Does the method of radiologic surveillance affect survival after resection of stage I non–small cell lung cancer?

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Objectives: Controversy persists regarding appropriate radiographic surveillance strategies after lung cancer resection. We compared the impact of surveillance computed tomography scan versus chest radiography in patients who underwent resection for stage I lung cancer.

Methods: A retrospective analysis was performed of all patients undergoing resection for pathologic stage I lung cancer from January 2000 to April 2013. After resection, follow-up included routine history and physical examination in conjunction with chest radiography or computed tomography at the discretion of the treating physician. Identification of successive lung malignancy (ie, recurrence at any new site or new primary) and survival were recorded.

Results: There were 554 evaluable patients, with 232 receiving routine postoperative computed tomography and 322 receiving routine chest radiography. Postoperative 5-year survival was 67.8% in the computed tomography group versus 74.8% in the chest radiography group ($P = .603$). Successive lung malignancy was found in 27% (63/232) of patients receiving computed tomography versus 22% (72/322) receiving chest radiography ($P = .19$). The mean time from surgery to diagnosis of successive malignancy was 1.93 years for computed tomography versus 2.56 years for chest radiography ($P = .046$). For the computed tomography group, 41% (26/63) of successive malignancies were treated with curative intent versus 40% (29/72) in the chest radiography group ($P = .639$). Cox proportional hazard analysis indicated imaging modality (computed tomography vs chest radiography) was not associated with survival ($P = .958$).

Conclusions: Surveillance computed tomography may result in earlier diagnosis of successive malignancy versus chest radiography in stage I lung cancer, although no difference in survival was demonstrated. A randomized trial would help determine the impact of postoperative surveillance strategies on survival. (*J Thorac Cardiovasc Surg* 2015;149:45-53)

See related commentary on pages 53-4.

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Currently, there is no consensus on the optimal method of radiographic follow-up after resection of stage I non–small cell lung cancer (NSCLC). Patients undergoing resection for pathologic stage I NSCLC are still at risk of developing recurrence and¹⁻⁴ developing a new primary lung cancer at an estimated rate of 1 to 6 cases per 100 person-years.⁵⁻⁹ The risk of identifying lung cancer in a high-risk group of smokers in the National Lung Screening Trial (NLST) was approximately 0.6% per person-year.¹⁰ Because of the substantial combined risk of recurrence and development of new primary lung cancers, multiple guidelines have been recommended for routine postoperative radiographic surveillance after resection for NSCLC (Table E1).^{9,11-13}

Recently published results from the NLST demonstrated that routine low-dose computed tomography (CT) scans of patients at high risk for developing a first primary lung cancer offered a lung cancer–specific survival benefit compared with routine chest radiograph. However, it is unclear what impact radiographic surveillance will have on survivors of resected NSCLC, who are subject to competing risks of recurrence and new primary lung cancer.

Abbreviations and Acronyms

CONSORT	= Consolidated Standards of Reporting Trials
CT	= computed tomography
CXR	= chest x-ray
NLST	= National Lung Screening Trial
NSCLC	= non-small cell lung cancer
PET	= positron emission tomography

Although CT has evolved as the standard for routine postoperative surveillance, there remains a paucity of data demonstrating a distinct survival advantage for CT over less-expensive imaging follow-up. A recent single-arm prospective trial suggested that minimal-dose CT may be beneficial in the postoperative surveillance of patients with stage I to III NSCLC.¹⁴ Historically, however, routine postoperative CT surveillance has resulted in inconsistent results regarding earlier detection of recurrence or new primary lung cancer, with no conclusive evidence of improvement in survival (Table E2).^{4-6,14-20}

We performed a comparison of recurrence patterns and survival of patients with resected stage I NSCLC who underwent routine CT versus chest x-ray (CXR) for postoperative surveillance. Our objective was to determine whether routine CT imaging led to earlier diagnosis of recurrence or new primary lung cancer and, if so, whether early detection translated into a survival benefit. Our primary hypothesis was that CT surveillance would result in earlier detection and secondarily that earlier detection would increase survival.

PATIENTS AND METHODS

All patients treated for pathologic stage I (T1-T2a N0 M0) NSCLC by pulmonary resection between January 2000 and April 2013 at Barnes-Jewish Hospital were identified from a prospective database and retrospectively analyzed in accordance with a protocol approved by the institutional review board at the Washington University School of Medicine. Patients were staged using the seventh edition of the lung cancer TNM staging system. Initial exclusion criteria included (1) malignancy within 5 years before resection (except squamous and basal cell skin carcinoma or carcinoma in situ) or a patient with contralateral nodules at the time of resection of the index lesion; (2) induction therapy; (3) incomplete resection; (4) missing surveillance records; (5) variability in surveillance imaging modality; (6) clinically detected recurrence before initiation of surveillance; (7) death before initiation of surveillance; and (8) age less than 18 years. Figure E1 shows a Consolidated Standards of Reporting Trials (CONSORT) diagram of the patient selection.

