Does Intensive Follow-up Alter Outcome in Patients with Advanced Lung Cancer?

Rachel Benamore, MB BChir, MRCP, FRCR, Frances A. Shepherd, MD, FRCPC,† Natasha Leighl, MD, FRCPC,† Melania Pintilie, MSc,‡ Milan Patel, MD, FRCPC,† Ronald Feld, MD, FRCPC,† and Stephen Herman, MD, FRCPC**

Background: Despite aggressive multimodality treatment, 5-year survival of stage III non-small cell lung cancer (NSCLC) remains <30%. To detect relapse, progression, or development of a second primary cancer early, many clinicians perform follow-up scans. To assess the impact of routine scanning, we compared clinical trial patients who had study-mandated scans with those treated off-study who had less intensive radiologic follow-up.

Methods: The hospital cancer registry and trials databases were searched for patients with locally advanced NSCLC who had undergone multimodality treatment with curative intent. Baseline demographics were collected as well as frequency and results of clinical and radiologic follow-up.

Results: Forty trial patients and 35 nontrial control patients were identified. Trial patients underwent significantly more imaging, particularly in the first 2 years (2.9 versus 2.0 body scans per year, $p = 0.0016$; 1.1 versus 0.4 brain scans per year, $p < 0.001$) but did not have more frequent follow-up visits. Forty-five cancers were detected (41 relapses, four metachronous primary tumors) in 44 (59%) patients. Of these, 28 (64%) sought medical attention that led to detection before a scheduled appointment or procedure. There was no significant difference in time to relapse or second primary in trial and nontrial patients ($p = 0.80$). Twenty-three patients had localized relapse, but only 15 could be treated with curative intent. Despite the trial group demonstrating a higher number of asymptomatic cancers and being offered potentially curative therapy more frequently, there was no significant difference in survival between trial and nontrial patients.

Conclusion: In patients with locally advanced NSCLC, frequent cross-sectional imaging does not alter survival after combined modality therapy.

Key Words: Non-small cell lung cancer, Diagnostic imaging, Computed tomography, Follow-up.

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From the Departments of *Radiology, †Medicine, and ‡Biostatistics, University Health Network and University of Toronto, Toronto, Ontario, Canada.

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Address for correspondence: Rachel Benamore, Department of Radiology, University Health Network and University of Toronto, Toronto, Ontario, Canada. E-mail: rachel.benamore@orh.nhs.uk

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Lung cancer accounts for the largest number of cancer-related deaths in North America.[1] For patients with early-stage non-small cell lung cancer (NSCLC), surgery is the treatment of choice, followed by adjuvant chemotherapy.[2–4] Approximately one third of NSCLC patients present with locally advanced tumors (stages IIIA and IIIB), and for some of these patients, a combined modality treatment approach undertaken with potentially curative intent may be appropriate.[5] There is a lack of evidence in the published literature regarding optimal follow-up of NSCLC treated with curative intent.[6] In patients with locally advanced lung cancer, arguments have been made for intensive follow-up as relapse rates are high, but little is known about the effectiveness of follow-up regimens, and there is a lack of evidence to suggest that earlier treatment of recurrence leads to better outcomes. Edelman et al.[7] described the following principles for the use of diagnostic tests in the evaluation of patients after potentially curative cancer therapy: (1) the interval between examinations and the duration of testing should be consistent with the maximal risk of recurrence and the natural history of the tumor; (2) tests should be directed at the most likely sites of recurrence and should have high positive and negative predictive values; (3) therapy should be available that will result in cure, significant prolongation of life, or palliation of symptoms; (4) initiation of earlier therapy should improve outcome; (5) increased risk of second malignancies should guide tests. Potential negative aspects of routine tests include increased patient anxiety, increased cost, investigation of incidental findings at routine scanning, and unnecessary intervention.

In our institution, when patients attend for routine follow-up, history and physical examination, a chest radiograph (CXR), and biochemical blood tests are performed routinely, approximately every 3 months for 2–3 years and then every 6 months to 5 years (Table 1). Further diagnostic tests such as computed tomography (CT) or magnetic resonance imaging (MRI) are performed only when there is a clinical suspicion of relapse. However, for patients who are enrolled in clinical trials, routine cross-sectional imaging often forms part of the study follow-up protocol. Our institution participated in two North American Intergroup trials of combined modality therapy for stage III NSCLC,[8,9] and following closure of these studies, patients were treated in an identical fashion using the same chemotherapy, radiotherapy,

