography scan (PET/CT) scan compared with those who did not have a PET/CT scan (32% vs 26% at 5 years, p = 0.42).

in short-term surgical outcomes. Compared with open lobectomy, VATS lobectomy has similar oncologic outcomes and an arguably equivalent assessment of mediastinal lymph node stations with lower complication rates and length of hospital stay [25–27].

Imaging has also evolved, allowing improvements in preoperative staging with the addition of PET, because adding PET to preoperative CT scans improves the

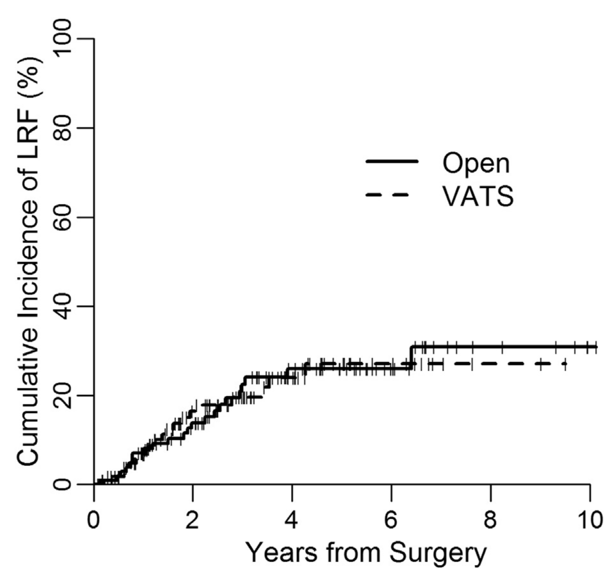

Fig 4. Cumulative incidence curve shows time to local/regional failure (LRF) in patients who underwent video-assisted thoracoscopic surgery (VATS) compared with open thoracotomy (27% vs 26% at 5 years, p = 0.99).

sensitivity and specificity compared with CT scans alone [28, 29]. PET/CT also has a high negative predictive value (95%) and positive predictive value (74%) for mediastinal lymph node detection, which can be used advantageously when selecting patients for invasive procedures (eg, mediastinoscopy). In addition, the accuracy of nodal sampling during an anatomic resection can affect staging, adjuvant therapy recommendations, and oncologic outcomes; for example, inaccurate staging of N1 nodal stations or undefined N1 stations has been associated with higher LRF rates [30]. However, despite these improvements in surgical approach and preoperative imaging, LRF remains a significant problem in these pa-tients. Because lung cancer is a highly invasive and aggressive disease, our advances (eg, in imaging) are likely relatively modest "from the perspective of the tumor," and microscopic tumor infiltration into local/regional tissues remains relatively prevalent despite a negative PET scan [31].

Compared with the University of North Carolina study of patients who underwent resection from 1996 to 2006, the current more modern cohort was more likely to undergo PET/CT for preoperative staging (89% vs 34%) and VATS (51% vs 8%), indicating a shift in preoperative workup and surgical technique. Nevertheless, the LRF rates appear similar in the two cohorts. The fraction of patients pathologically staged was similar in the two groups (26% in the current study versus 24% in the prior study), suggesting that this comparison is reasonable.

The use of adjuvant RT in early-stage NSCLC has fallen out of favor, an appropriate change in practice driven largely by the detriment in survival seen in the meta-analysis [32, 33]. Postoperative RT as delivered in the trials included in the meta-analysis is clearly potentially toxic. Nonetheless, given the apparent persistent presence of LRFs in these patients, the potential role of adjuvant postoperative RT using modern techniques might be worth reexamining.