Surveillance

Each patient had an initial postoperative visit with the treating surgeon, consisting of a physical examination and a CXR, 2 to 4 weeks after resection. Subsequently, patients were followed by routine visits that consisted of a thorough history and physical examination and either CXR or CT scan. The imaging modality was chosen at the discretion of the treating physician. Certain surgeons consistently used CXRs for

surveillance, whereas others initially used CXR and then transitioned to regimens that included a mixture of CXRs and CT or CT only. Some surgeons who used CT initially transitioned to a combination of CXR and CT. Surgeon "intent" could not be reliably determined for this subset of patients; thus, they were not included in the final analysis. In a separate analysis, there was no association between the treating surgeon and the overall survival (Figure E2). CXRs tended to be used more in the early period of this study. The mean date of resection for patients undergoing routine CT surveillance was May 15, 2009, and June 1, 2005, for CXR ($P < .001$). CT scans included sections of the thorax and upper abdomen (including liver and adrenal glands) and were done with or without contrast, although the default was low-dose noncontrast CT. Generally, the standard follow-up regimen included a baseline CT scan approximately 3 months after resection, with follow-up imaging every 6 months for the first 2 to 3 years and then annually thereafter for at least 5 years. Standard CT technique included 5-mm contiguous sections until 2009 and 3-mm contiguous sections thereafter. Surveillance was defined as routine follow-up of asymptomatic patients after the initial postoperative visit for screening for recurrence or new primary lung cancer. For this study, patients were categorized in the CT group if they had routine CT scans or in the CXR group if they had routine CXR for surveillance. To minimize heterogeneity of follow-up, patients were excluded from the study if (1) the modality of their surveillance imaging switched because of changes in attending physician or in surveillance protocol for reasons not related to suspicion of recurrence; (2) they alternated between CXR and CT; or (3) they had routine positron emission tomography (PET) scans. False-positive surveillance scans resulting in invasive procedures, including bronchoscopy, needle biopsy, and surgical resection, were noted.

Patient and Surveillance Characteristics

There were 1140 patients who underwent resection for pathologic stage I lung cancer. Of these, 586 patients were excluded for malignancy within the previous 5 years ($n = 217$), induction therapy ($n = 21$), incomplete resection ($n = 16$), missing surveillance records, including those who followed up with an outside physician without accessible records ($n = 163$), inconsistency in imaging modality used for surveillance or routine PET imaging ($n = 149$), recurrence before initiation of surveillance ($n = 7$), expiration before initiation of surveillance ($n = 12$), and age less than 18 years of age at the time of treatment ($n = 1$). Of the 149 patients excluded for inconsistency in imaging method, 123 switched the method because of a change in follow-up physician or protocol, 22 alternated between CT and CXR surveillance, 3 had routine CXR surveillance but had their successive malignancy detected by imaging obtained for unrelated issues, and 1 had routine PET imaging.

Among the 554 patients included, 232 underwent routine surveillance with CT and 322 underwent routine surveillance with CXR (Table 1). The median duration of follow-up was 2.5 years (range, 0.3-9.9 years) for the CT group and 3.5 years (range, 0.1-13.1 years) for the CXR group. There were no significant differences between the groups in most baseline characteristics, with the exception of pathologic T stage of index tumor, type of surgical resection, and adjuvant therapy (Table 1).

Successive Malignancy and Survival

Successive malignancy was defined as recurrence or new primary lung cancer. The Martini and Melamed's criteria³ were used to identify new primary lung cancers as lesions that were (1) of different histology than the index cancer; (2) found in a different lobe, with no evidence of extrapulmonary or lymphatic metastasis; or (3) found at least 2 years after the index cancer. Successive malignancies were categorized according to whether they were detected during a scheduled or unscheduled visit, the presence of relevant symptoms at time of detection, and the imaging modality responsible for detection. Relevant symptoms included dyspnea or cough, pleuritic chest pain, hemoptysis, pneumonia, pneumothorax, hoarseness, weight loss, musculoskeletal pain, subcutaneous mass or

TABLE 1. Baseline characteristics and mean number of follow-up imaging performed for computed tomography and chest x-ray groups

Characteristic	CT (n = 232)	CXR (n = 322)	P value
Male gender	101 (44%)	121 (38%)	.158
Caucasian race	211 (91%)	283 (88%)	.253
Age (mean ± SD)	65 ± 11	66 ± 11	.346
Charlson index (preoperative) (mean ± SD)	0.91 ± 0.94	0.91 ± 1.08	.927
Tumor size (cm) (mean ± SD)	2.3 ± 1.1	2.4 ± 1.1	.332
T2a tumor	94 (41%)	103 (32%)	.039
Tumor histology			.366
Adenocarcinoma	128 (55%)	159 (49%)	
Bronchoalveolar	24 (10%)	28 (9%)	
Squamous	41 (18%)	69 (21%)	
Adenosquamous	5 (2%)	8 (2%)	
Carcinoid	20 (9%)	43 (13%)	
Other or mixed	14 (6%)	15 (5%)	
Resection procedure			.002
Wedge	46 (20%)	27 (8%)	
Segmentectomy	17 (7%)	19 (6%)	
Lobectomy	152 (66%)	260 (81%)	
Sleeve	7 (3%)	6 (2%)	
Bilobectomy	4 (2%)	4 (1%)	
Wedge and lobectomy	5 (2%)	3 (1%)	
Pneumonectomy	1 (0.4%)	3 (1%)	
Adjuvant therapy	48 (21%)	11 (3%)	<.001
Chemotherapy	39 (17%)	7 (2%)	
Radiation	8 (3%)	3 (1%)	
Chemoradiation	1 (0.4%)	1 (0.3%)	
No. of follow-up CT or CXR per year (mean ± SD)			
First year	1.74 ± 0.81	2.12 ± 0.86	<.001
Second year	1.74 ± 0.83	1.66 ± 0.72	.310
After second year	1.34 ± 0.55	1.25 ± 0.47	.122
Overall	1.56 ± 0.51	1.58 ± 0.56	.605