TABLE 1. Follow-up Regimens for Intergroup Trial and Nontrial Patients

Trial	Tests at Initial Follow-up	Definition of Subsequent Follow-up	Tests at Subsequent Follow-up
INT 0160	Biochemistry, CXR, CT of chest and upper abdomen, CT or MRI of brain. Bone scan only if indicated by symptoms or chemistry	Every 3 mo for 2 yr, then every 6 mo thereafter	Biochemistry, CXR at each visit. CT of chest, upper abdomen and CT or MRI of brain every 6 mo for 3 yr, then as required. Bone scan only if indicated by symptoms or chemistry
INT 0139	Biochemistry, CXR, CT of chest and upper abdomen, CT or MRI of brain and bone scan only if indicated by symptoms or chemistry	Every 2 mo for 1 yr, then every 3 mo for 2 yr, then every 6 mo thereafter	Biochemistry, CXR at each visit. CT of chest and upper abdomen and CT/MRI of brain at 12, 18, 24 mo and yearly thereafter. Bone scan only if indicated by symptoms or chemistry
Nontrial patients	Biochemistry, CXR only. Further tests if clinically indicated	Regular clinical review approximately every 3 mo for 2–3 yr and every 6 mo for 2–3 yr	Biochemistry, CXR only. Further tests if clinically indicated

CXR, chest radiograph; CT, computed tomography; MRI, magnetic resonance imaging.

and surgical protocols. By comparing patients treated on study who had study-mandated follow-up scans with those treated off-study with less intensive radiologic follow-up, we sought to answer the following questions: (1) How, when, and where is relapse detected? (2) Does intensive radiologic follow-up detect relapse at an earlier stage, and, if so, can curative treatment be offered and outcomes improved? (3) Does an abnormality detected on a routine scan precipitate a change in patient management?

PATIENTS AND METHODS

Patient Identification

Trial patients

Our hospital cancer trials database was searched retrospectively for all patients enrolled in the Southwest Oncology Group 9416 (Intergroup [INT] 0160) and INT 0139. INT 0160 was limited to patients with T3 or T4 superior sulcus tumors with N0 or N1 disease (node negative at mediastinoscopy). INT 0139 patients all had mediastinoscopy-proven N2 disease. In both studies, patients underwent neoadjuvant chemoradiotherapy (CT/RT) consisting of two cycles of etoposide and cisplatin and radiotherapy (45 Gy in 25 fractions). Patients in INT0160 then proceeded to surgical resection. Patients in INT 0139 were randomized into surgical and nonsurgical arms; the nonsurgical patients received 2 more weeks of radiotherapy to a total dose of 63 Gy. In both trials, two additional cycles of etoposide and cisplatin were administered postoperatively or post-radiation.

Nontrial patients

Approval for this study was granted by the ethics committee of the University Health Network. The hospital cancer registry was searched retrospectively for all consecutive patients who presented with the same stage disease and were offered similar definitive treatment in the posttrial era.

Any patients who progressed on treatment or who did not undergo follow-up were excluded. For all patients, the following data were collected: baseline demographics at presentation including age, sex, tumor cell type and stage at presentation, treatment, response, pathologic stage at resection (if surgery was performed), date and frequency of clinical and radiologic follow-up, and whether this was "scheduled" (as part of a clinical trial protocol or routine clinical follow-up in nontrial patients) or "unscheduled" (symptom driven).

Follow-up

Initial follow-up for all patients was defined as the first encounter occurring after completion of all treatment. Table 1 details the follow-up regimens for the various patient groups. In all patients, biochemistry consisted of electrolytes, creatinine, aspartate transaminase, alanine transaminase, alkaline phosphatase, calcium, and lactate dehydrogenase. The nontrial patients were followed regularly with history, physical examination, CXR, and routine biochemistry. Further radiologic examinations were only arranged when there was a clinical suspicion of relapse. All patients had at least 2 years of follow-up.

Relapses

Relapse was defined as recurrence after response to primary therapy or the development of a metachronous tumor. Relapses were recorded as detected during a scheduled or unscheduled radiologic procedure and also according to presence of symptoms. Methods of detection of relapse were recorded, including physical examination and CXR; cross-sectional imaging of the chest, body, or brain; and other investigations. The site of relapse was described as thoracic or extrathoracic. Local thoracic recurrence was defined as recurrent tumor at the previous primary tumor site or nodal disease that might be amenable to surgery or radical radiotherapy. Case notes and radiology records were reviewed to determine whether clinical or radiologic findings suggestive of relapse altered management.

Survival and Statistical Analyses

The study was a two-cohort design. The number of hospital visits and diagnostic tests were compared between the trial and nontrial groups, assuming Poisson distribution.

