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Computed Tomography Screening for Lung Cancer:

Mediastinal Lymph Node Resection in Stage IA Nonsmall Cell Lung Cancer Manifesting as Subsolid and Solid Nodules

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Abstract

Objective—To compare long-term survival rates of patients with first, primary, clinical stage IA nonsmall cell lung cancer from a large cohort undergoing computed tomography screening with and without mediastinal lymph node resection (MLNR) under an IRB-approved common protocol from 1992 to 2014.

Background—Assessing survival differences of patients with and without MLNR manifesting as solid and subsolid nodules.

Methods—Long-term Kaplan-Meier (K-M) survival rates for those with and without MLNR were compared and Cox regression analyses were used to adjust for demographic, computed tomography, and surgical covariates.

Results—The long-term K-M rates for 462 with and 145 without MLNR was 92% versus 96% ($P = 0.19$), respectively. For 203 patients with a subsolid nodule, 151 with and 52 without MLNR, the rate was 100%. For the 404 patients with a solid nodule, 311 with and 93 without MLNR, the rate was 87% versus 94% ($P = 0.24$) and Cox regression showed no statistically significant difference ($P = 0.28$) when adjusted for all covariates. Risk of dying increased significantly with increasing decades of age (hazard ratio [HR] 2.3, 95% confidence interval [CI] 1.4–3.8), centrally located tumor (HR 2.5, 95% CI 1.2–5.2), tumor size 21 to 30 mm (HR 2.7, 95% CI 1.2–6.0), and invasion beyond the lung stroma (HR 3.0, 95% CI 1.4–6.1). For the 346 patients with MLNR, tumor size was 20 mm or less; K-M rates for the 269 patients with and 169 patients without MLNR were also not significantly different (HR 2.1, $P = 0.24$).

Conclusions—It is not mandatory to perform MLNR when screen-diagnosed nonsmall cell lung cancer manifests as a subsolid nodule.

Keywords

clinical stage IA; lung cancer; mediastinal lymph node resection; nonsmall cell; solid nodule; subsolid nodule

With the US Preventive Services Task Force (USPSTF) and the Centers for Medicare and Medicaid Services (CMS) recommending screening for high-risk smokers,^{1,2} computed tomography (CT) screening will be implemented throughout the United States based on results of large screening studies.^{3,4}

Standard surgical management for stage I nonsmall cell lung cancer (NSCLC) has been lobectomy with mediastinal lymph node resection (MLNR), either using systematic or sampling approaches. The National Comprehensive Cancer Network (NCCN) guidelines in 2014,⁵ however, reflect the changing trends in surgical management as they suggest that it may be appropriate to perform sublobar resections of small cancers. NCCN also recognized that the CT appearance of the cancer serves as an indicator of tumor aggressiveness, and others have raised questions as to whether MLNR is always necessary.^{6–8}

Although meta-analyses comparing lobectomy with sublobectomy have been performed, they have not provided an answer as shown by the recent systematic review.⁹ A single randomized trial (ACOSOG Z-30) comparing systematic resection with sampling of mediastinal lymph nodes has been performed which demonstrated that the sampling resulted in less chest tube drainage and shorter operative time than systematic resection.^{10,11} Other evidence has accrued from clinical practice,^{7,8,12} and there is increasing recognition that tumor aggressiveness and other factors (eg, cell type, CT appearance) should be considered.

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For this reason, we decided to compare long-term survival of lung cancer patients who do or do not undergo MLNR in a large prospective cohort undergoing CT screening for lung cancer.

METHODS

This study draws from the database of the diagnosed cases of NSCLC identified as a result of CT screening in the I-ELCAP cohort. The screenings were performed under an Institutional Review Board-approved common protocol at each of the participating institutions since its start in 1992, continuing through to 2014. This study includes solitary primary NSCLCs identified in current, former, or never-smokers aged 40 and older who had no prior diagnosis of lung cancer.^{18,19} Those with multiple cancers identified on the CT scan before surgery were excluded. Included, however, were all cases which had additional lung cancers identified in the resected pathology specimen that were not identified before surgery. For this study, the updated classification for adenocarcinoma^{20–22} was used. All cases of typical carcinoids were excluded.

All cases of NSCLCs in the I-ELCAP cohort were classified by their appearance on thin-section CT scan before surgery as being either solid or subsolid (nonsolid and part-solid).^{23,24} Tumor diameter was determined by averaging the length and width of the tumor on the CT images showing the largest tumor size using lung windows.^{18,19}

The I-ELCAP protocol encourages the development of new knowledge through its ongoing screening research and coupled treatment research program, but once lung cancer is diagnosed, treatment is a matter of medical practice and the protocol does not dictate decisions of practice. However, since the potential benefit of screening is due to surgical treatment, the concern is to learn from the treatment intervention practices, and thus close documentation of the intervention and complications of the intervention was required. The choice of intervention, including the extent of lung and lymph node, was determined by each surgeon and patient, including the decision whether to intervene at all. All of the participating institutions have institutional standards for their treatment programs and for documentation of the actual procedures and results.

All instances of thoracic surgery for first solitary primary lung cancer prompted by the low-dose CT screening were documented in the management system. Staging classification was made centrally based on the AJCC 6th edition. Tumor diameter based on the average of length and width rather than a single measurement of size was used. The clinical stage of all cases was determined based on the CT scans (and positron emission tomography [PET], if done), performed closest in time to the recommendation for biopsy of a nodule using standard criteria. The extent of surgery, whether MLNR was performed, outcome, and follow-up were documented by the principal investigator at each participating institution. All cases with either mediastinal lymph node sampling or complete resection were classified as having MLNR. If no mediastinal lymph nodes were resected, either with or without resection of intrapulmonary or hilar lymph nodes, the case was classified as not having MLNR. Tumor invasion of the pleura, blood vessels, or lymphatics in the resected specimen were documented. Pathologic tumor diameter (pT) was based on the average of the length

and width of the tumor in the resected specimen provided by the pathologist at the institution where the surgery was performed.