CT, Computed tomography; CXR, chest x-ray; SD, standard deviation.

swelling, or neurologic changes. Also included were all new-onset symptoms noted in the records by the physician as suspicious for recurrence or warranting further imaging and symptoms that prompted an unscheduled visit in which recurrence or new primary was subsequently diagnosed. For treatment of successive malignancies, therapy was defined as “curative intent” when it included surgical resection or stereotactic radiation therapy for a localized pulmonary lesion or solitary brain or adrenal metastasis, or definitive chemoradiation for locoregional disease, such as an isolated recurrence in mediastinal lymph nodes. “Palliative therapy” was defined as chemotherapy alone, radiation therapy for symptom management, or pain management.

Overall survival was defined as starting from the date of resection for the index lung cancer and ending on the date of expiration or censored at date of last observation of follow-up. For cancer-specific survival, all deaths were reviewed and cause of death was determined by the authors (TDC and SBC). Time to diagnosis of successive malignancy was defined as starting from the date of resection for the index lung cancer and ending on the date of diagnosis of successive malignancy.

Statistical Analysis

Means for parametric continuous data were compared using *t* tests. Counts and proportions for categorical data were compared using

TABLE 2. Characteristics of successive malignancies diagnosed during follow-up

Characteristic	CT (n = 63)	CXR (n = 72)	P value
Type			.275
New primary	14 (22%)	22 (31%)	
Recurrence	49 (78%)	50 (69%)	
Region			.187
Extrathoracic	16 (25%)	10 (14%)	
Thoracic	41 (65%)	51 (71%)	
Both	6 (10%)	11 (15%)	
Location			.295
Local	3 (5%)	4 (6%)	
Regional	11 (17%)	14 (19%)	
Distant	34 (54%)	36 (50%)	
Local and regional	5 (8%)	1 (1%)	
Local and distant	1 (2%)	0	
Regional and distant	9 (14%)	17 (24%)	
Symptomatic at time of detection	32 (51%)	58 (81%)	<.001
Detected during scheduled surveillance	46 (73%)	33 (46%)	.001
Treatment			.670
Curative	26 (41%)	29 (40%)	
Palliative	29 (46%)	37 (51%)	
Refused	0	1 (1%)	
None	1 (1%)	1 (1%)	
Unknown	7 (11%)	4 (6%)	

CT, Computed tomography; CXR, chest x-ray.

chi-square tests. Overall and cancer-specific survival curves were constructed using the Kaplan–Meier method and compared using log-rank tests. Multivariate analysis of prognostic effect of covariates on overall and cancer-specific survival was performed using Cox proportional hazard analysis. To account for potentially confounding covariates and imbalance between the CT and CXR groups with respect to resection procedure and tumor T-stage, propensity score matching using the nearest-neighbor caliper method was carried out to match the CT and CXR groups on the basis of covariates of age, perioperative Charlson comorbidity index, sublobar resection, T-stage of index tumor, and adjuvant therapy with a caliper radius of 0.03 of the logit of the standard deviation of the propensity score. All statistical tests were 2-sided. Analyses were conducted using SPSS version 21.0 (IBM, Armonk, NY). Propensity score matching was performed using the Propensity Score Matching for SPSS plug-in, version 3.0 (Felix Thoemmes, Cornell University, Ithaca, NY).

RESULTS
Successive Malignancies

Recurrence or new primary lung cancer was found in 24% (135/554) of patients (Table 2). Overall, successive malignancy was found in 27% (63/232) in the CT group and 22% (72/322) in the CXR group (*P* = .195). The rate of successive malignancy was 10.7% per person-year for CT and 6.3% per person-year for CXR (*P* = .002). The majority of successive malignancies had thoracic manifestation. The rate of new primary lung cancers overall was 2.1% per person-year. In the CT group, 9 of 232 patients (4%) had false-positive surveillance imaging that

FIGURE 1. A-C, Kaplan-Meier curves for overall survival, cancer-specific survival, and time to diagnosis of relapse. CT, Computed tomography; CXR, chest x-ray.

resulted in an invasive diagnostic procedure (bronchoscopy, biopsy, or surgery) versus 1 of 322 patients (0.3%) in the CXR group ($P = .002$). Among patients developing successive malignancy, 49% (31/63) in the CT group were asymptomatic at presentation versus 19% (14/72) in the CXR group ($P < .001$).

Among patients with successive malignancy, time to diagnosis was shorter for the CT group ($P = .046$) (Figure 1), with mean times of 1.93 versus 2.56 years for CXR and median times of 1.56 versus 1.63 years for CXR (95% CI, 1.29-1.83 vs 1.03-2.23).