One factor that has been hypothesized as contributing to the toxic effects of RT seen in the meta-analysis is RT field size. RT planning used in the studies included in the meta-analysis predated the three-dimensional era, so fields were large; for example, including the entire mediastinum, with or without the ipsilateral supraclavicular region and contralateral hilum. Advances in radiation oncology, such as three-dimensional planning and intensity modulated RT, allow for more conformal dose delivery that better targets the high-risk areas. Indeed, two small studies published after the initial meta-analysis using smaller three-dimensional–planned RT fields, better targeting the areas at risk, suggested improved oncologic outcomes with postoperative RT [8, 34].

A number of factors have been associated with an increased risk of LRF, including type of operation (eg, nonanatomic sublobar resection), positive margins, larger tumor size, limited mediastinal lymph node sampling, and the presence of lymphovascular space invasion or visceral pleural invasion [6, 7, 10, 14, 17, 20, 24, 35–37]. We found similar findings with gender (men), lymphovas-cular space invasion, higher T stage (T3, T4), N1 disease, and higher overall stage (stage II to III) being associated with a higher rate of LRF. However, even in the "lower-risk" patients (eg, T1 N0, T2 N0), LRF remains an issue in the present study (18% and 26%, respectively) and in others' series (T1-2 N0, 5-year LRF 19%) [20].

Negative surgical margins but with a margin distance of less than 1.5 to 2 cm has also been associated with a higher risk of LRF [38, 39], with some reports showing worse local control if the margin distance is less than the maximum tumor diameter [38, 39]. Consistent with the literature, we found a nearly significant increase in LRF in patients who did not have a margin distance greater than the maximum tumor diameter and nonsignificant trends in those with smaller margins and in those with central tumors [38, 39].

The results presented highlight that LRF remains a clinical problem. This, coupled with improvements in RT planning and delivery techniques, might make it reasonable to reconsider the role of adjuvant postoperative RT in these patients to help improve local/regional control and survival. Although challenging, a prospective trial to restudy the role of postoperative RT in this setting is reasonable to consider. Two modest-sized studies of postoperative conformal RT in early-stage lung cancer have suggested improvements in local control and survival [8, 34], suggesting that a larger study might be worthwhile.

This study has several limitations. First, the data extraction was retrospective; however, we were able to gather the desired clinical and pathologic factors from the medial records. Our hospital has had an electronic medical record for approximately 22 years, and the pathology and operative notes were thus readily available. Further, the retrospective nature would likely tend to underreport LRFs, and the noted LRF rates might thus be considered as minimum values.

Second, patients were not evaluated in a consistent manner after the operation (eg, postoperative scans were not always done regularly). Again, this issue would tend to underestimate the apparent rates of LRF, and we thus believe our conclusions remain valid.

Third, the patients studied were treated during a 10-year interval. Changes in surgical, staging, and treatment techniques during the study period may have influenced the LRF rates. However, broadly speaking, the LRF rates in the 1996 to 2006 cohort and in the 2007 to 2015 cohorts were similar, suggesting that pooling of patients during this period may be reasonable. Further, all of these patients were treated in a single institution, thus perhaps reducing interprovider factors that might, over time, confound the outcomes.

Fourth, the cohort consists of a heterogeneous patient population, and thus, results for our largest subset of the earliest stage cases (ie, T1-2 N0) are reported separately, with higher stages excluded.

Fifth, fewer than three mediastinal lymph node stations were sampled during the operation in 55% of patients. This may have contributed to the elevated LRF rate, because several consensus groups have recommended that at least three stations be sampled [40].

Finally, our sample size was smaller compared with prior studies, which limited our analysis of LRF rates in patient subgroups; however, in the subgroups with enough patients to analyze (T1 N0 and T2 N0), LRF rates were similar to our 1996 to 2006 cohort; again, suggesting that pooling of patients over this time period may be reasonable.

Conclusion

Despite the use of contemporary staging procedures and surgical techniques for early-stage NSCLC, LRF occurs in approximately 1 of 4 patients. The observed rates of LRF are similar to those that were reported more than a decade ago, suggesting LRF remains a persistent problem. The use of additional local treatments, such as conformal RT, should be reevaluated as a means to further improve outcomes.