The NSCLC was considered to be peripherally located if tumor was within 20 mm of the costal pleura, otherwise it was considered to be centrally located.

Statistical Analyses

Chi-square or Fisher exact test (for small numbers) was used to compare the characteristics of the patients who with and without MLNR (Table 1), only for those manifesting as a subsolid nodule (Table 2), and only for those manifesting as a solid nodule (Table 3). Characteristics included demographic information, CT findings before surgery, type of surgical resection, and pathologic findings.

Kaplan-Meier (K-M) lung cancer-specific survival rates comparing patients with and without MLNR were constructed as of the date of diagnosis, inherently conditional on not dying of any other cause, in all resected cases (Fig. 1). Log-rank test was used to compare the K-M survival curves of patients who had MLNR with those who did not have MLNR. Any death resulting from treatment was considered a lung cancer death. Follow-up time from diagnosis onward—to death from lung cancer, last contact, or December 31, 2014, whichever came first—was calculated for each case. The date and cause of death were obtained from the patient's physician and/or family members. Survival analysis was performed for all cases of lung cancer. It is well-established that aggressiveness, uptake on PET scans, and survival rates differ for cancers manifesting as a subsolid nodule from those manifesting as a solid nodule,²⁴ and thus the analyses were performed separately for these 2 manifestations of lung cancers.

Further analysis of the risk of dying of NSCLC was performed using Cox regression analysis. The Cox hazard ratio (HR) of dying with NSCLC for patients who had MLNR as compared with the reference group of patients who did not have MLNR (Table 4). Cox analysis was performed to determine the univariate (unadjusted) HR followed by determination of HR when adjusting sequentially for the background characteristics, CT findings, surgical procedure, and pathology findings. Results were summarized in a forest plot which provides the resulting HRs and 95% confidence intervals (CIs) (Fig. 2).

Propensity scoring was also used to address concerns about potential confounding. Multivariate logistic regression analysis was used to calculate the propensity score for each patient to indicate their probability of undergoing MLNR using both their baseline risk factors, CT findings, and type of surgery. Two propensity score adjustments were used—one based on propensity score stratification and the other one by performing covariate adjustments. Using each of the propensity score adjustment approaches, Cox proportional-hazard regression was performed to evaluate the effect of MLNR on lung cancer-specific survival.

Usefulness of PET for assessing mediastinal lymph node involvement was examined among patients who had a preoperative PET scan and MLNR (Table 5). Statistical analyses were performed using the SAS (SAS, version 9.4, Cary, NC) statistical package.

RESULTS

Among the 68,500 smokers and never-smokers who underwent CT screening for lung cancer, a solitary first primary NSCLC was diagnosed as a result of baseline and annual repeat screenings in 817 participants. Of these 817 participants, 664 (81%) had cT1aN0M0 (clinical stage IA) NSCLC and 627 of the 664 participants underwent surgical resection. For these 627 NSCLC patients, the median tumor diameter on the CT scan before surgery was 13 mm [interquartile range (IQR) 10–18], and upon surgical resection, the median tumor size in the pathologic specimen was 13 mm (IQR 10–18) as well. As the focus of this study was on small, stage IA screen-diagnosed NSCLCs, the 20 patients whose pathologic tumor sizes was more than 30 mm in diameter were excluded. This left 607 clinical N0M0 patients whose tumor diameter in the pathologic specimen was 30 mm or less (pT1a), and these patients were the focus of this study. At baseline, the median age of the 607 patients with cancer was 64 (IQR 58–69) years, and among the current and former smokers, the median pack-years of cigarette smoking was 45 (IQR 33–65).

Of the 607 patients, the lung cancer manifested as a subsolid nodule in 203 and as a solid nodule in 404. Among those with solid nodules, 346 were 20 mm or less in diameter.

Comparison of MLNR With no MLNR

Patients undergoing MLNR more frequently completed college (38% vs 28%; $P = 0.02$), were current smokers (48% vs 41%; $P = 0.01$), had a centrally located cancer (32% vs 21%; $P = 0.02$), and lobectomy (84% vs 65%; $P < 0.0001$) (Table 1).

The K-M lung cancer survival rate for patients with or without MLNR was 92% (95% CI 89%–95%) versus 96% (95% CI 93%–99%, $P = 0.19$) (Fig. 1). Deaths from lung cancer occurred only in the patients whose cancer manifested as a solid nodule, so that further analyses were performed separately for cancers manifesting as a subsolid (Table 2) and solid nodule (Table 3).

Comparison of MLNR With no MLNR: NSCLC Manifesting as a Subsolid Nodule

Of the 203 patients, the 151 undergoing MLNR compared with the 52 without MLNR more frequently were current smokers (34% vs 21%; $P = 0.03$), had a centrally located cancer (28% vs 15%; $P = 0.06$), and lobectomy (81% vs 52%; $P < 0.0001$) (Table 2).