A relapse was defined as either recurrence after response to primary therapy or a second malignancy. The proportions of imaging that detected a relapse were compared between the trial and nontrial groups using a generalized linear model with a logistic link. The proportions of relapses at each point in time were calculated using the cumulative incidence function. Because some patients died before experiencing a relapse, the comparison between the two groups was performed using Gray's test. Survival measured from the end of the treatment was calculated using the Kaplan-Meier approach, and the groups were compared using the log-rank test.

RESULTS

Patient Characteristics

Fifty-six patients enrolled in INT 0160 and INT 0139 initially were identified. Sixteen were excluded for the following reasons: progressive disease during treatment (nine patients), death before follow-up (five patients), lost to follow-up (one patient), cell type not NSCLC (one patient). Therefore, a total of 40 trial patients were enrolled (11 with superior sulcus tumors and 29 N2 nodal disease). After review of the hospital cancer registry, 69 potential nontrial patients were identified. Thirty-four patients were excluded for the following reasons: incorrect tumor stage after full staging investigations (14 patients), incomparable treatment (five patients), disease progression during treatment (four patients), death before follow-up (two patients), lost to follow-up (eight patients), cell type not NSCLC (one patient). Therefore, a total of 35 nontrial patients were enrolled (11 with superior sulcus tumors and 24 with N2 nodal disease). Table 2 summarizes the baseline characteristics of the two patient groups.

Follow-up

The median duration of follow-up was 77 months (range, 50–117) for trial patients and 44 months (range, 23–76) for nontrial patients (Table 2). This difference is due to the adoption of the trial treatment into standard practice after the trials closed. For both trial and nontrial patients, the frequency of follow-up, lab tests, and radiologic examinations is greater than that stated in the methods, as this also includes symptomatic presentations between scheduled visits. As shown in Table 3, there was no statistical difference in the frequency of follow-up visits between the trial and nontrial groups. However, trial patients underwent significantly more imaging, particularly in the first 2 years (2.9 versus 2.0 body scans per year, $p = 0.0016$; 1.1 versus 0.4 brain scans per year, $p < 0.0001$). Significance was not changed when controlling for age, gender, histology, and type of trial.

Relapses and Survival

Up to the time of detection of first relapse, a total of 388 and 166 cross-sectional imaging studies were performed in the trial and nontrial patients, respectively ($p = 0.09$) (Table 4, Figure 1). In total, 45 relapses were detected (41 recurrences and four metachronous primary tumors) in 44 (61% at 5 years) patients. As shown in Figure 1, 24 recurrences and three metachronous primary tumors were detected in 26 trial

TABLE 2. Clinical Characteristics

	Trial ($n = 40$) %	Nontrial ($n = 35$) %	Total ($n = 75$) %	p
Median age, yr	60.5	60	60	0.83
Gender				
Female	15 (37)	15 (43)	30	
Male	25 (63)	20 (57)	45	0.64
Median duration of follow-up, mo				
Alive patients	77	44	58	0.0002
All patients	48	33	36	
Stage*				
IIB	7 (18)	6 (17)	13	0.63
IIIA	30 (75)	24 (69)	54	
IIIB	3 (7)	5 (14)	8	
Histology				
Adenocarcinoma	16 (40)	16 (46)	33	
Squamous carcinoma	15 (37)	13 (37)	28	0.70
Large cell carcinoma	4 (10)	2 (6)	6	
Adenosquamous carcinoma	1 (3)	1 (3)	2	
Undifferentiated	4 (10)	3 (8)	7	
Treatment				
CT/RT and surgery	26 (65)	20 (57)	46	
CT/RT alone	14 (35)	15 (43)	29	
Postinduction CT	30 (75)	18 (51)	48	
Boost CT/RT	4 (10)	2 (6)	6	

Percentages are calculated for each of the trial and nontrial groups.
*Clinical stage before treatment.
CT, chemotherapy; RT, radiotherapy.

TABLE 3. Comparison of Frequency of Follow-up Visits, Blood Tests, and Radiologic Examinations per Patient

	Trial	Nontrial	p
0–2 yr of follow-up (n = 75)			
Average no. of visits per year	4.6	4.6	0.91
Average no. of CXRs per year	4.4	3.9	0.14
Average no. of lab tests per year	3.6	2.4	0.013
Average no. of brain scans per year	1.1	0.4	<0.0001
Average no. of body CT scans per year*	2.9	2.0	0.0016
2–5 yr of follow-up (n = 48)			
Average no. of visits per year	3.0	3.2	0.54
Average no. of CXRs per year	2.6	2.6	0.83
Average no. of lab tests per year	2.3	1.7	0.27
Average no. of brain scans per year	0.8	0.5	0.04
Average no. of body CT scans per year*	2.0	1.5	0.11
>5 yr of follow-up (n = 18)			
Average no. of visits per year	2.1	2.4	0.66
Average no. of CXRs per year	2.0	1.5	0.56
Average no. of lab tests per year	1.3	1.8	0.56
Average no. of brain scans per year	0.04	0.3	0.17
Average no. of body CT scans per year*	0.8	1.2	0.41

