Is palpation of the nonresected pulmonary lobe(s) required for patients with non–small cell lung cancer? A prospective study

Robert James Cerfolio, MD, FACS, FCCP,* and Ayesha S. Bryant, MSPH, MD†

Objective: Video-assisted lobectomy is an increasingly used technique to treat patients with non–small cell lung cancer but it does not usually afford lung palpation.

Methods: A prospective study was conducted on patients with tumors amenable to video-assisted lobectomy (noncentral lesion and <5 cm) who underwent open lobectomy via thoracotomy. All patients underwent 64-slice helical computed tomographic scan with intravenous contrast at 5-mm intervals and had integrated 2-deoxy-2-18F-fluoro-D-glucose positron emission tomography computed tomography 30 days or less before thoracotomy. Unsuspected malignant pulmonary nodules that were palpated and removed (from a different lobe than the one resected) and that were not imaged preoperatively were defined as cancer that would have been missed by video-assisted lobectomy.

Results: From January 2006 to February 2007, 166 patients had non–small cell lesions that were resected via thoracotomy, despite being amenable to video-assisted surgery, by one surgeon. Thirty-seven (22%) patients had pulmonary nodules that probably would have been missed by video-assisted lobectomy; 14 (8.4%) of these nodules were malignant. These were unsuspected M1 pulmonary lesions in 9 patients and unsuspected different types of primary non–small cell lung cancers in 5 patients. All missed lesions were less than 6 mm and in different lobes from the one resected. Nine (64%) of these 14 patients' primary known lesions were pathologic T1 lesions. Nine patients received adjuvant chemotherapy because of these unsuspected M1 nodules.

Conclusions: Open lobectomy that affords palpation of the rest of the lung may discover nonimaged malignant pulmonary nodules in different lobes in 8% to 9% of patients with non–small cell lung cancer despite preoperative fine-cut chest computed tomographic scan with contrast and integrated integrated 2-deoxy-2-18F-fluoro-D-glucose positron emission tomography computed tomographic scanning. The clinical impact of these findings is unknown.

Lung cancer remains the most common cause of cancers deaths worldwide, and 80% of lung cancers are non–small cell lung cancer (NSCLC). These types of tumors are potentially curable if detected early and surgically resected. Recently, many centers and surgeons have adopted video-assisted thoracic surgery (VATS) techniques to perform pulmonary resection for bronchogenic malignancy mainly because it is touted as less invasive and leads to quicker recovery in most patients.^{1,2} In addition, it has been purported to have similar oncologic efficacy, and in a few series from several experienced VATS surgeons the long-term survival is reported to be similar to that of open techniques. In 2005 we³ performed a prospective study that showed the inaccuracies of clinical staging compared with pathologic staging. Only about 50% of patients had their stage correctly predicted despite use of the most sophisticated preoperative imaging studies available. Some patients had malignant nodules that were missed despite the use of

From the Division of Cardiothoracic Surgery, University of Alabama at Birmingham, Birmingham, Ala.

Read at the Eighty-seventh Annual Meeting of The American Association for Thoracic Surgery, Washington, DC, May 5–9, 2007.

*Professor of Surgery, Chief of Section of Thoracic Surgery at University of Alabama at Birmingham, Division of Cardio-Thoracic Surgery, Department of Surgery.

† Assistant Professor, Department of Epidemiology, University of Alabama at Birmingham School of Public Health; Clinical Researcher, Division of Cardio-thoracic Surgery, Department of Surgery.

Received for publication May 3, 2007; revisions received Aug 6, 2007; accepted for publication Aug 16, 2007.

Address for reprints: Robert J. Cerfolio, MD, Professor of Surgery, Chief of Thoracic Surgery, Division of Cardiothoracic Surgery, University of Alabama at Birmingham, 703 19th St S, ZRB 739, Birmingham, AL 35294 (E-mail: Robert.cerfolio@ccc.uab.edu).