Survival

In unmatched analysis, overall survival was similar between the groups, with 5-year survival of 67.8% for CT versus 74.8% for CXR (mean survival, 7.00 vs 9.19 years; median survival, 7.63 years vs not reached; $P = .603$) (Figure 1) (95% CI, 5.78-9.48). Five-year cancer-specific survival was 74.1% for CT versus 85.5% for CXR ($P = .032$) (Figure 1). Among patients with successive malignancy, there was no difference in overall survival, with 5-year survival of 33.5% for CT and 40.2% for

CXR (mean, 4.24 vs 5.34 years; median, 3.96 vs 3.47 years; $P = .843$) (95% CI, 2.71-5.21 vs 2.72-4.22). Among patients with successive malignancy, cancer-specific survival was similar, with 5-year survival of 39.1% for CT and 50.7% for CXR (mean, 4.47 vs 6.51 years; median, 4.44 vs 5.70 years; $P = .353$) (95% CI, 3.33-5.54 vs 3.47-7.93). These results were unchanged if survival was measured from date of diagnosis of successive malignancy.

Multivariate Analysis and Propensity Matching

In a Cox proportional hazard model, modality of surveillance imaging was not associated with survival ($P = .958$), and only age, Charlson comorbidity index, and type of resection (sublobar vs nonsublobar resection) were associated with survival (Table 3). Identical results were seen in a model for cancer-specific survival (Table E3).

By using a caliper-based method, 174 propensity-matched pairs were identified (Table E4). There was no significant difference in overall or cancer-specific survival between the groups. Time to diagnosis of successive malignancy trended toward being shorter for CT

TABLE 3. Regression analysis for overall survival

Covariate	Hazard ratio	95% CI	P value
Imaging (CXR vs CT)	0.988	0.629-1.551	.958
Age	1.051	1.029-1.073	<.001
Charlson index	1.359	1.151-1.605	<.001
Resection (sublobar vs nonsublobar)	2.577	1.614-4.115	<.001
Tumor T-stage (1 vs 2a)	0.862	0.510-1.456	.578
Tumor size	1.108	0.876-1.401	.393
Histology (non-BAC vs BAC)	1.581	0.812-3.077	.178
Adjuvant therapy (absent vs present)	0.691	0.389-1.226	.206
Gender (male vs female)	1.265	0.864-1.852	.227
Race (non-Caucasian vs Caucasian)	1.085	0.566-2.080	.806

BAC, Bronchioloalveolar carcinoma; CI, confidence interval; CT, computed tomography; CXR, chest x-ray.

(median, 1.60 vs 2.10 years for CXR) (95% CI, 1.23-1.96 vs 0.87-3.34; $P = .058$) (Figure 2).

There was no difference between groups in the proportion of successive malignancies that were treated with curative intent, accounting for 41% (26/63) in the CT group versus 40% (29/72) in the CXR group ($P = .907$) (Figure E3). Overall and cancer-specific

survivals were similar between groups when successive malignancy was treated with curative intent ($P = .369$) or when patients received palliative therapy ($P = .655$) (Figure E3). Overall and cancer-specific survivals were also similar between groups among patients developing new primary lung cancers.

In both groups, those given palliative treatment had shorter survival compared with patients given curative-intent treatment, with a median difference of 52 months (median survival, 2.64 vs 6.98 years; $P < .001$). Patients whose successive malignancy was detected during a scheduled follow-up visit had similar overall and cancer-specific survival versus those who presented outside of a scheduled follow-up. The difference between overall survival of patients with asymptomatic versus symptomatic presentation of successive malignancy trended toward statistical significance (mean, 5.41 vs 4.78 years; median, 4.98 vs 3.23 years; $P = .070$) (95% CI, 3.30-6.66 vs 2.45-4.00). However, asymptomatic patients were more likely to be offered curative-intent treatment compared with those presenting symptomatically (56% [25/45] vs 33% [30/90]; $P = .013$) and to have longer cancer-specific

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FIGURE 2. A-C, Kaplan-Meier curves for propensity-matched overall survival, cancer-specific survival, and time to diagnosis of relapse. CT, Computed tomography; CXR, chest x-ray.

survival (mean, 6.32 vs 5.45 years; median, 6.15 vs 3.47 years; $P = .019$) (95% CI, 4.88-7.42 vs 2.67-4.27).

DISCUSSION

Given significant variability in the risk of recurrence and treatment strategies for early-stage versus locally advanced NSCLC, we chose to examine the stage I population alone. These data demonstrate that for pathologic stage I NSCLC, surveillance with CT imaging was associated with earlier detection of successive malignancy compared with CXR imaging in the unmatched comparison with a similar trend in the propensity-matched comparison. Patients with successive malignancy who underwent CT were more likely to be diagnosed at an asymptomatic stage or at a scheduled follow-up visit than those who underwent CXR. Patients with asymptomatic successive malignancies were significantly more likely to receive curative-intent treatment compared with those presenting symptomatically. However, there was no demonstrable improvement in overall survival with CT surveillance versus CXR. Furthermore, despite the association between CT and the detection of asymptomatic successive malignancies, CT did not result in a greater likelihood of patients receiving curative-intent therapy. Thus, earlier identification of lesions by CT and identification of asymptomatic lesions did not result in a survival benefit in our cohort.