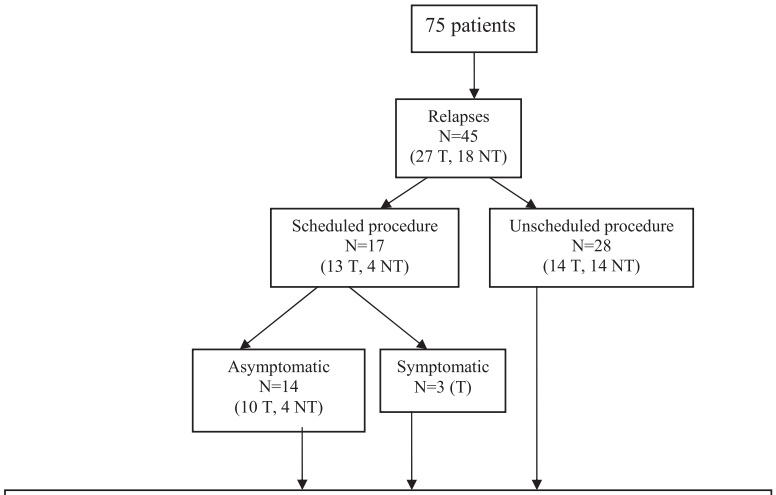
*Body scans usually comprised computed tomography of the chest, upper abdomen, and occasionally the pelvis. For the purposes of this analysis, they are counted as separate examinations to reflect the practice of separate billing and reporting. CXRs, chest radiographs; CT, computed tomography.

TABLE 4. Summary of Scans Performed and Scan Results up to and Including the Detection of First Relapse

	Trial Patients			Nontrial Patients			
Relapses	**No. of Scans**	**No. Showing Relapse**	**%**	**No. of Scans**	**No. Showing Relapse**	**%**	***p***
All cross-sectional imaging	388	35	11	166	25	18	0.092
Brain imaging	94	10	13	19	9	50	0.0062
Body imaging	294	25	10	147	16	12	0.46

patients (63% at 5 years) and 17 recurrences and one metachronous tumor in 18 nontrial patients (60% at 5 years, Figure 2). Twenty-eight of the 44 patients with relapse (64%) sought medical attention that led to the detection of relapse before a scheduled appointment or procedure (14 trial patients and 14 nontrial patients). In fact, trial patients were as likely to have relapse detected with an unscheduled procedure as with routine study protocol tests (14 versus 13 relapses).

A total of 454 biochemical investigations were performed up to and including the time of relapse. Fifty-six (12.3%) were abnormal, with no other evidence of relapse. In contrast, in the 44 patients with confirmed relapse, biochemistry was normal in 39 (88.6%) and suspicious in five (11.4%) at the time of relapse. There was no patient in whom abnormal biochemistry was the sole presenting feature of relapse. CT scans of the abdomen were usually confined to the upper



Physical examination or CXR	1 Trial 4 Non-trial	- -	12 Trial 6 Non-trial	13 (48%) 10 (56%)
CT chest	5 Trial -	3 Trial -	7 Trial 12 Non-trial	15 (56%) 12 (67%)
CT abdomen	- -	3 Trial -	8 Trial 4 Non-trial	10 (37%) 4 (22%)
CT or MRI brain	4 Trial -	- -	5 Trial 7 Non-trial	9 (33%) 7 (39%)
Other radiological investigation	- -	- -	2 Trial 2 Non-trial	2 (7%) 2 (11%)
Isolated thoracic local recurrence	1 Trial 1 Non-trial	1 Trial -	2 Trial 1 Non-trial	4 2
Treated with curative intent	1 Trial -	1 Trial -	- -	2 0
Metachronous primary tumor	3 Trial -	- -	- 1 Non-trial	3 1
Treated with curative intent	3 Trial -	- -	- -	3 -
Isolated brain metastases	4 Trial -	- -	4 Trial 5 Non-trial	8 5
Treated with curative intent	4 Trial -	- -	3 Trial 2 non-trial	7 2

Other radiological investigation included bone scan and CT neck

FIGURE 1. Detection of relapses and metachronous primary tumors for both the trial (T) and nontrial (NT) patients. Scheduled procedures include physical examination and chest radiograph (CXR), which detected the asymptomatic relapses in the nontrial group. Other radiologic investigations included bone scan and computed tomography (CT) of the neck.