Mediastinal lymph node resection confirmed that 150 of the 151 patients were pathologic N0M0. The single exception was a patient with a part-solid nodule in the left upper lobe (solid component measured 12 mm in diameter) who had a single ipsilateral station 6 lymph node metastasis (among the 9 lymph nodes that were removed, 5 N1 lymph nodes were also positive) and was thus pathologic N2M0. Invasion beyond the stroma to adjacent structures was identified in 13 (6%) of the 203 patients (7 to the pleura, 5 to adjacent angiolymphatic structures, and 1 to both); 12 had MLNR and 1 did not. The diameter of the solid component of the subsolid nodule on the CT scan before resection was 0 mm for 74 (36%) (eg, a nonsolid nodule), less than 3 mm for 8 (4%), 3 to 5 mm for 49 (24%), 6 to 9 mm for 34 (17%), 10 to 14 mm for 31 (15%), and 15 to 30 mm (3%) for 7. None had a solid component

that was more than 30 mm. The K-M lung cancer-specific survival rate was 100%, regardless of whether they had MLNR or not.

Comparison of MLNR With no MLNR: NSCLC Manifesting as a Solid Nodule

Of the 404 patients, 311 with MLNR compared with the 93 without MLNR more frequently had a college education (38% vs 28%; $P = 0.07$) and had lobectomy/bilobectomy (86% vs 72%; $P = 0.002$) (Table 3).

Of the 93 patients who did not have MLNR, 44 underwent hilar lymph node resection only (stations 10–12), of which 3 (7%) had intrapulmonary or hilar lymph node metastases (Table 3). Of the 311 patients who underwent MLNR, 279 (89.7%) were confirmed as pathologic N0M0, 15 (4.8%) had N1 lymph node metastases only, and 17 (5.4%) had N2 lymph node metastases.

Kaplan-Meier lung cancer survival rate for patients for 311 with and 93 without MLNR was 87% (95% CI 83%–92%) versus 94% (95% CI 88%–99%, $P = 0.24$). The K-M lung cancer survival rate for those with and without MLNR by pathologic tumor diameter was 95% versus 95% ($P = 0.93$) for those ≤ 10 mm; 84% versus 95% ($P = 0.18$) for those 11 to 20 mm, and 81% versus 87% ($P = 0.71$) for those 21 to 30 mm.

Cox Regression Survival Analysis for NSCLC Manifesting as a Solid Nodule

The Cox survival analysis (Table 4) and forest plot (Fig. 2) resulted in the unadjusted HR of 1.7 (95% CI 0.7–4.5), meaning that the risk of dying was 70% higher for patients who had MLNR as compared with the reference group of patients who did not, although the difference was not statistically significant. When adjusted for all other variables given in Table 3, HR remained 1.7 (95% CI 0.6–4.8).

Table 4 shows that NSCLC survival was significantly lower with increasing decades of age (HR 2.3, 95% CI 1.4–3.8), centrally located tumor (HR 2.5, 95% CI 1.2–5.2), tumor size 21 to 30 mm (HR 2.7, 95% CI 1.2–6.0), and invasion beyond the stroma (HR 3.0, 95% CI 1.4–6.1).

Focusing on the 346 cases whose pathologic tumor size was 20 mm or less, K-M survival rates for the 269 patients with and 77 patients without MLNR were not significantly different (88% vs 95%; $P = 0.23$). Cox regression analysis resulted in an unadjusted HR (HR 2.1, 95% CI 0.6–6.9, $P = 0.24$), and when adjusted for all other variables in Table 4, the HR remained the same (HR 2.0, 95% CI 0.6–6.8, $P = 0.29$); the effect of MLNR was again not statistically significant in either models. In the multivariate analysis, only 2 of the 4 variables previously significant remained, increasing decades of age (HR 2.9, 95% CI 1.3–4.2) and invasion beyond the stroma (HR 4.9, 95% CI 1.1–5.9).

Cox regression survival analysis using 2 methods of propensity scoring resulted in essentially the same HR (stratified: HR 1.7, 95% CI 0.6–4.7; and adjusted: HR 1.8, 95% CI 0.7–4.8), neither being statistically significant.

Lymph Node Metastases

Of the 93 patients who did not have MLNR, 44 underwent hilar LN resection only (stations 10–12), of which 3 (7%) had intrapulmonary or hilar lymph node metastases (Table 3).

Of the 311 patients who underwent MLNR, 279 (89.7%) were confirmed as pathologic N0M0, 15 (4.8%) had N1 lymph node metastases only, and 17 (5.4%) had N2 lymph node metastases. The frequency of N2 metastases increased with increasing tumor size: it was 3% (3/100) for those with pathologic tumor diameter ≤ 10 mm, 7% (11/169) with tumor size 11 to 20 mm, and 7% (3/42) with tumor size 21 to 30 mm. The frequency of N2 LN metastases by cell type was highest among the other cell types (nonadenocarcinoma/nonsquamous carcinomas) (17% = 5/29), followed by adenocarcinoma (5% = 11/225) and squamous cell carcinoma (2% = 1/57). The frequency of N2 metastases was similar for peripheral and central cancers (5.3% = 11/208 vs 5.8% = 6/103; $P = 0.84$). For these 17 patients with N2 LN metastases, the metastases were located in the following stations: among the 9 patients with upper lobe NSCLC, 5 had the lymph node metastases and were in stations 2 to 4, but the other 4 were in stations 7 to 9; among the 7 patients with lower-lobe NSCLC, 6 had the lymph node metastases in stations 5 to 9 and 1 in station 4; and the single patient with a right middle lobe NSCLC had N2 metastases in station 4R.

PET Results

Of the 151 patients whose NSCLC manifested as a subsolid nodule, 42 had a PET scan and none had abnormal mediastinal uptake. MLNR confirmed all to have pathologic stage IA disease (Table 5). No abnormal mediastinal uptake was noted on the PET scan for the 12 patients who did not undergo MLNR. The single case of pN2 lymph node metastases did not have a PET scan.