The appropriate modality and regimen for postoperative radiographic surveillance of patients after surgical resection for NSCLC remain unresolved. Although findings from the NLST trial indicate improved mortality with CT screening for a first primary lung cancer among high-risk smokers,¹⁰ it is unproven whether CT surveillance after resection for lung cancer improves mortality from a second lung cancer (Table E2). A primary goal of postoperative surveillance after lung resection is the early detection of new primary lung cancers, which have been shown to occur at a rate of 1% to 6% per person-year (with most studies reporting 1%-2% per person-year).⁵⁻⁹ Intuitively, the risk of developing a new primary lung cancer would seem higher among patients who have undergone resection for lung cancer compared with high-risk smokers without a history of lung cancer as represented in the NLST. The risk of new primary lung cancer is additive to the risk of recurrence in previously resected patients, and our data reinforce the lack of clarity in whether intensive surveillance improves survival of patients with recurrence, even with earlier detection.

Various studies have similarly examined the effectiveness of surveillance CT imaging of patients after resection for lung cancer. A widely cited rationale for the use of CT imaging in surveillance of patients with early-stage lung cancer is to detect new primary lung cancers early.^{5,6,11} In a study of patients in stage I and II undergoing CT surveillance after resection,⁵ scheduled CT scans detected

a majority of successive malignancies, consistent with our observation. Most series have demonstrated that the rate of new primary lung cancer development after cancer resection is 1% to 2% per person-year.⁶⁻⁹ Likewise, we observed a rate of new primary lung cancers of 2.1% per person-year for our patients with pathologic stage I NSCLC. Others have observed that the majority of second primary lung cancers were detected at stage I and treated by surgical resection.⁵ We demonstrated that new primary lung cancers were associated with significantly longer survival than recurrences. Furthermore, among patients diagnosed with new primaries, CT was not associated with significantly longer survival. Thus, it remains unclear whether surveillance CT imaging enhances the survival of patients who develop new primary lung cancers.

Hanna and colleagues¹⁴ studied a population with predominantly early-stage NSCLC (79% stage I) who underwent surveillance with simultaneous CXR and minimal-dose CT scans and found that minimal-dose CT resulted in improved sensitivity and negative predictive value versus CXR in the detection of successive malignancies. They demonstrated that patients whose successive malignancies were detected asymptotically had a markedly greater rate of curative-intent treatment compared with symptomatic patients and that those treated with curative intent had improved survival compared with those treated palliatively. We did not observe a significant difference in the rate of curative-intent treatment for the CT and CXR groups, even though CT surveillance was more likely to detect successive malignancies asymptotically. The minimal-dose CT evaluated by Hanna and colleagues¹⁴ results in less radiation exposure (0.2 mSv) but may be limited in the ability to delineate early subsolid adenocarcinomas or mediastinal recurrence. Our observations suggest that the efficacy of CT imaging in detecting successive malignancies asymptotically may not be a sufficiently reliable surrogate marker for assessing impact on treatment or survival.

The results of our study are consistent with those from earlier studies that have directly compared CT with radiograph follow-up regimens. Nakamura and colleagues¹⁷ reported similar survival for patients in stage I by using surveillance with CT and CXR versus CXR alone. Benamore and colleagues¹⁵ found that, for patients with stage IIB-III, follow-up with routine CT offered earlier detection of successive malignancy but did not result in improved survival versus CXR. Virgo and colleagues,¹⁸ comparing nonintensive and intensive follow-up that included more frequent CT imaging, found that intensive follow-up did not improve survival. Likewise, Younes and colleagues²⁰ observed that routine follow-up with CT and CXR did not improve survival compared with symptom-prompted follow-up.

Any survival advantage with CT surveillance must be considered in the context of cost-effectiveness and potential hazards of false-positive CT imaging that may result in unnecessary cost and patient morbidity. Postoperative CT imaging has been associated with a nontrivial false-positive rate of 50% for patients with stage I-IV disease.²¹ Hanna and colleagues¹⁴ found that the positive predictive value of minimal-dose CT was significantly lower than that of CXR for surveillance of patients with stage I-IV (25.1% vs 91.7%). Furthermore, reports have demonstrated that 4% to 5% of patients undergoing CT surveillance underwent invasive diagnostic procedures for false-positive imaging.^{5,21} The rate of false-positives necessitating invasive diagnostic procedures of 4% in our CT group was similar and was higher than in the CXR group. Therefore, the use of intensive CT screening carries a small but meaningful risk of unnecessary invasive procedures.

We certainly recognize the significant limitations of our study in its retrospective approach and the potential lack of power based on our cohort size to detect an actual survival difference. Because we sought to identify and compare patients who consistently received CXR or CT surveillance imaging, we had to exclude patients whose surveillance protocol was inconsistent in the imaging modality used for routine surveillance. The lack of difference in the rate of curative intent therapy may be related to a nonsignificant increase in the number of new primary cancers diagnosed in the CXR group versus the CT group given that the length of follow-up was longer for the CXR group, allowing for more time to diagnose new primary lesions. Our simple power calculation indicated that with a power of 80% and an alpha level of 5%, our sample size was sufficient to detect a 29% difference in median survival; differences less than 29% could not be detected. Given the limitations of our sample size, we have included sample size calculations for theoretic scenarios of surveillance trials in [Table E5](#). It was also not possible to assess whether the quality of life of patients was enhanced or diminished by earlier diagnosis of successive malignancies in the CT group. The ongoing IFCT-0302 trial,²² comparing follow-up using CXR versus CT and bronchoscopy, will help determine the survival benefits of intensive follow-up after resection.