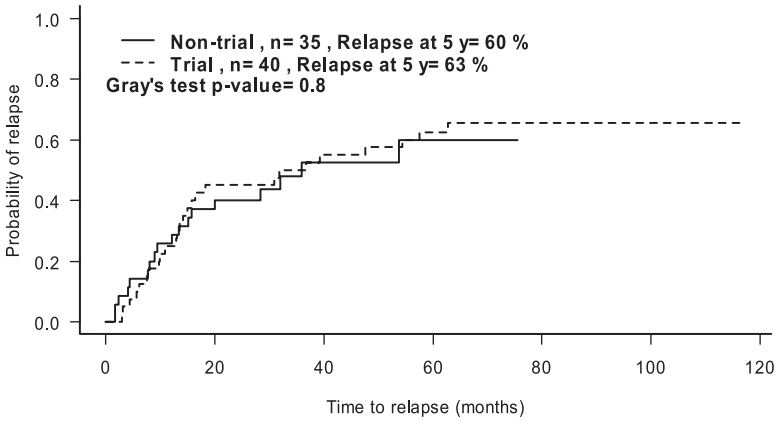


FIGURE 2. Comparison of time to development of relapse or second primary tumor in trial and nontrial patients.

abdomen to cover the liver and adrenal glands. However, 39 pelvic CT scans were also performed in some patients. Only one demonstrated pelvic lymphadenopathy in a patient with widespread metastases that were detected on the upper abdominal scan as well.

As can be seen in Figure 2, there was no significant difference in the time to disease relapse or second primary tumor in trial and nontrial patients ($p = 0.80$). Thoracic recurrence was infrequent, occurring in only 19% of patients with adenocarcinoma and 15% of patients with squamous carcinoma (Figure 3A). In contrast, extrathoracic relapse (Figure 3B) was significantly more frequent in patients with adenocarcinoma (adenocarcinoma 51% versus squamous 17% at 5 years, $p = 0.003$).

Treatment at the Time of Relapse or Second Primary

There was no significant difference in management of relapses detected by symptoms or routine scans. In the trial group, there were three asymptomatic metachronous tumors, all treated with curative intent. One lung cancer was detected by routine CXR; the patient was treated surgically and is still

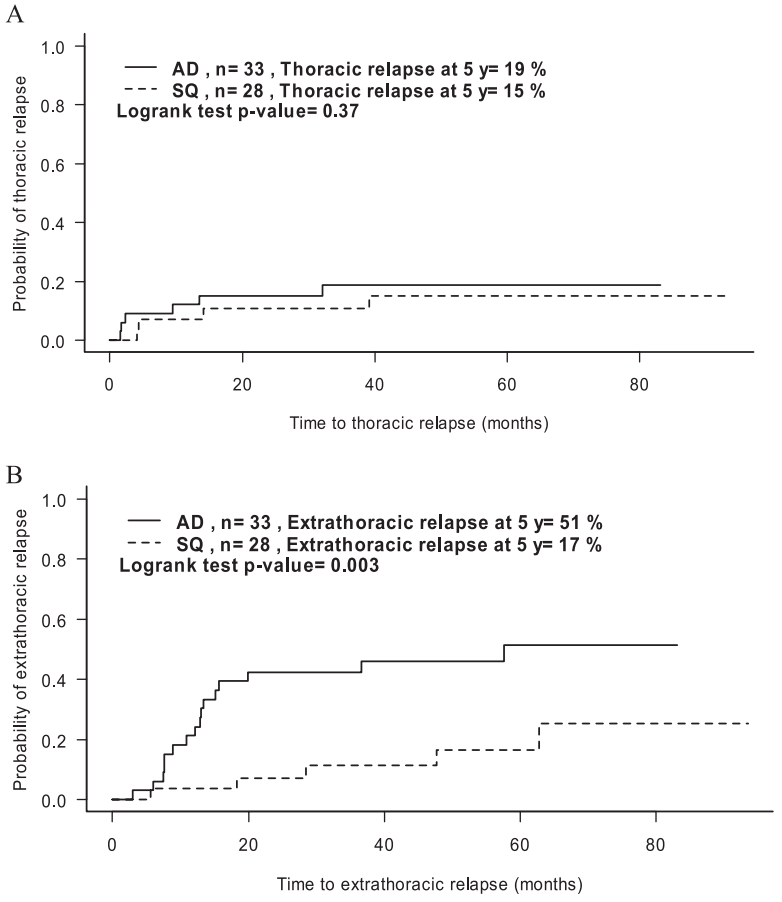


FIGURE 3. Interval between end of treatment and intrathoracic (*A*) and extrathoracic (*B*) relapse, according to histology. AD, adenocarcinoma; SQ, squamous carcinoma.