J Thorac Cardiovasc Surg 2008;135:261-8
0022-5223/\$34.00

Copyright © 2008 by The American Association for Thoracic Surgery

doi:10.1016/j.jtcvs.2007.08.062

Abbreviations and Acronyms

CT	= computed tomography
FDG-PET/CT	= 2-deoxy-2-18F-fluoro-D-glucose positron emission tomography computed tomography
maxSUV	= maximum standardized uptake value
NSCLC	= non-small cell lung cancer
PET	= Positron emission tomography
UAB	= University of Alabama at Birmingham
VATS	= video assisted thoracoscopic surgery

integrated 2-deoxy-2-18F-fluoro-D-glucose computed tomographic scans (FDG-PET/CT) and fine-cut, 64-multislice chest computed tomography (CT) scan using intravenous contrast. The finding of missed or nonimaged malignant pulmonary nodules for patients who undergo thoracotomy for metastasectomy is well chronicled and is estimated to be 11% to 48%, with most series reporting approximately 20%.⁴⁻¹⁰ Therefore, many surgeons believe that bimanual lung palpation is best for patients who undergo metastasectomy. Does this concept apply for those with NSCLC? The objective of this study was to evaluate the incidence of non-imaged pulmonary nodules discovered at the time of open thoracotomy via bimanual lung palpation that were missed by the preoperative chest CT scan and integrated FDG-PET/CT in patients who had NSCLC that was potentially removable by VATS.

Patients and Methods

This was a prospective cohort study over 13 months (January 2006 to February 2007). Entry criteria mandated patients have a chest CT and an integrated FDG-PET/CT scan within 4 weeks of surgery, pathologically confirmed NSCLC, and a VAT-able lesion as defined below. Chest CT scan had to be at least 64 slices, with 5-mm cuts, and patients had to receive intravenous contrast. Exclusion criteria were any pathologic condition other than NSCLC, including metastatic disease, preoperative radiation therapy, or patient age less than 19 years. Patients who underwent metastasectomy were eliminated from this study because of their involvement in another prospective study evaluating a similar question in patients with other types of cancer besides NSCLC. The chest CT scans and the integrated FDG-PET/CT scan that were performed at our institution were performed as described previously.^{11,12} An estimated TNM stage of the tumor was derived after the integrated FDG-PET/CT scan and after the chest CT scan.¹³ The University of Alabama at Birmingham (UAB) Institutional Review Board approved this study, and it separately approved the prospective database used to compile these data. Patient consent was obtained for inclusion in our prospective database only.

A pre-study statistical power analysis where $\alpha = .05$ and a power of 80% in a 2-sided test was used to determine the sample size required for this series. Incidence was approximated at 8% for purposes of sample size calculation. Summaries for continuous variables are presented as medians. Frequencies with percentages were generated for categorical variables. Categorical values were

Figure 1. Study algorithm: There were 1384 operations performed by one surgeon from January 2006 until February 2007, and 628 were pulmonary resections. Of those, 302 were eligible for this study. **NSCLC**, Non-small cell lung cancer; **VATS**, video-assisted thoracic surgery; **CW**, chest wall.

compared by analysis of variance, the χ^2 test, or the Fisher exact tests. Continuous variables were compared by the Student *t* test for normally distributed variables and the Wilcoxon test for nonnormally distributed variables.

Definitions

A “VATable NSCLC lesion” was defined as any nodule or mass less than 5 cm that did not invade nor extrinsically compress a lobar or more central bronchus. A bronchoscopic examination without evidence of cancer in the segmental or lobar bronchus was also required for a lesion to be considered VATable for this study. A “non-VATable” pulmonary lesion was defined as any other nodule or mass in the lung. A non-imaged pulmonary nodule, also labeled a nodule that “would have been missed had a VATS lobectomy been performed,” was defined as a pulmonary nodule in a lobe other than the one that contained the known described primary lesion and it was not described on the chest CT or the integrated PET/CT scan reports. Missed pulmonary nodules were then later subdivided as malignant nonimaged pulmonary nodules or benign nonimaged pulmonary nodules on the basis of the pathologic examination.

Results

As shown in Figure 1, there were 1384 patients who underwent surgery by one surgeon from January 2006 to February 2007. Six-hundred twenty-eight patients underwent pulmonary resection and 166 had VAT-able NSCLC lesions (as

TABLE 1. Characteristics of patients by group (group 1, no pulmonary nodules nonimaged; group 2, benign pulmonary nodules missed; and group 3, malignant pulmonary nodule nonimaged)