Of the 311 patients whose NSCLC manifested as a solid nodule, 142 had a PET scan and underwent MLNR, abnormal mediastinal uptake was noted in 6, but none of them had any lymph node metastases upon resection (Table 5). The remaining 136 had a negative mediastinal PET scan, and of these, 125 (92%) were confirmed as having pN0 disease, whereas 7 (5%) had pN2 and 4 (3%) only had pN1 disease.

DISCUSSION

With the increase in CT screening for lung cancer as a result of the USPSTF and final CMS announcement,^{1,2} clinicians will be increasingly faced with the challenge of how best to treat early clinical stage I lung cancer, and balancing the benefits and risks of performing standard lobectomy with MLNR which has long been considered standard of care,^{25,26} although even with more limited parenchymal and lymph node resection.

The extent of MLNR has also changed over time. Initially, complete MLNR was deemed necessary as a definitive treatment of lung cancer,^{10,25,27} but the recommendation has changed as a result of a randomized trial (ACOSOG Z-30) comparing mediastinal sampling with complete dissection, which showed equivalence of the outcomes of 2 approaches, both for recurrence and survival rates, in patients with T1 disease who had pN0 or nonhilar N1 lesions.¹⁰ This trial also concluded that there was significantly more chest tube drainage and

longer operative time with complete lymph dissection.¹¹ Although the trial included patients with stage IA to IIIB disease, the majority had stage I disease (423 with stage IA, 418 with stage IB). The frequency of positive mediastinal lymph nodes was low (4%), which may have been due in part to the study design which required negative results of sampling of segmental, lobar, hilar, and lobe-specific mediastinal lymph nodes before the patient being randomly assigned to complete lymph node dissection or sampling. The frequency of mediastinal lymph node metastases in the randomized trial, which presumably had lung cancers manifesting as both solid and subsolid nodules, was 4%.¹⁰ In our study, mediastinal metastases found as a result of MLNR when there were no N1 lymph node metastases occurred in 4% (11/258) of patients whose cancer manifested as a solid nodule and in 0.7% (1/151) of those manifesting as a subsolid nodule, with the resulting overall rate of 3% (12/409).

There are only 2 overlapping studies comparing MLNR with no MLNR,^{28,29} both based on the surveillance, epidemiology, and end results program (SEER) data which do not provide clinical staging when pathologic staging is available. Patients who had clinical staging alone without subsequent MLNR will always have lower survival rates and higher recurrence rates when compared with those who were confirmed by MLNR as not having mediastinal metastases. Interestingly, in one SEER study,²⁹ the 5-year lung cancer survival rates for those with stage I disease with and without MLNR was 63% versus 58% ($P < 0.0001$). This difference of 5% may very well reflect the percentage of those with clinical N0M0 disease who actually had higher stage disease, and thus there may be no difference at all had the clinical status for both groups been compared.

Others have shown high survival rates for lung cancers which manifested as part-solid nodules, particularly for cases found in the context of screening.^{6,17,30–34} Sone et al classified the lung cancers diagnosed in their baseline and annual repeat screenings as nonsolid and part-solid, and found that all cancers which manifested as nonsolid or part-solid nodules were Noguchi type A to C adenocarcinomas.³⁰ The 10-year lung cancer survival rate for Noguchi types A and B was 100%, and it was lower for Noguchi type C, because 1 of 19 cases of part-solid nodules died. We also had a single patient who had already developed mediastinal lymph node metastases among the 203 cases manifesting as subsolid nodules. Vazquez et al,³¹ in the context of CT screening, had previously demonstrated 100% 10-year lung cancer survival rate for adenocarcinoma-in-situ (100% lepidic) and MIA (90%–99% lepidic), whereas the survival rate decreased to 95% when the lepidic component was between 1% and 90%. The National Hospital Organization Shikoku Cancer Center reported on 492 consecutive patients with CT scans available before resection, and found that patients whose lung cancer manifested as a part-solid nodule with the solid component being less than 50% of the entire nodule had a disease-free survival rate of 100% as compared with a slightly lower rate of 95.5% for those whose solid component was 50% or more.⁶ In a multi-institutional study reported by Yano et al³⁵ of 1737 clinical stage I patients with sublobar resection of their adenocarcinomas, it was found that patients whose percentage of the solid component was less than 25% of the entire nodule size had an all-cause survival rate of 96.7% as compared with 92.7% for those whose solid component was 25% or more.

Even in the 404 patients with NSCLC manifesting as a solid nodule, the long-term 10-year lung cancer-specific survival was very high, regardless of whether MLNR (sampling or complete) was or was not performed (87% vs 94%; $P = 0.24$). The high lung cancer survival rate of 94% of patients without MLNR in our study suggests that relatively few patients were understaged. Currently, between 48% and 79% of patients have MLNR in different surgical series of lung cancer cases including cases from community hospitals.^{7,8,10,36,37} Other studies have demonstrated minimal benefit on loco-regional recurrence or staging with lobe-specific lymph node sampling.³⁸ Some studies suggest that there may be additional potential adverse events in performing lymph node resection such as ischemic bronchial stumps, chyle leaks, longer operative time, greater blood loss and chest tube drainage, and recurrent nerve palsy.^{11,32,39,40}

Limitations include potential differences in surgical management, particularly in MLNR assessment across surgeons and hospitals, and the lack of randomization to MLNR or none. However, the frequency of lymph node metastases is similar to that found in the randomized trial in which all lymph node were either resected completely or sampled. As these cancers are found in the context of screening, they are typically small and in early stage. Also, we did not distinguish between lymph node sampling and dissection; thus effect of MLNR sampling versus dissection was not examined in this study.