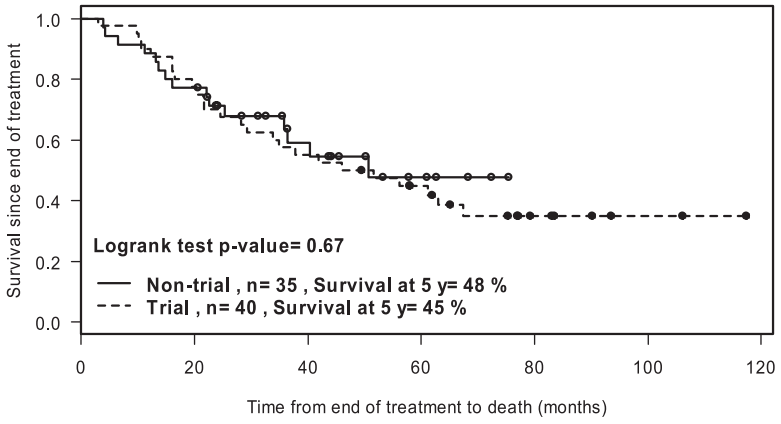


FIGURE 4. A comparison of survival for trial and nontrial patients from the start of the follow-up period at the completion of definitive treatment.

alive 3 years later. Lung and esophageal cancers were detected by routine CT scans, with the patients surviving 28 and 20 months, respectively, following treatment. One nontrial patient, who initially underwent pneumonectomy, had a metachronous symptomatic lung carcinoma that was treated palliatively with chemoradiotherapy.

Isolated local thoracic recurrence was only detected in six (14%) patients (Figure 1), of which only two trial patients could be treated with curative intent. One asymptomatic patient underwent a completion pneumonectomy, but died 4 months later from disseminated metastatic disease; the other patient was symptomatic, underwent completion pneumonectomy, and is still alive 2 years later. These numbers are too small to permit further statistical analysis.

Thirteen patients developed isolated brain metastases. Four of eight trial patients were asymptomatic, with solitary brain metastases, and all underwent treatment with curative intent. A further five symptomatic patients with solitary metastases also underwent attempted curative therapy (three trial and two nontrial patients). Median survivals were 24.8 and 21.9 months for brain metastases detected routinely and symptomatically, respectively.

Overall, 23 patients had localized relapses (Figure 1), but only 15 of these could be treated with curative intent (12 of 15 trial patients and three of eight nontrial patients). Despite the trial group demonstrating a higher number of asymptomatic relapses and being offered potentially curative therapy more frequently, there was no significant difference in the length of survival between trial and nontrial patients (Figure 4).

Similarly, there was no difference in survival from the time of relapse or second primary ($p = 0.13$). Although patients who were asymptomatic at the time relapse was detected (by routine scanning) appeared to survive longer than symptomatic patients, they were identified significantly sooner after the end of treatment ($p = 0.037$) in keeping with lead time bias (Figure 5) and their overall survival from the date of completion of therapy was not longer than that of symptomatic patients.

DISCUSSION

Follow-up of patients with NSCLC is aimed at early detection of relapse or metachronous primary tumors and management of treatment-related complications. However, the early detection of relapse or second primary cancer should, in and of itself, not be a primary end point if potentially curative therapy is not available. Thus, a more rigorous end point for follow-up studies would be overall survival. Most studies have concentrated on examining methods of follow-up in early-stage resected NSCLC,[10] whereas the issues surrounding locally advanced lung cancer are more complex. Relapse rates are much higher in this group of patients, although the pattern of relapse tends to be similar with the majority of relapses being systemic and frequently multiple. This suggests that for the majority of patients, curative therapy at the time of relapse will not be an option.

Westeel et al.[11] followed 192 patients intensively with cross-sectional imaging following complete resection of NSCLC. Median survival was 24 months from the date of operation and 7 months from the date of relapse. They showed no difference in disease-free interval between asymptomatic and symptomatic patients, although they reported significantly longer survival in patients who were asymptomatic at the time of recurrence. They concluded that intensive follow-up with CT and bronchoscopy prolongs survival. Our study does not support these findings and in fact suggests a lead-time bias, with no significant difference in overall survival between intensive routine CT scanning and symptom-driven investigation. However, all our patients had locally advanced disease compared with only 36% of the patients of Westeel et al., and our study population was small.