	No missed pulmonary nodules (n = 129)	Benign missed pulmonary nodule (n = 23)	Missed malignant pulmonary nodule (n = 14)
Median age	62	64	65
Gender (male)	83 (64%)	13 (57%)	9 (64%)
Operative procedures			
Resected	122 (95%)	23	14
Not resected	7 (5%)	0	0
Histology of preoperatively imaged lesion			
Adenocarcinoma	59 (45%)	8 (35%)	4 (29%)
Squamous	55 (43%)	12 (52%)	7 (50%)
BAC	6 (5%)	2 (9%)	2 (14%)
Carcinoid	4 (3%)	1 (4%)	0 (0%)
Other	5 (4%)	0 (0%)	1 (7%)
MaxSUV of preoperatively imaged pulmonary nodule, median (range)	4.1 (<2.5–16.4)	4.3 (<2.5–12.2)	4.95 (<2.5–13.9)
Location of CT scan at UAB	106 (82%)	16 (70%)	11 (79%)
Outside	23 (18%)	7 (30%)	3 (21%)

BAC, Bronchoalveolar carcinoma; maxSUV, maximum standardized uptake value; CT, computed tomographic; UAB, University of Alabama at Birmingham.

defined above) The most common causes for a lesion to be considered non-VAT-able were tumor size greater than 5 cm and a history of previous radiation. Patient characteristics are shown in Table 1. Univariate analysis showed a statistically significant difference only in the maximum standardized uptake value (maxSUV) of the preoperatively imaged pulmonary nodules. Patients who had CT scans performed at outside institutions were not more likely to have missed, nonimaged pulmonary nodules. The 14 patients with a missed malignant pulmonary nodule (nodules discovered only via bimanual lung palpation, not finger palpation) had a higher median maxSUV (5.0) than did the 152 patients who did not have a missed malignant nodule (4.1; $P = .045$). The data are stratified into three groups: those with no palpated nonimaged pulmonary nodules, those with benign nonimaged pulmonary nodules, and those with malignant nonimaged pulmonary nodules. As shown, 37 (22%) patients had a nodule that was nonimaged. Fourteen (8.4%) of these missed nodules were malignant. Table 2 depicts the pathologic characteristics of these 14 patients who had nonimaged malignant nodules. There were unsuspected M1 pulmonary lesions (nodules of the same histologic type as that in the primary, preoperatively imaged tumor but in a different lobe) in 9 patients and unsuspected different types of NSCLC primary tumors in the remaining 5 patients. All nonimaged lesions were 6 mm or less and all were, by definition, in different lobes from the one resected. Nine (64%) of the 14 patients with a primary larger lesion had pathologic T1 lesions, and 3 (21%) had T2, and 2 had T4 (because they had 2 nodules of the same histologic type in the same lobe). Thus these 2 latter patients had

2 nonimaged malignant nodules, 1 in the lobe that was resected and 1 in a different lobe. Table 3 shows the distribution of the nonimaged nodules by the location of the known primary NSCLC. When we collapse this information, we find that patients with lower lobe cancers had a higher incidence of nonimaged pulmonary nodules (44% compared with 16%; $P < .01$) and a higher incidence of nonimaged malignant pulmonary nodules (16% compared with 6%, $P = .04$).

Finally, in addition to the patients with nonimaged pulmonary nodules, there were other patients who had a pathologic stage that differed from the predicted clinical PET/CT-suggested stage (not including those with T-stage disagreements). There were 12 patients who had unsuspected metastatic NSCLC in one or more mediastinal lymph nodes (N2 disease).

Discussion

Patient selection is an important component of successful surgical outcomes for patients with NSCLC. This entails not only the careful assessment of the patient's cardiopulmonary risks before the operation, but also their oncologic stage, which determines the best treatment strategies during the operation. For example, the discovery of metastatic disease in a mediastinal (N2) lymph node before pulmonary resection often changes the preoperative management. Similarly, the discovery of pathologic N1, N2, or M1 disease after resection often changes the postoperative therapy as well. Therefore, meticulous intraoperative staging is a critical aspect of the operation and removal of the suspected or known malignant pulmonary nodule alone is insufficient.

TABLE 2. Clinical and pathologic characteristics of the 14 patients who had missed malignant nodules by preoperative chest CT and FDG-PET/CT scan