CONCLUSIONS

Consistent with our primary hypothesis, our study suggests that for patients with stage I lung cancer treated by surgical resection, routine surveillance CT was associated with earlier diagnosis of recurrence or new primary lung cancer compared with routine CXR. However, this earlier diagnosis did not result in a demonstrable difference in treatment approach or overall survival. By recognizing the limitations of our study but

also acknowledging the consistency of our findings with the findings of others, we conclude that the appropriate imaging modality and regimen for surveillance remain unclear and unsubstantiated and recommend that a randomized controlled, multi-institutional prospective clinical trial be performed to help define the appropriate radiographic modality for surveillance after resection for lung cancer.

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Discussion

Dr Robert Korst (*Paramus, NJ*). The question of how to follow patients with lung cancer after potentially curative treatment remains unresolved but has recently begun to focus on the role of CT scanning in this capacity. This focus has been potentiated by the findings of the NLST, which demonstrated that screening CT saves lives in individuals who meet high-risk criteria.

Whether or not to use CT to follow patients after curative resection is a 2-part question: First, is it effective in detecting metachronous lung cancer, and, second, even if it is effective, does it enhance survival? Dr Crabtree and colleagues should be commended because they are attempting to address both of these questions in their study. Although an emerging body of literature has suggested that CT is a sensitive test for the detection of recurrent and new primary lung cancer in the surveillance setting, few studies have addressed the survival part of the question in detail.

Although the study is retrospective and perhaps somewhat underpowered, it is well carried out and the data are complete. In addition, when it was discovered that the CT and CXR groups were not identical with regard to tumor stage and type of resection, the authors used propensity score matching and a multivariate analysis to try and compensate.

I have 3 questions regarding the study. My first question has to do with the lack of a difference in survival between the 2 groups. This may be because there was no difference in the percent of patients offered curative-intent treatment between the 2 groups. It is intuitive that patients who are followed with CT will have their secondary disease picked up sooner, with more patients being asymptomatic, thereby allowing more attempts at curative resection or curative treatment. Although the first 2 of these were indeed demonstrated in this study, it didn't translate into more patients undergoing curative treatments. Why do you think this is? Could it be because the patients in the CXR group were more likely to have second primary cancers discovered or at least equally as likely to have second primary cancers discovered? I know it didn't reach statistical significance. Given that CT is more sensitive than CXR for detecting pulmonary nodules, how do you explain the fact that a greater proportion of patients, or at least as many patients, had second primary lung cancers in the CXR group compared with the CT group?

Dr Crabtree. Specifically to address that last question, we did attempt to look at the new primary lung cancers that were diagnosed as a subset, and the numbers get smaller, so it becomes harder to analyze. Patients in the CXR cohort were accrued earlier in the study with a median length of follow-up of 3.5 years versus 2.5 years for the CT group. There was a nonsignificant difference

in the overall rate of new primary lesions diagnosed, with more in the CXR group. Also, the median time to diagnosis of new primary lesions was longer in the CXR group versus CT (~3.7 vs 2.1 years). It is possible that the longer follow-up for the CXR group resulted in the identification of more new primary lesions. This may have contributed to the similar rates of curative intent treatment between the groups. Again, however, it could be a sample size issue. There were only 14 new primary lesions in the CT group and 22 in the CXR group.

Dr Korst. It would be intuitive that more patients would be detected with second primary lung cancers in the CT group. Another potential explanation for the lack of a difference in curative-intent treatments between the 2 groups could be that the CT group could have been less physically fit or had worse pulmonary function than the CXR group. I know you had a comorbidity index in there. This is kind of implied, because in the CT group, patients were 2.5 times more likely to have a limited resection at the time of their initial operation than the CXR group. Did you look at that? Do you know if that was the case? There was a profound difference in the groups between the types of operations done at the first time around, and perhaps those patients, their pulmonary functions were poorer. Maybe that is why they didn't undergo curative-intent treatments the second time around.

Dr Crabtree. That is a great point. I don't have an objective answer for you on that. The higher proportion of limited resections may have contributed to this difference in the unmatched comparison; however, our propensity-matched analysis took into account the disparity in the proportion of limited resections, which ultimately demonstrated no difference in survival. Our comorbidity index was similar between the groups and was also used in the propensity matching model, so I can't objectively say that the patients in the CT cohort were sicker.

Dr Korst. Sure. Although I agree with the overall conclusion of the article, which is obviously that a formal randomized, controlled trial should be performed; this will obviously take years to accomplish. On the basis of your results, and I know you have a lot of surgeons in your practice, is anyone going to change anything?

