Timing of Local and Distant Failure in Resected Lung Cancer

Implications for Reported Rates of Local Failure

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Introduction: Most adjuvant lung cancer trials only report first sites of failure. The relative timing of local (i.e., local/regional) versus distant recurrence after surgery could potentially affect reported rates of local failure. We assessed this phenomenon in a large group of patients undergoing surgery for early-stage lung cancer.

Methods: This institutional review board-approved retrospective study identified all patients who underwent surgery at Duke University Medical Center for pathologic stages I to II non-small cell lung cancer between 1995 and 2005. Medical records and pertinent radiographs were reviewed to assess for local and distant sites of recurrence. Both first and subsequent failures were examined. The time interval between surgery and date of local and/or distant failure was compared using the Mann-Whitney *U* test.

Results: Of 975 patients undergoing surgery, 250 patients developed recurrent disease (43 local only, 110 distant only, and 97 both). The median time from surgery to local failure was 13.9 months (range, 1–79). The median time to distant failure was 12.5 months (range, 1–79 months). These were not significantly different ($p = 0.34$). Among 97 patients who experienced both local and distant failure, 72 (74%) failed at both sites simultaneously, 19 (20%) failed at local sites first, and 6 (6%) failed at distant sites first.

Conclusions: The time interval from surgery to either local or distant failure is not significantly different. Patterns of failure analyses in which only first sites of failure are scored will underestimate the frequency of local recurrence. Nevertheless, the magnitude of this error is expected to be small.

Key Words: Non-small cell lung cancer, Local recurrence, Distant recurrence, Patterns of failure.

(*J Thorac Oncol.* 2010;5: 211–214)

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Disclosure: The authors declare no conflicts of interest.

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Presented at the 49th Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), October 28 – November 1, 2007 in Los Angeles, CA.

ISSN: 1556-0864/10/0502-0211

Surgery is the preferred initial treatment for early-stage non-small cell lung cancer (NSCLC). Adjuvant chemotherapy is often recommended, depending on disease stage, size of the primary tumor, and other pathologic characteristics. Postoperative radiation therapy is generally not recommended in the absence of positive surgical margins or other adverse features.

The risk of local (i.e., local/regional) recurrence after surgery for early-stage NSCLC is generally considered to be small in comparison with the risk of distant recurrence. Nevertheless, reported rates of local failure after surgery for stage I NSCLC vary from as low as 6 to 8%[1–3] to as high as 20 to 28%.[4–6] Reported rates for stage II disease range from 20 to 40%.[7–9]

An accurate understanding of patterns of failure after surgery is essential to guide appropriate adjuvant therapy. In prospective studies, for ease of reporting, typically, only first sites of failure are recorded. Patterns of failure are most commonly reported as: local only, distant only, or local plus distant. Awareness of the relative timing of local and distant failure is necessary if only first sites of failure are scored. For example, the rate of local failure may be underreported if distant failures become clinically evident earlier in the natural history of the disease.

We have previously assessed the rate of local failure after surgery for early-stage NSCLC at Duke.[10] In this report, we analyze the relative timing of local versus distant failure, to assess whether this issue may affect rates of local failure reported in prospective studies.

PATIENTS AND METHODS

This institutional review board-approved retrospective study was performed by searching the Duke Comprehensive Cancer Center database for patients who underwent surgery for T1–2 N0–1 NSCLC at Duke University between 1995 and 2005. Patients who received neoadjuvant therapy (chemotherapy and/or radiation therapy), presented with synchronous primary lung tumors, or had a prior history of lung cancer were excluded. The patient's medical records and pertinent radiologic imaging were reviewed to characterize each patient's demographic information, obtain surgical and pathologic details, and score patterns of failure after surgery.

Although follow-up was not standardized, patients were generally seen every 3 to 6 months after surgery for the first 5 years and annually thereafter. Follow-up imaging typically consisted of a chest x-ray. Further imaging, including computed tomography (CT), magnetic resonance imaging, bone scan, and positron emission tomography (PET), was obtained at the discretion of the treating physician and was generally obtained when patients presented with concerning symptoms or the chest x-ray was abnormal. Similarly, at the time of recurrence, radiographic studies were performed at the discretion of the treating physicians.