These results from a multi-institutional study strongly suggest that MLNR may not be always necessary. Our results corroborate the importance of confirming whether the lung cancer manifests as solid nodule or a subsolid one using thin-slice CT images, and that tumor histology and tumor location may also be a critical factor. The results indicate that the survival is equivalent with those who undergo MLNR and those who do not, and that the potential morbidity of the MLNR can thus be avoided, particularly when the nodule is subsolid. The results further suggest that lung cancers manifesting as subsolid nodules and less than 30 mm diameter should be considered as candidates for sublobar resection without MLNR. Similarly, peripherally located cancers manifesting as a solid nodule that are less than 20 mm in diameter should be considered as candidates for sublobar resection without MLNR. An alternative might be to do only sampling of the lobe-specific lymph stations in these cases according to the location of the cancer.³⁸

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Conflicts of interest: Dr Yankelevitz is a named inventor on a number of patents and patent applications relating to the evaluation of diseases of the chest including measurement of nodules. Some of these, which are owned by Cornell Research Foundation (CRF), are nonexclusively licensed to General Electric. As an inventor of these patents, Dr Yankelevitz is entitled to a share of any compensation which CRF may receive from its commercialization of these patents. He also serves on the scientific advisory board (unpaid) for Give-A-Scan, Lung Cancer Alliance and serves as a consultant for Accumetra, LLC.

Dr Henschke is the President and serves on the board of the Early Diagnosis and Treatment Research Foundation. She receives no compensation from the Foundation. The Foundation is established to provide grants for projects, conferences, and public databases for research on early diagnosis and treatment of diseases. Recipients include, I-ELCAP, among others. The funding comes from a variety of sources including philanthropic donations, grants and contracts with agencies (federal and non-federal), imaging and pharmaceutical companies relating to image processing assessments. The various sources of funding exclude any funding from tobacco companies or tobacco-related sources. Dr Claudia Henschke is also a named inventor on a number of patents and patent applications relating to the evaluation of pulmonary nodules on CT scans of the chest which are owned by CRF. Since 2009, Dr Henschke does not accept any financial benefit from these patents including royalties and any other proceeds related to the patents or patent applications owned by CRF.

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References

1. Moyer VA, Force USPST. Screening for lung cancer: U. S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2014; 160:330–338. [PubMed: 24378917]
2. Centers for Medicare and Medicaid Services. , editor. Centers for Medicare and Medicaid Services (CMS). Proposed Decision Memo for Screening for Lung Cancer with Low Dose Computed Tomography (LDCT) (CAG-00439N). 2014.
3. Henschke CIYDF, Libby DM, Pasmantier MW, et al. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med.* 2006; 355:1763–1771. [PubMed: 17065637]
4. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med.* 2011; 365:395–409. [PubMed: 21714641]
5. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology (NCCN Guidelines). Lung Cancer Screening; 2014. Version 1 Available at: http://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf. Accessed March 27, 2015
6. Seki N, Sawada S, Nakata M, et al. Lung cancer with localized ground-glass attenuation represents early-stage adenocarcinoma in nonsmokers. *J Thorac Oncol.* 2008; 3:483–490. [PubMed: 18449000]
7. Altorki NK, Yip R, Hanaoka T, et al. Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules. *J Thorac Cardiovasc Surg.* 2014; 147:754–762. [discussion 62–4]. [PubMed: 24280722]
8. Flores R, Bauer T, Aye R, et al. Balancing curability and unnecessary surgery in the context of computed tomography screening for lung cancer. *J Thorac Cardiovasc Surg.* 2014; 147:1619–1626. [PubMed: 24332102]
9. Taioli E, Yip R, Olkin I, et al. Survival after sublobar resection for early-stage lung cancer: methodological obstacles in comparing the efficacy to lobectomy. *J Thorac Oncol.* 2016; 11:400–406. [PubMed: 26749486]
10. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. *J Thorac Cardiovasc Surg.* 2011; 141:662–670. [PubMed: 21335122]
11. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *Ann Thorac Surg.* 2006; 81:1013–1019. [discussion 9–20]. [PubMed: 16488712]
12. Wisnivesky JP, Henschke CI, Swanson S, et al. Limited resection for the treatment of patients with stage 1A lung cancer. *Ann Surg.* 2010; 251:550–554. [PubMed: 20160639]
13. Henschke CI, Yankelevitz DF, Yip R, et al. Lung cancers diagnosed at annual CT screening: volume doubling times. *Radiology.* 2012; 263:578–583. [PubMed: 22454506]
14. Hasegawa M, Sone S, Takashima S, et al. Growth rate of small lung cancers detected on mass CT screening. *Br J Radiol.* 2000; 73:1252–1259. [PubMed: 11205667]
15. Yankelevitz DF, Reeves AP, Kostis WJ, et al. Small pulmonary nodules: volumetrically determined growth rates based on CT evaluation. *Radiology.* 2000; 217:251–256. [PubMed: 11012453]
16. Yankelevitz DF, Gupta R, Zhao B, et al. Small pulmonary nodules: evaluation with repeat CT: preliminary experience. *Radiology.* 1999; 212:561–566. [PubMed: 10429718]
17. Anami Y, Iijima T, Suzuki K, et al. Bronchioloalveolar carcinoma (lepidic growth) component is a more useful prognostic factor than lymph node metastasis. *J Thorac Oncol.* 2009; 4:951–958. [PubMed: 19543119]
18. Henschke CI, Yankelevitz DF, Smith JP, et al. Screening for lung cancer: the early lung cancer action approach. *Lung Cancer.* 2002; 35:143–148. [PubMed: 11804686]
19. International Early Lung Cancer Action Program Investigators Group. Pages. Available at: <http://www.ielcap.org/sites/default/files/I-ELCAP%20protocol-v21-3-1-14.pdf>. Accessed May 11, 2016

20. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol.* 2011; 6:244–285. [PubMed: 21252716]
21. Van Schil PE, Sihoe AD, Travis WD. Pathologic classification of adenocarcinoma of lung. *J Surg Oncol.* 2013; 108:320–326. [PubMed: 24006216]
22. Travis, WD., Brambilla, E., Burke, AP., et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Fourth. Lyon, France: International Agency for Research on Cancer; 2015.
23. Henschke CI, Yankelevitz DF, Mirtcheva R, et al. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. *AJR Am J Roentgenol.* 2002; 178:1053–1057. [PubMed: 11959700]
24. Yankelevitz D, Yip R, Smith JP, et al. CT Screening for Lung Cancer. Nonsolid Nodules in Baseline and Annual Repeat Rounds Radiology. 2015; 277:555–564. [PubMed: 26101879]
25. Shimkin MB, Connelly RR, Marcus SC, et al. Pneumonectomy and lobectomy in bronchogenic carcinoma. A comparison of end results of the Overholt and Ochsner clinics. *J Thorac Cardiovasc Surg.* 1962; 44:503–519. [PubMed: 13988545]
26. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg.* 1995; 60:615–622. [discussion 22-3]. [PubMed: 7677489]
27. Johnson J, Kirby CK, Blakemore WS. Should we insist on radical pneumonectomy as routine procedure in the treatment of carcinoma of the lung? *J Thorac Surg.* 1958; 36:309–315. [PubMed: 13576560]
28. Varlotto JM, Recht A, Nikolov M, et al. Extent of lymphadenectomy and outcome for patients with stage I nonsmall cell lung cancer. *Cancer.* 2009; 115:851–858. [PubMed: 19140203]
29. Osarogiagbon RU, Yu X. Mediastinal lymph node examination and survival in resected early-stage non-small-cell lung cancer in the surveillance, epidemiology, and end results database. *J Thorac Oncol.* 2012; 7:1798–1806. [PubMed: 23154551]
30. Sone S, Nakayama T, Honda T, et al. Long-term follow-up study of a population-based 1996-1998 mass screening programme for lung cancer using mobile low-dose spiral computed tomography. *Lung Cancer.* 2007; 58:329–341. [PubMed: 17675180]
31. Vazquez M, Carter D, Brambilla E, et al. Solitary and multiple resected adenocarcinomas after CT screening for lung cancer: histopathologic features and their prognostic implications. *Lung Cancer.* 2009; 64:148–154. [PubMed: 18951650]
32. Sugi K, Nawata K, Fujita N, et al. Systematic lymph node dissection for clinically diagnosed peripheral non-small-cell lung cancer less than 2 cm in diameter. *World J Surg.* 1998; 22:290–294. [discussion 4-5]. [PubMed: 9494422]
33. Kadota K, Villena-Vargas J, Yoshizawa A, et al. Prognostic significance of adenocarcinoma in situ, minimally invasive adenocarcinoma, and nonmucinous lepidic predominant invasive adenocarcinoma of the lung in patients with stage I disease. *Am J Surg Pathol.* 2014; 38:448–460. [PubMed: 24472852]
34. Carter D, Vazquez M, Flieder DB, et al. Comparison of pathologic findings of baseline and annual repeat cancers diagnosed on CT screening. *Lung Cancer.* 2007; 56:193–199. [PubMed: 17239983]
35. Yano M, Yoshida J, Koike T, et al. Survival of 1737 lobectomy-tolerable patients who underwent limited resection for cStage IA non-small-cell lung cancer. *Eur J Cardiothorac Surg.* 2015; 47:135–142. [PubMed: 24699203]
36. Boffa DJ, Allen MS, Grab JD, et al. Data from The Society of Thoracic Surgeons General Thoracic Surgery database: the surgical management of primary lung tumors. *J Thorac Cardiovasc Surg.* 2008; 135:247–254. [PubMed: 18242243]
37. Little AG, Rusch VW, Bonner JA, et al. Patterns of surgical care of lung cancer patients. *Ann Thorac Surg.* 2005; 80:2051–2056. [discussion 6]. [PubMed: 16305843]
38. Shapiro M, Kadakia S, Lim J, et al. Lobe-specific mediastinal nodal dissection is sufficient during lobectomy by video-assisted thoracic surgery or thoracotomy for early-stage lung cancer. *Chest.* 2013; 144:1615–1621. [PubMed: 23828253]
39. Satoh Y, Okumura S, Nakagawa K, et al. Postoperative ischemic change in bronchial stumps after primary lung cancer resection. *Eur J Cardiothorac Surg.* 2006; 30:172–176. [PubMed: 16730184]

40. Izbicki JR, Thetter O, Habekost M, et al. Radical systematic mediastinal lymphadenectomy in non-small cell lung cancer: a randomized controlled trial. *Br J Surg.* 1994; 81:229–235. [PubMed: 8156344]

FIGURE 1.

Kaplan-Meier lung cancer survival curve for 607 patients with clinical N0M0 nonsmall cell lung cancer manifesting either as a solid or subsolid nodule: patients with MLNR (n = 462) and without MLNR (n = 145). Median pathology tumor size was 13 mm in both groups.

FIGURE 2.

The hazard ratio (HR) of the risk for dying of clinical stage I nonsmall cell lung cancer (cNOM0) manifesting as a solid nodule for patients who had MLNR as compared with the reference group of patients who did not have MLNR.