References

1. Paoletti L, Pastis NJ, Denlinger CE, Silvestri GA. A decade of advances in treatment of early-stage lung cancer. Clin Chest Med 2011;32:827–38.
2. Lafitte JJ, Ribet ME, Prévost BM, Gosselin BH, Copin MC, Brichet AH. Postresection irradiation for T2 N0 M0 non-small cell carcinoma: a prospective, randomized study. Ann Thorac Surg 1996;62:830–4.
3. Feld R, Rubinstein LV, Weisenberger TH. Sites of recurrence in resected stage I non-small-cell lung cancer: a guide for future studies. J Clin Oncol 1984;2:1352–8.
4. Kato H, Ichinose Y, Ohta M, et al. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. N Engl J Med 2004;350:1713–21.
5. Bedini AV, Cataldo I, Valente M, Ravasi G. Five-year recurrence probabilities in 330 patients curatively resected for stage Ia bronchogenic carcinoma. Tumori 1987;73:131–7.
6. Lardinois D, Suter H, Hakki H, Rousson V, Betticher D, Ris HB. Morbidity, survival, and site of recurrence after mediastinal lymph-node dissection versus systematic sampling after complete resection for non-small cell lung cancer. Ann Thorac Surg 2005;80:268–74; discussion 274–5.
7. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615–22; discussion 622–3.
8. Trodella L, Granone P, Valente S, et al. Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial. Radiother Oncol 2002;62:11–9.
9. Sawyer TE, Bonner JA, Gould PM, Deschamps C, Lange CM, Li H. Patients with stage I non-small cell lung carcinoma at postoperative risk for local recurrence, distant metastasis, and death: implications related to the design of clinical trials. Int J Radiat Oncol Biol Phys 1999;45:315–21.
10. Harpole DH Jr, Herndon JE 2nd, Young WG Jr, Wolfe WG, Sabiston DC Jr. Stage I nonsmall cell lung cancer. A multivariate analysis of treatment methods and patterns of recurrence. Cancer 1995;76:787–96.
11. Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg 1995;109:120–9.
12. Immerman SC, Vanecko RM, Fry WA, Head LR, Shields TW. Site of recurrence in patients with stages I and II carcinoma of the lung resected for cure. Ann Thorac Surg 1981;32:23–7.
13. Gauger J, Patz EF Jr, Coleman RE, Herndon JE 2nd. Clinical stage I non-small cell lung cancer including FDG-PET Imaging: sites and time to recurrence. J Thorac Oncol 2007;2:499–505.
14. Kelsey CR, Marks LB, Hollis D, et al. Local recurrence after surgery for early stage lung cancer: an 11-year experience with 975 patients. Cancer 2009;115:5218–27.
15. Stephens RJ, Girling DJ, Bleehen NM, Moghissi K, Yosef HM, Machin D. The role of post-operative radiotherapy in non-small-cell lung cancer: a multicentre randomised trial in patients with pathologically staged T1-2, N1-2, M0 disease. Medical Research Council Lung Cancer Working Party. Br J Cancer 1996;74:632–9.
16. Feng QF, Wang M, Wang LJ, et al. A study of postoperative radiotherapy in patients with non-small-cell lung cancer: a randomized trial. Int J Radiat Oncol Biol Phys 2000;47:925–9.
17. Sawyer TE, Bonner JA, Gould PM, et al. Factors predicting patterns of recurrence after resection of N1 non-small cell lung carcinoma. Ann Thorac Surg 1999;68:1171–6.
18. Luzzi L, Voltolini L, Campione A, et al. Pneumonectomy vs lobectomy in the treatment of pathologic N1 NSCLC: could the type of surgical resection dictate survival? J Cardiovasc Surg (Torino) 2003;44:119–23.
19. Matsuoka K, Sumitomo S, Misaki N. Prognostic factors in patients with pathologic T1-2N1M0 disease in non-small cell carcinoma of the lung. J Thorac Oncol 2007;2:1098–102.
20. Saynak M, Veeramachaneni NK, Hubbs JL, et al. Local failure after complete resection of N0-1 non-small cell lung cancer. Lung Cancer 2011;71:156–65.
21. Edge S, Byrd DR, Comptom CC, Fritz AG, Greene FL, Trotti A 3rd (eds). AJCC cancer staging handbook: from the AJCC cancer staging manual. 7th edition. New York: Springer; 2009.
22. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070–6.
23. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351–60.
24. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719–27.
25. Rueth NM, Andrade RS. Is VATS lobectomy better: perioperatively, biologically and oncologically? Ann Thorac Surg 2010;89:S2107–11.
26. Chen FF, Zhang D, Wang YL, Xiong B. Video-assisted thoracoscopic surgery lobectomy versus open lobectomy in patients with clinical stage non-small cell lung cancer: a meta-analysis. Eur J Surg Oncol 2013;39:957–63.
27. D'Amico TA, Niland J, Mamet R, Zornosa C, Dexter EU, Onaitis MW. Efficacy of mediastinal lymph node dissection during lobectomy for lung cancer by thoracoscopy and thoracotomy. Ann Thorac Surg 2011;92:226–31; discussion 231–2.
28. Pieterman RM, van Putten JW, Meuzelaar JJ, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. N Engl J Med 2000;343:254–61.
29. Vansteenkiste JF, Stroobants SG, De Leyn PR, et al. Lymph node staging in non-small-cell lung cancer with FDG-PET scan: a prospective study on 690 lymph node stations from 68 patients. J Clin Oncol 1998;16:2142–9.
30. Saynak M, Hubbs J, Nam J, et al. Variability in defining T1N0 non-small cell lung cancer impacts locoregional failure and survival. Ann Thorac Surg 2010;90:1645–9; discussion 1649–50.
31. Yilmaz U, Wong TZ, Marks LB. How good is PET in detecting previously-occult metastatic cancer at diagnosis? Int J Radiat Oncol Biol Phys 2017 Nov 15 [in press accepted manuscript].
32. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. Lancet 1998;352:257–63.