The results of our study are similar to those of Walsh et al.,[12] who assessed the development of relapse or second primary tumor in 358 patients who had undergone surgical resection for lung cancer. Of this group, 111 had locally advanced disease and 55% of this subgroup relapsed. Nearly half of the patients with a symptomatic relapse sought medical attention before a scheduled appointment. They concluded that regular monitoring does not appear to be cost-effective and that patients whose relapse was detected asymptomatically had no overall survival advantage but were diagnosed earlier, suggesting lead-time bias. This finding is confirmed by our data. Lamont et al.[13] followed 124 patients with resected lung cancer with annual CT scans of the chest and concluded that second lung cancers may be amenable to

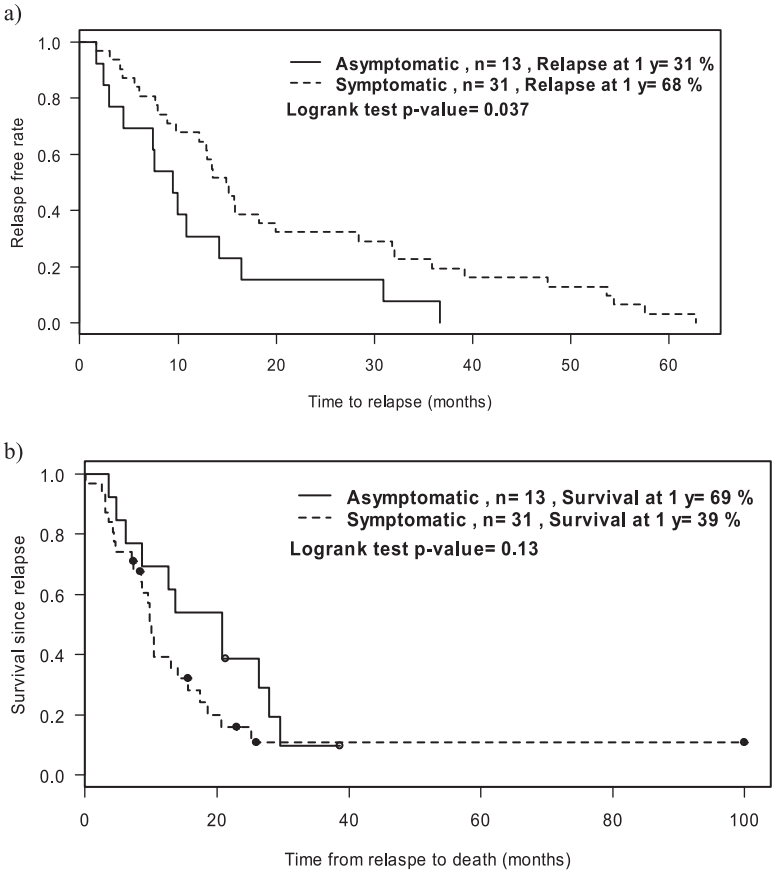


FIGURE 5. A comparison of interval between the end of treatment and relapse (*a*) and survival since relapse (*b*) in symptomatic and asymptomatic patients.

surgery, but local recurrence has a poor prognosis, as confirmed by our study.

Although some patients may be reassured by intensive follow-up, many experience significant anxiety. The impact of awaiting test results or investigating false-positive findings must be taken into account. Given that nearly two thirds of patients developed symptoms between scheduled appointments and investigations, this suggests that the current follow-up regimens are suboptimal. All our patients were followed by their cancer specialists, the cost effectiveness of which has been questioned.[14,15] Moore et al.[16] have suggested that nurse practitioner follow-up results in fewer investigations yet similar survival and is preferred by many patients.

Our trial patients were followed with standard dose CT. Low-dose CT (LDCT) has shown promise in the context of screening for lung cancer,[17] although it has a high false-positive rate. LDCT has not been studied extensively as a follow-up tool, although one small prospective study[18] showed that regular LDCT of the thorax is effective in detecting recurrence after attempted curative resection of NSCLC. However, the impact of this on survival is unknown. Our hospital currently is comparing LDCT with CXR follow-up in a cohort of completely resected patients with NSCLC.

In our study, 13 (29%) patients relapsed first in the brain, and four of these patients were asymptomatic. Yokoi et al.[19] performed frequent follow-up CT brain examinations in 128 patients following surgical resection for lung cancer. Seven of 11 relapses were asymptomatic (the majority being in patients with stage IIIA disease). They noted a marked difference in median survival in the asymptomatic group. We observed no significant difference in survival between asymptomatic and symptomatic relapses in the brain or in other organs, but the numbers of patients are small and the INT 0160 and INT 0139 follow-up regimens were less intensive than those of Yokoi et al. Five of nine trial patients presented with symptomatic brain metastases between scheduled scans. Carolan et al.[20] found that in patients with advanced NSCLC, the brain was the first site of relapse in 18%, but in patients younger than 60, the risk of relapse was 25%. Our incidence of brain relapse in this study is at the higher end of quoted figures, which may reflect the relatively young study population, the advanced local stage of disease, and also early detection of asymptomatic metastases. The high rate of brain relapse in patients with stage III NSCLC has prompted a prospective, randomized trial of prophylactic cranial irradiation versus observation alone in this population. The trial is open in Europe and North America and should be supported vigorously. It is unknown what impact follow-up with MRI scans of the brain may have on survival, as this is now considered the accepted standard of diagnostic test.