Dr Crabtree. We have over the years transitioned to CT, again, for the same reason, that we instinctively think that CT should be better, although we haven't been able to prove it. I think we have anecdotally changed the frequency of imaging. Rather than doing a CT scan every 3 months, we have consistently tried to go to every 6 months for 2 years, and then once a year. I think looking to the future, though, we may be thinking one-sided about this. We are trying to say one size fits all for all patients, but it may be in a trial that we determine that there is a way to customize it according to the tumor, perhaps a genomic signature or lymphovascular invasion. Maybe there are multiple factors that not only affect how we treat those patients but also how we follow them in terms of the frequency and the imaging modality.

Dr Harvey Pass (*New York, NY*). You measured the time to death from the time of the detection of the recurrence; is that right?

Dr Crabtree. We measured the time of death starting from the time of resection at the original operation, and the goal of that is to potentially eliminate or limit the lead-time bias that you would see in some of the screening trials.

Dr Pass. But if you are going to give potentially curative treatment and the patient has recurrence, then you want to see how long that patient is going to live and if he/she is going to die quicker because of later disease, as with symptomatic patients. That may be what you really want to find.

Dr Crabtree. So you're asking me if we went from the time of diagnosis of the recurrence?

Dr Pass. Yes, exactly, how long they live from the time of the diagnosis in each group.

Dr Crabtree. We did a separate analysis on that, which I didn't present, and the survival from the time of diagnosis of recurrence was still similar. Again, it could be a sample size issue.

Dr Pass. The biology of a second primary is a lot different than patients with local or systemic recurrence. You say you broke down the data with regard to CT and CXR for second primaries. Did you do that for patients who had a locoregional or systemic recurrence only?

Dr Crabtree. The truth is, as the Toronto group presented last year, I don't think it matters whether we call it a recurrence or a new primary, as long as the goal of treatment was curative. We did look at recurrences separately, however. The time to diagnosis of recurrences was similar between the cohorts (1.3 vs 1.4 years) and shorter compared with the time to diagnosis of new primary lesions. Also, overall survival was similar for recurrences, although we did not break them down further into systemic versus locoregional.

Dr Joshua Sonett (*New York, NY*). Given the number of patients who were needed for the NLST, I was impressed that you picked up any difference with the asymptomatic and the earlier diagnosis with such a small cohort. Given that, I wouldn't expect you to find a survival difference with such a small cohort.

I have 2 questions. If you are designing a prospective study, how many patients do you think you would need? Think of the large volume with the NLST. Two, given the results of the NLST, which put these patients basically in the high-risk group where we think they are going to have a survival advantage with a CT scan every year, how would you randomize them to not getting a CT scan?

Dr Crabtree. To answer your first question, I think one of the reasons we were able to detect a difference is because we had such a long accrual time and a follow-up time. For a randomized trial, I did a couple of models to look at that. If we use the International Association for the Study of Lung Cancer data, if we looked at specifically IA lung cancers and did a 3-year accrual and 5 years of follow-up, with a 90% power to detect a 20% difference, with approximately 10% attrition rate, we would need approximately 2000 patients in each group. If we specifically did the same parameters for just IIIA disease, then we would need approximately 700 patients in each group with that follow-up time. What was the second question, Dr Sonett?

Dr Sonett. How do you reconcile just getting CXRs when these patients are in the high-risk group for the NLST for surveillance?

Dr Crabtree. This was a retrospective study.

Dr Sonett. No, if you did a prospective study.

Dr Crabtree. If we did, I think we would have a discussion and would likely be looking at examining different types of CT scan, whether it be low-dose or contrast CT or even, again, the consideration of PET-CT for more advanced-stage disease. I suspect it would be hard to find enough surgeons who would agree on performing a CXR in a randomized study.

EDITORIAL COMMENTARY

Lung cancer survivors need lung cancer screening

Raja M. Flores, MD

See related article on pages 45-53.

Surveillance of patients with lung cancer after curative resection is essentially just screening for lung cancer. The success of screening relies on identifying early disease

and implementing curative surgery. A critical element of successful screening is the proper identification of a high-risk group. What better group than those who have already had lung cancer? A computed tomography (CT) screening program evaluating 20 year-old nonsmokers for lung cancer would clearly result in failure because the incidence of disease in this patient population is close to zero. The National Lung Screening Trial (NLST) clearly identified a group of smokers at a high enough risk of developing lung cancer to demonstrate a mortality reduction when CT screening was followed by early surgical intervention.¹ The trial included 33 different sites across the nation and cost more than US\$250 million to conduct. The outcome of the trial proved that treatment of smaller, earlier stage tumors resulted in a better cure rate than larger, later stage tumors. We do not need to spend resources on another randomized

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FIGURE E1. Overall CONSORT diagram for surveillance imaging after resection for pathologic stage I lung cancer. *CT*, Computed tomography; *CXR*, chest x-ray; *NSCLC*, non–small cell lung cancer; *PET*, positron emission tomography.

FIGURE E2. Kaplan–Meier curves for overall survival based on treating surgeon.

FIGURE E3. CONSORT diagram of diagnosis, treatment, and survival of successive malignancy using CT or CXR for postoperative surveillance. There are 8 patients in CT group and 6 patients in CXR group who had no treatment, who refused, or who had unknown treatment status. *CT*, Computed tomography; *CXR*, chest x-ray.