33. Burdett S, Rydzewska L, Tierney J, et al. Postoperative radiotherapy for non-small cell lung cancer. Cochrane Database Syst Rev 2005:CD002142.
34. Mayer R, Smolle-Juettner FM, Szolar D, et al. Postoperative radiotherapy in radically resected non-small cell lung cancer. Chest 1997;112:954–9.
35. Lee JH, Machtay M, Kaiser LR, et al. Non-small cell lung cancer: prognostic factors in patients treated with surgery and postoperative radiation therapy. Radiology 1999;213: 845–52.
36. Warren WH, Faber LP. Segmentectomy versus lobectomy in patients with stage I pulmonary carcinoma. Five-year survival and patterns of intrathoracic recurrence. J Thorac Cardiovasc Surg 1994;107:1087–93; discussion 1093–4.
37. Hsu HC, Wang CJ, Huang EY, Sun LM. Post-operative adjuvant thoracic radiotherapy for patients with completely resected non-small cell lung cancer with nodal involvement: outcome and prognostic factors. Br J Radiol 2004;77:43–8.
38. Sawabata N, Ohta M, Matsumura A, Nakagawa K, et al. Optimal distance of malignant negative margin in excision of nonsmall cell lung cancer: a multicenter prospective study. Ann Thorac Surg 2004;77:415–20.
39. Schuchert MJ, Pettiford BL, Keeley S, et al. Anatomic segmentectomy in the treatment of stage I non-small cell lung cancer. Ann Thorac Surg 2007;84:926–32.
40. Ettinger DS, Kris MG. Update: NCCN non-small cell lung cancer clinical practice guidelines. J Natl Compr Canc Netw 2004;2:9–13.