Disease recurrence at the surgical resection margin, ipsilateral hilum, and/or mediastinum was considered a local failure. All other sites of failure, including the supraclavicular fossa and contralateral hilum, were considered distant failures. Nodal failures were defined as a new or enlarging lymph node ≥1 cm on short axis on CT or hypermetabolic on PET, which in the patient's subsequent clinical follow-up was consistent with a true local failure. Local and distant failures were scored independently. All failures were reviewed by two authors (J.B. and C.K.) and often required clinical judgment, in as much as pathologic documentation was not always performed.

When local and distant failures were detected in the same patient within 30 days of one another, this was defined as a "simultaneous failure." When local and distant failures occurred more than 30 days apart, this was defined as a "sequential failure." The time interval between surgery and date of failure for local and distant recurrence was compared using the Mann-Whitney *U* test.

RESULTS

We identified 975 patients who underwent surgery for T1–2 N0–1 NSCLC in the defined interval. Median follow-up was 33 months (range, 1–149). Patient characteristics and surgical/pathologic details are found in Table 1. Most patients had stage I disease (45% IA and 40% IB). Hilar lymph nodes (N1, levels 10–14) were sampled in 81% of patients. The median number of N1 lymph nodes sampled was 4 (range, 1–31). Mediastinal lymph nodes (N2, levels 1–9) were sampled or dissected in 85% of patients. The median number of mediastinal lymph node stations examined was 4 (range, 1–9). Surgical margins were positive in 4% of patients.

Adjuvant chemotherapy was administered to 7% of patients, most frequently carboplatin and paclitaxel, although a number of regimens were used. Adjuvant radiation therapy was given to 3%, primarily for positive surgical margins.

Disease recurrence developed in 250 patients. Local recurrence was identified in 140 patients, and distant failure was identified in 207 patients. Local recurrences were confirmed by means of biopsy in 47%, PET in 33%, and CT in 20%. Distant recurrences were confirmed by biopsy in 50%, PET in 25%, and other imaging (CT, magnetic resonance imaging, or bone scan) in 25%. The 5-year actuarial rate of local and distant recurrence was 23% (95% confidence interval, 19–26%) and 34% (95% confidence interval, 30–39%), respectively.[10]

TABLE 1. Patient Characteristics

Characteristic	*N* (%)
Age, yr	
Median (range)	67 (20–93)
Gender	
Male	533 (55)
Female	442 (45)
Race	
White	824 (85)
Black	124 (13)
Other	23 (2)
Surgical procedure	
Wedge	161 (17)
Segmentectomy	41 (4)
Lobectomy	668 (68)
Sleeve resection	36 (4)
Pneumonectomy	69 (7)
Surgical approach	
Open	600 (62)
VATS	375 (38)
Hilar lymph node sampling	
Yes	790 (81)
No	185 (19)
Mediastinal lymph node sampling	
Yes	824 (85)
No	151 (15)
Size, cm	
Median, range	2.6 (0.3–13)
Histology	
Adenocarcinoma	441 (45)
Squamous cell	358 (37)
Large cell	48 (5)
Bronchioloalveolar	28 (3)
Adenosquamous	6 (1)
NSCLC NOS	94 (10)
Histologic differentiation	
Well	77 (8)
Moderate	424 (43)
Poor	298 (31)
NS	176 (18)
Lymphovascular space invasion	
Yes	210 (22)
No/NS	765 (78)
Visceral pleural invasion	
Yes	201 (21)
No/NS	774 (79)
Pathologic stage	
IA	435 (45)
IB	385 (39)
IIA	43 (4)
IIB	112 (11)
Surgical margins	
Negative	939 (96)
Positive	36 (4)
Adjuvant chemotherapy	
Yes	65 (7)
No	910 (93)
Adjuvant radiation therapy	
Yes	33 (3)
No	941 (97)

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

Of the 250 failures, 43 (17%) were confined to local sites, 110 (44%) were confined to distant sites, and 97 (39%) included both local and distant sites (Figure 1). Of the 97 patients who failed at both local and distant sites, most (74%) did so simultaneously. Only six patients developed a sequential local recurrence, documented more than 30 days after a distant recurrence was identified (Figure 2). Thus, the crude rate of local failure would be underestimated by 0.6% (6 of 975) if only first sites of failure are reported.