TABLE 1

Characteristics of 607 Patients With Resected Non-small Cell Lung Cancer (Clinical N0M0 Disease and Tumor Diameter pT1a) With and Without Mediastinal Lymph Node Resection

	Mediastinal Lymph Node Resection		
	With (n = 462)	Without (n = 145)	<i>P</i> *
Background			
Male sex	234 (51%)	73 (50%)	0.95
Median age (IQR)	64 (58–69)	63 (59–71)	0.38
<55	59 (13%)	25 (17%)	0.17
55	403 (87%)	120 (83%)	
White ethnicity	393 (85%)	122 (84%)	0.79
College education	177 (38%)	40 (28%)	0.02
Smoking history			
Current smoker	222 (48%)	59 (41%)	0.01
Former smoker	217 (47%)	68 (47%)	
Never smoker	23 (5%)	18 (12%)	
Median pack-years among smokers (IQR) [†]	46 (34–66)	44 (30–65)	0.31
Comorbidity			
COPD	59 (13%)	19 (13%)	0.92
Cardiac disease	22 (5%)	10 (7%)	0.32
Vascular disease	97 (21%)	34 (23%)	0.53
Other disease	175 (38%)	50 (34%)	0.46
Findings on baseline CT scan			
Nodule consistency of the cancer (CA)			
CA manifested as a solid nodule	311 (67%)	93 (64%)	0.48
CA manifested as a subsolid nodule	151 (33%)	52 (36%)	
Any emphysema	179 (39%)	54 (37%)	0.75
Findings on CT before surgery			
Tumor in central location on CT	146 (32%)	31 (21%)	0.02
PET scan before surgery	184 (40%)	50 (34%)	0.25
No uptake in mediastinum	178 (97%) [§]	48 (96%) [§]	
Tumor cell type			
Adenocarcinoma	376 (81%)	109 (75%)	0.26
Squamous cell	57 (12%)	23 (16%)	
Other cell types	29 (6%)	13 (9%)	
Surgery			
Lobectomy/bilobectomy	389 (84%)	94 (65%)	<.0001
Pathology specimen			
Median tumor diameter (IQR)	13 (10–18)	13 (9–18)	0.40
Tumor diameter			
10 mm	147 (32%)	53 (37%)	0.56
11–20 mm	250 (54%)	72 (50%)	

	Mediastinal Lymph Node Resection		
	With (n = 462)	Without (n = 145)	<i>P</i> *
21–30 mm	65 (14%)	20 (14%)	0.52
Tumor invasion beyond stroma [‡]	114 (25%)	32 (22%)	
Death due to NSCLC			
CA manifested as a solid nodule	30 (10%)	5 (5%)	
CA manifested as a subsolid nodule	0 (0%)	0 (0%)	

* Chi-square or Fisher exact test.

[†] Among 439 smokers with MLND and 127 smokers without MLND.

[‡] Pleural or angiolymphatic invasion.

[§] Percentage among patients who had PET scan before surgery.

PET indicates positron emission tomography.

TABLE 2

Characteristics of 203 Patients With Resected Nonsmall Cell Lung Cancer Manifesting as a Subsolid Nodule (Clinical N0M0 and Tumor Diameter pT1a)

	Mediastinal Lymph Node Resection		
	With (n = 151)	Without (n = 52)	P
Background			
Male sex	68 (45%)	21 (40%)	0.56
Median age (IQR)	65 (58–70)	64 (59–71)	0.81
<55	20 (13%)	11 (21%)	0.17
≥55	131 (87%)	41 (79%)	
White ethnicity	125 (83%)	38 (73%)	0.13
College education	58 (38%)	14 (27%)	0.14
Smoking history			
Current smoker	51 (34%)	11 (21%)	0.03
Former smoker	89 (59%)	31 (60%)	
Never smoker	11 (7%)	10 (19%)	
Median pack-years among smokers (IQR) *	42 (30–61)	36 (27–60)	0.36
Comorbidity			
COPD	10 (7%)	3 (6%)	1.00
Cardiac disease	4 (3%)	0 (0%)	0.57
Vascular disease	25 (17%)	12 (23%)	0.29
Other disease	61 (40%)	20 (38%)	0.81
Findings on baseline CT scan			
Median diameter of solid component	8 (5–13)	8 (6–13)	0.54
Diameter of solid component			
None	53 (35%)	21 (40%)	0.77
<3 mm	5 (3%)	3 (6%)	
3–5 mm	39 (26%)	10 (19%)	
6–9 mm	24 (16%)	10 (19%)	
10–14 mm	25 (17%)	6 (12%)	
15–30 mm	5 (3%)	2 (4%)	
Any emphysema	36 (24%)	9 (17%)	0.33
Findings on CT before surgery			
Tumor in central location on CT [‡]	43 (28%)	8 (15%)	0.06
PET scan before surgery	42 (28%)	12 (23%)	0.50
No uptake in mediastinum	42 (100%) [§]	12 (100%) [§]	
Tumor cell type			
Adenocarcinoma	151 (100%)	52 (100%)	N/A
Surgery			
Lobectomy/bilobectomy	122 (81%)	27 (52%)	<0.0001
Pathology specimen			

	Mediastinal Lymph Node Resection		
	With (n = 151)	Without (n = 52)	P
Median tumor diameter (IQR)	13 (10–18)	11 (8–14)	0.02
Tumor diameter			
10 mm	47 (31%)	24 (46%)	0.10
11–20 mm	81 (54%)	24 (46%)	
21–30 mm	23 (15%)	4 (8%)	
Tumor invasion beyond stroma [‡]	12 (8%)	1 (2%)	0.19

* Among 140 smokers with MLND and 42 smokers without MLND.

[‡] Pleural or angiolymphatic invasion.

[‡] Peripheral if tumor within 20 mm of the costal pleura, otherwise central.

[§] Percentage among patients who had PET scan before surgery.

PET indicates positron emission tomography.