TABLE E1. Recent guidelines for radiographic surveillance after resection for non-small cell lung cancer^{9,11-13}

Agency (y)	Recommendations
American Association for Thoracic Surgery (2012) ¹¹	High-resolution CT for first 4 y (with baseline CT at 6 mo and scans at least every 6 mo for first 3 y), then annual low-density CT annually thereafter
American College of Chest Physicians (2013) ⁹	Chest CT every 6 mo for 2 y, annually thereafter
European Society of Medical Oncology (2010) ¹²	CT every 6 mo for 2 y, annually thereafter
National Comprehensive Cancer Network (2012) ¹³	Helical chest CT with or without contrast every 6-12 mo for 2 y, chest CT without contrast annually thereafter

CT, Computed tomography.

TABLE E2. Findings from surveillance studies of non-small cell lung cancer survivors^{4-6,14-20}

Reference	Patients and comparison	Findings
Benamore and colleagues (Canada, 2007) ¹⁵	n = 75, stage IIB-III, routine CXR and CT vs routine CXR with CT done on clinical suspicion	No significant difference in disease-free or overall survival
Chiu and colleagues (Taiwan, 2003) ¹⁶	n = 73, stage I-IV, follow-up with concurrent CXR and LDCT	Majority of relapses were detected by LDCT. LDCT more sensitive than CXR.
Hanna and colleagues (Canada, 2014) ¹⁴	n = 271, stage I-IV, follow-up with concurrent CXR and MnDCT	Majority of relapses were detected asymptotically. MnDCT more sensitive than CXR. Asymptomatic relapses had greater rate of curative treatment and longer survival.
Lamont and colleagues (USA, 2002) ⁶	n = 124, stage I-III, follow-up with CT and CXR	Majority of relapses were detected by follow-up CT.
Lou and colleagues (USA, 2013) ⁵	n = 1294, stage I-II, follow-up with CT	Majority of relapses were detected by follow-up CT.
Nakamura and colleagues (Japan, 2010) ¹⁷	n = 1389, stage I-IIIB, follow-up by pulmonologists with CXR and CT vs thoracic surgeons with CXR	No significant difference in survival for stage I, CXR/CT group had longer survival for stage II-III.
Virgo and colleagues (USA, 1995) ¹⁸	n = 182, stage I-IIIA, intensive vs nonintensive follow-up	No significant difference in survival.
Walsh and colleagues (USA, 1995) ⁴	n = 358, stage I-IIIB	Asymptotically detected relapses not associated with longer survival.
Westeel and colleagues (France, 2000) ¹⁹	n = 192, stage I-IV, follow-up with CXR, CT, and bronchoscopy	Asymptotically detected relapses associated with longer survival.
Younes and colleagues (Brazil, 1999) ²⁰	n = 130, stage I-IIIB, routine CXR and CT vs symptom-prompted follow-up	No significant difference in disease-free or overall survival.

CT, Computed tomography; CXR, chest x-ray; LDCT, low-dose computed tomography; MnDCT, minimal-dose computed tomography.

TABLE E3. Regression analysis for cancer-specific survival

Covariate	Hazard ratio	95% CI	P value
Imaging (CXR vs CT)	0.686	0.396-1.187	.178
Age	1.041	1.015-1.069	.002
Charlson index	1.282	1.030-1.595	.026
Resection (sublobar vs nonsublobar)	1.893	1.040-3.443	.037
Tumor T-stage (1 vs 2a)	0.719	0.379-1.361	.311
Tumor size	1.032	0.774-1.375	.831
Histology (non-BAC vs BAC)	1.863	0.738-4.702	.188
Adjuvant therapy (absent vs present)	0.633	0.321-1.246	.186
Gender (male vs female)	1.078	0.663-1.753	.762
Race (non-Caucasian vs Caucasian)	0.873	0.368-2.069	.757

BAC, Bronchioloalveolar carcinoma; CI, confidence interval; CT, computed tomography; CXR, chest x-ray.

TABLE E4. Matched groups from propensity score analysis (C-statistic 0.640)

Characteristic	CT (n = 174)	CXR (n = 174)	P value
Age (mean ± SD)	66 ± 10	68 ± 10	.134
Charlson index (mean ± SD)	0.90 ± 0.94	0.89 ± 1.01	.956
T2a tumor	56 (32%)	47 (27%)	.291
Resection (sublobar)	33 (19%)	33 (19%)	1.0
Adjuvant therapy	10 (6%)	10 (6%)	1.0

CT, Computed tomography; CXR, chest x-ray; SD, standard deviation.

TABLE E5. Theoretic sample size calculation for a clinical trial of stage IA or stage IIIA non–small cell lung cancer based on 3-year accrual and additional 5-year follow-up

Median survival in control group	Power	Assumed improvement in median survival	Sample size per group	Assuming 10% attrition	Assuming 20% attrition
119*	0.8	20%	1380	1534	1725
119*	0.9	20%	1847	2053	2309
23†	0.8	20%	464	516	580
23†	0.9	20%	621	690	863

*Median survival pathologic stage IA NSCLC. †Median survival pathologic stage IIIA NSCLC. Median survival based on Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol.* 2007;2:706-14.

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