Patients who developed recurrent disease confined to local sites (n = 43) underwent comprehensive restaging examinations to evaluate for distant metastases before initiation of salvage local therapy (surgery and/or radiation therapy). For those patients who developed a recurrence apparently confined to distant sites (n = 110), most underwent either CT (44%) or PET (33%) imaging to evaluate for a concurrent local recurrence. The remainder either had a chest x-ray performed (17%) or underwent no imaging of the chest (6%).

There was no difference in the time interval between surgery and the development of a local failure and the time interval between surgery and the development of a distant failure (p = 0.34) (Figure 3). The median time from surgery to local failure was 13.9 months (range, 1–79). The median time from surgery to distant failure was 12.5 months (range, 1–79).

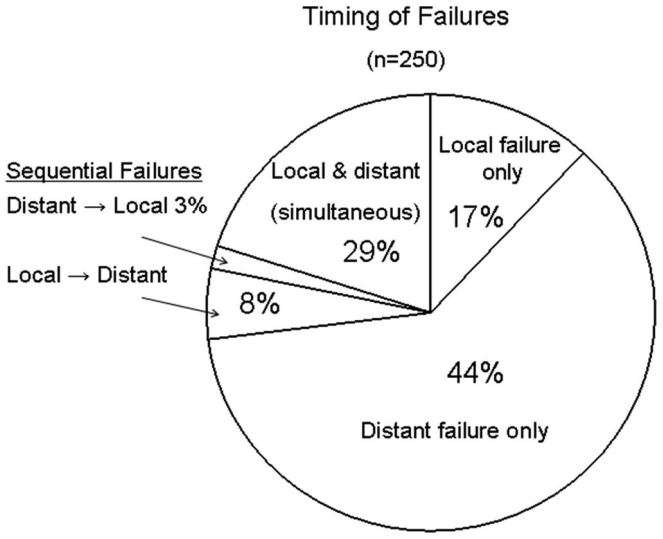

FIGURE 1. Distribution of failures among 250 patients with stages I to II non-small cell lung cancer who recurred after surgery. Local (i.e., local/regional) and distant failures developing within 30 days of each other were considered "simultaneous."

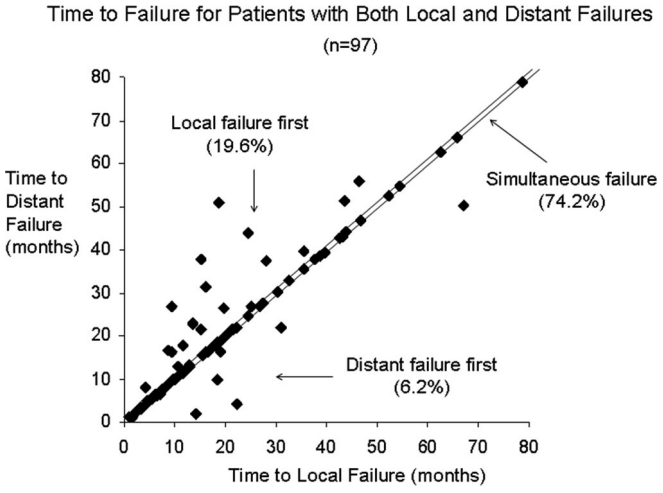

FIGURE 2. Time to local and distant failure is displayed for 97 patients with stages I to II non-small cell lung cancer who developed both a local and distant recurrence. A line of unity is shown.