TABLE 3

Characteristics of 404 Patients With Resected Nonsmall Cell Lung Cancer Manifesting as a Solid Nodule (Clinical N0M0 and Tumor Diameter pT1a)

	Mediastinal Lymph Node Resection		
	With (n = 311)	Without (n = 93)	P
Background			
Male sex	166 (53%)	52 (56%)	0.67
Median age (IQR)	63 (58–68)	63 (59–71)	0.23
<55	39 (13%)	14 (15%)	0.53
55	272 (87%)	79 (85%)	
White ethnicity	268 (86%)	84 (90%)	0.29
College education	119 (38%)	26 (28%)	0.07
Smoking history			
Current smoker	171 (55%)	48 (52%)	0.18
Former smoker	128 (41%)	37 (40%)	
Never smoker	12 (4%)	8 (9%)	
Median pack-years among smokers (IQR) *	47 (35–68)	48 (33–65)	0.62
Comorbidity			
COPD	49 (16%)	16 (17%)	0.74
Cardiac disease	18 (6%)	10 (11%)	0.10
Vascular disease	72 (23%)	22 (24%)	0.92
Other disease	114 (37%)	30 (32%)	0.44
Findings on baseline CT scan			
Any emphysema	143 (46%)	45 (48%)	0.68
Findings on CT before surgery			
Tumor in central location on CT [‡]	103 (33%)	23 (25%)	0.13
PET scan before surgery	142 (46%)	38 (41%)	0.41
No uptake in mediastinum	136 (96%)	36 (95%)	0.68
Tumor cell type			
Adenocarcinoma	225 (72%)	57 (61%)	0.12
Squamous cell	57 (18%)	23 (25%)	
Other	29 (9%)	13 (14%)	
Surgery			
Lobectomy/bilobectomy	267 (86%)	67 (72%)	0.002
Pathology specimen			
Median tumor diameter (IQR)	13 (10–17)	14 (10–19)	0.40
Tumor diameter			
10 mm	100 (32%)	29 (31%)	0.67
11–20 mm	169 (54%)	48 (52%)	
21–30 mm	42 (14%)	16 (17%)	
Tumor invasion beyond stroma [‡]	102 (33%)	31 (33%)	0.92
Lymph node metastases			

	Mediastinal Lymph Node Resection		
	With (n = 311)	Without (n = 93)	P
N1 only	15 (5%)	3 (3%)	0.27
N2 with N1	6 (2%)	0 (0%)	
N2 only	11 (4%)	0 (0%)	

* Among 299 smokers with MLND and 85 smokers without MLND.

[†] Pleural or angiolymphatic invasion.

[‡] Peripheral if cancer was within 20 mm of the costal pleura, otherwise it was central.

PET indicates positron emission tomography.

TABLE 4

Cox Regression Analysis of Risk of Dying of Clinical N0M0 Nonsmall Cell Lung Cancer Manifesting as a Solid Nodule When Adjusting for all Other Characteristics

	Multivariate Cox Regression			
	95% CI			P
	HR	Lower CI	Upper CI	
MLNR (as compared with reference without MLNR)	1.7	0.6	4.8	0.28
Background				
Male sex (Ref: female)	1.3	0.6	2.8	0.51
Age (in decade)	2.3	1.4	3.8	0.001
White ethnicity	0.7	0.3	1.8	0.42
College education	0.8	0.4	1.8	0.57
Smoking history				
Current smoker (ref: never smoker)	1.1	0.1	10.2	0.95
Former smoker (ref: never smoker)	1.5	0.2	14.8	0.71
Pack-years of smoking (10-pack)	1.1	0.9	1.2	0.30
Comorbidity				
COPD	0.8	0.3	2.0	0.63
Cardiac disease	0.3	0.0	2.9	0.32
Vascular disease	0.9	0.3	2.3	0.80
Other disease	0.6	0.2	1.4	0.23
Findings on baseline CT scan				
Any emphysema (Ref: no emphysema)	1.8	0.9	3.7	0.12
Findings on CT before surgery				
Tumor in central location on CT (Ref: peripheral)	2.5	1.2	5.2	0.01
Tumor cell type				
Adenocarcinoma		Ref.		
Squamous cell (Ref: adenocarcinoma)	0.4	0.1	1.0	0.05
Other cell types (Ref: adenocarcinoma)	0.8	0.2	2.5	0.67
Surgery				
Lobectomy/bilobectomy (Ref: sublobectomy)	1.1	0.4	3.1	0.88
Pathology specimen				
Tumor diameter				
21–30 mm (Ref: diameter 20 mm)	2.7	1.2	6.0	0.02
Tumor invasion beyond stroma	3.0	1.4	6.1	0.003

TABLE 5

Mediastinal Lymph Node Metastases Identified by Mediastinal Lymph Node Resection (MLNR) in Patients With Clinical N0M0 Nonsmall Cell Lung Cancer Manifesting Either as a Subsolid Nodule or as a Solid Nodule

	<u>Results of Mediastinal Lymph Node Resection</u>			
	<u>Subsolid Cancer</u>		<u>Solid Cancer</u>	
	pN2	pN0	pN2/N3	pN0/N1
PET result *				
Positive	0	0	0	6
Negative	0	42	7	129
Total	0	42	7	135

Lung cancer manifesting as a subsolid nodule: sensitivity = 0/0; specificity = 42/42 (100%); positive predictive value = 0/0; negative predictive value = 42/42 (100%).

Lung cancer manifesting as a solid nodule: sensitivity = 0/7 (0%); specificity = 129/135 (96%) (95% CI 92%–99%); positive predictive value = 0/6 (0%); negative predictive value = 129/136 (95%) (95% CI 91%–99%).

* Uptake in mediastinum.

PET indicates positron emission tomography.