It is well known that patients with previously treated NSCLC are at an increased risk of developing second primary tumors, most commonly in the aerodigestive tract and pub-

lished data suggest less than 20% 5 year survival.[21,22] Intensive follow-up with CT may detect new lung cancers at a stage when they are amenable to surgery, but the impact on outcome is unknown.[18,23] Four new primary tumors were detected (5% of patients) in our study, three of which were treated with curative intent. This is a lower figure than some studies suggest,[13] but this may reflect the higher recurrence rate and overall poorer survival in the context of locally advanced lung cancer.

At present, there is no good evidence to advocate the use of cross-sectional imaging as a screening tool in the follow-up of NSCLC, and this lack of data is reflected in the varying guidelines on best follow-up practice (Table 5). Patients who have undergone radiotherapy rarely have a normal CXR or CT post-treatment. Although filling in of radiation-induced bronchiectatic change on CT may be indicative of local recurrence,[27] CXR and CT cannot reliably distinguish necrotic tumor or fibrous scar tissue from residual tumor, with sensitivity and specificity for CT being 67%–77% and 85%, respectively.[28,29] In patients with previously treated lung cancer, the sensitivity and specificity of PET for detecting relapse range from 70% to 100% and 67% to 97%, respectively, even in asymptomatic patients.[30–32] In patients with suspected relapse, CT seems poor at accurately assigning extent of relapse when compared with PET (24% versus 86%).[33] CT underestimated disease extent in 37% patients, which is important when considering potentially curative salvage therapy. However, increased uptake on PET can be seen following radiotherapy for up to 6 months.[30] All six patients in our series with local thoracic recurrence had histologic confirmation. Unfortunately, PET was not available in our institution, and we are therefore not able to determine what impact this would have had on timing of detection of relapse, treatment, or survival.

Sixty-four percent of our patients developed symptoms between scheduled visits. Although from our data it appears that several relapses were detected at routine appointments, if patients have a scheduled appointment in the near future, they may wait rather than presenting acutely with symptoms. This is a potential source of bias, and the proportion of patients developing symptoms of recurrence between visits may, in fact, be even higher. In no case did blood biochemistry alone detect relapse.

There are limitations to this study, namely, the small population size, and consequently there are wide confidence intervals for survival data. Although all patients had locally advanced disease, they comprised a heterogeneous population. However, we still demonstrated a significant difference in frequency of cross-sectional imaging after controlling for trial type and therefore also disease stage.

In summary, our results suggest that in patients with locally advanced NSCLC, routine blood tests are noncontributory and routine frequent cross-sectional imaging does not alter survival after definitive combined modality therapy because few patients relapse with curable disease.

TABLE 5. Summary of Follow-up Guidelines in Locally Advanced Lung Cancer

		Follow-up Recommendations			
		Post-Chemoradiotherapy		Post-Chemoradiotherapy and Surgery	
Guideline	**Stage**	**Clinical Follow-up**	**Radiologic Follow-up**	**Clinical Follow-up**	**Radiologic Follow-up**
American College of Radiology Appropriateness criteria, 2000[24]	IIIA	Every 2–4 mo for 2 yr; every 6 mo to 5 yr; yearly thereafter	CXR every 6 mo for 5 yr then yearly for life. Routine cross-sectional imaging not recommended until more effective salvage therapy is developed	Every 2–4 mo for 2 yr; every 6 mo to 5 yr; yearly thereafter	CXR every 6 mo for 5 yr then yearly for life. CT may replace CXR in high-risk patients
American Society of Clinical Oncology guidelines for unresectable NSCLC, 2003[5]	Nonresectable	Every 3 mo for 2 yr; every 6 mo to 5 yr; yearly thereafter	Yearly CXR may be reasonable to detect 2nd lung cancers. Cross-sectional studies should only be performed as indicated by the patient's symptoms	n/a	n/a
National Institute of Clinical Excellence of the United Kingdom, 2005[25]	Advanced	Every 1–2 mo for 6 mo		For 6 mo to check for postop complications	
National Comprehensive Cancer network clinical practice guidelines, 2006[26]		Every 4 mo for 2 yr; every 6 mo to 5 yr; annually thereafter			CXR as clinical follow up. CT chest 4–6 mo postop as baseline then annually

CXR, chest radiograph; NSCLC, non-small cell lung cancer; n/a, not available; CT, computed tomography.

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