DISCUSSION

Lung cancer is the leading cause of cancer mortality in the United States.[11] Notwithstanding optimal surgery, the risk of recurrence is high, even with early-stage disease. Lung cancer can recur at sites proximal to the original tumor (i.e., local/regional failure) or at distant sites. The risk of local recurrence after surgery for early-stage NSCLC has not been well defined but is generally felt to be low and overshadowed by the risk of distant recurrence. Nevertheless, few prospective studies report patterns of failure. Furthermore, the optimal method of reporting patterns of failure is not clear. Most prospective studies only report first sites of failure, as opposed to cumulatively assessing and recording sites of recurrence. Recording only the first site(s) of failure has obvious practical advantages. In addition, it could be argued that the importance of a local recurrence that is detected after distant metastases have developed is of little clinical consequence. Nevertheless, as systemic therapy improves,[12,13] achieving local control will likely assume greater importance.

To better study this issue, we assessed the risk of local and distant recurrence in a cumulative fashion in patients who underwent surgery for early-stage NSCLC at Duke Univer-

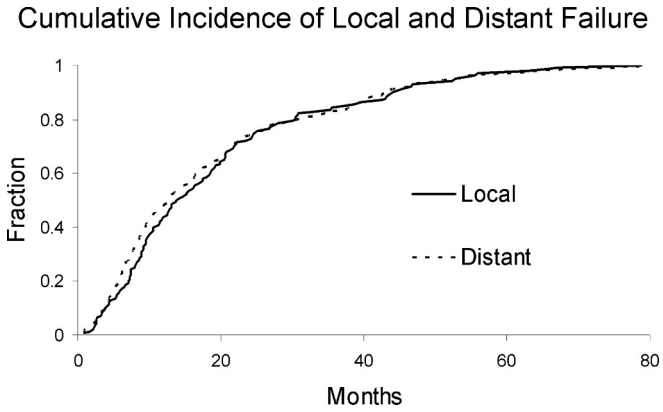

FIGURE 3. The cumulative incidence of local and distant failure for 250 patients with stage I to II non-small cell lung cancer who recurred after surgery. There was no difference in the time interval between local and distant failures (median 13.9 versus 12.5 months, respectively).

sity. The 5-year actuarial risk of local and distant recurrence was 23% and 34%, respectively, and has been previously reported.[10] In this analysis, we analyzed the timing of local and distant failures after surgery of early-stage NSCLC. We further estimated how much the risk of local recurrence would be underestimated if only first failures are scored.

We found that distant recurrences occur, on average, 12.5 months after surgery compared with 13.9 months for local recurrences, a difference which is not statistically significant. Furthermore, we found that most patients who recurred at local sites did so without evidence of distant disease or with synchronous distant metastases. Only 4.2% of local recurrences occurred more than 30 days after a distant failure. Put another way, when considering all recurrences, the crude local failure rate would be underestimated by less than 1% if only first sites of failure are scored. This would suggest that early-stage lung cancers, which are destined to recur at local/regional sites, likely disseminate early in the course of the disease. This may explain, in part, why randomized trials of postoperative radiation therapy (without chemotherapy) consistently improved local control but did not improve overall survival.[6,7,14] Unless distant disease is better controlled with chemotherapy, further local therapy will be of little consequence.

We acknowledge that there are limitations to our study. First, a systematic method of follow-up, including imaging, would be optimal to evaluate patterns of failure after surgery. Unfortunately, given the retrospective nature of this analysis and the 11-year time period which it covers, this was not the case. Second, a significant number of patients with "distant only" recurrences did not undergo optimal imaging of the chest at the time of recurrence. Thus, some local failures might not have been detected. Third, only approximately 50% of recurrences were pathologically confirmed. This is typical because many patients present shortly after initial treatment with clear progression and a biopsy is not always deemed necessary. It is important to note that the percentage of recurrences documented with biopsy and PET was similar between patients who developed a local versus distant recurrences. The primary strength of this study is the large number of patients who were carefully analyzed for patterns of failure after surgery for early-stage NSCLC.

In summary, we found that most local failures occur alone or synchronously with distant metastases. Reporting only first sites of failures does not seem to appreciably diminish the true rate of local recurrence in patients with early-stage NSCLC.

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