Pt No.	Clinical stage			Tumor location and size (cm)	Histology	Pathologic stage and histology	Impact on therapy
	CT stage	PET/CT stage	MaxSUV primary				
1	T1	T1	4.6	RLL, 2.3	Squamous cell	T1 N0 M1	Referred for radiochemotherapy.
	N0	N0		RML, 0.3			
2	T2	T2	4.0	RUL, 2.0	Squamous cell	T1 N0 M0	None
	N0	N0		RLL, 0.5	Carcinoid	T1 N0 M0	
3	T1	T0	<2.5	LUL, 2.5	Bronchoalveolar carcinoma	T4 N0 M1	Referred for chemotherapy
	N0	N0		LLL, 0.6			
4	T2	T2	3.7	LLL, 3.5	Adenocarcinoma	T1 N0 M0	Referred for chemotherapy
	N0	N0		LUL, 0.6	Adenocarcinoma	T1 N2 M0	
5	T2	T2	9.1	LUL, 4.4	Adenocarcinoma	T2 N0 M1	Referred for chemotherapy.
	N0	N1		LLL, 0.5			
6	T2	T2	7	RUL, 2.0	Squamous cell	T2 N0 M1	Referred for radiochemotherapy
	N0	N0		RLL, 0.6			
7	T1	T1	5.3	LLL, 2.2	Adenocarcinoma	T1 N0 M0	None
	N0	N0		LUL, 0.6	Mixed	T1 N0 M0	
8	T2	T2	8.1	RLL, 2.3	Squamous cell	T1 N0 M0	None
	N0	N0		RML, 0.5	Carcinoid	T1 N0 M0	
9	T1	T1	3.7	RLL, 1.2	Adenocarcinoma	T1 N0 M1	Referred for chemotherapy
	N0	N0		RML, 0.3			
10	T1	T1	8.0	LUL, 2.9	NSCLC	T1 N0 M1	Referred for chemotherapy
	N0	N0		LLL, 0.6			
11	T1	T1	4.0	LUL, 2.1	Squamous cell	T1 N2 M1	Referred for chemotherapy
	N2	N2		LLL, 0.5			
12	T2	T2	7.3	RUL, 4.9	Squamous cell	T4 N0 M1	Referred for radiochemotherapy
	N1	N0		RML, 0.6			
13	T2	T2	13.9	LUL, 3.5	Squamous	T1 N0 M0	None
	N2	N0		LLL, 0.5	Adenocarcinoma	T2 N0 M0	
14	T2	T3	3.5	RLL, 4.9	Bronchoalveolar carcinoma	T2 N2 M1	Referred for chemotherapy
	N0	N0		RUL, 0.6			

CT, Computed tomography; FDG-PET/CT, 2-deoxy-2-18F-fluoro-D-glucose positron emission tomography computed tomography; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe. Shaded boxes indicate an unsuspected nodule.

In this prospective study, we found that that 22% (37/166) of patients had a pulmonary nodule that was not imaged by the helical, thin-slice, contrasted chest CT scan and discovered only via bimanual lung palpation. None of these lesions was palpated via finger palpation of the surface of the lung as one is able to do during VATS. Fourteen (8.4%) of these patients had malignant nodules. Both of these results surprised us. However, an incidence of 20% to 40% of nonimaged nodules discovered at the time of bimanual lung palpation is consistent with the literature for patients who undergo thoracotomy and metastasectomy. We⁴ reported in 1994 that 29.2% of patients who had renal cell carcinoma had nodules that were missed by the preoperative chest CT scan but were discovered by bimanual palpation at the time of thoracotomy. Rena and associates⁸ reported in 2007 an 11% incidence of

nonimaged pulmonary metastasectomy for breast cancer. Parsons and associates⁵ in 2004 reported an incidence of 22% for metastasectomy. Thus, the literature demonstrates a significant number of nonimaged pulmonary nodules that are only discovered when the lung is carefully palpitated in between two hands at the time of open thoracotomy, despite the use of 5-mm cut CT scan. However, this information is only on those who undergo metastasectomy. The clinical impact of nonimaged pulmonary nodules for metastasectomy is real. The most significant predictor of survival in patients with soft tissue osteogenic sarcoma, melanoma, and renal cell carcinoma has been shown to be the ability to render the patient disease free.¹⁴ However, we do not know whether this concept also applies with patients who have NSCLCs that are not resected. Furthermore, we were surprised with

TABLE 3. Distribution of the missed pulmonary nodule based on the known preoperatively imagined nodule's location

Location of known preoperatively imagined primary	No. of patients in study with primary tumors in this lobar location	Location of missed nodule				
		RUL	RML	RLL	LUL	LLL
RUL	69 (42%)		■ ●●●●●● ●	■ ■ ●		
RML	9 (5%)					
RLL	16 (10%)	■ ●●	■ ■ ■ ■ ●●			
LUL	45 (27%)					■ ■ ■ ■ ●●
LLL	27 (16%)				●●● ●●●●●● ●	

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe. ■ = M1; ■ = another primary; ● = benign nodule.

this high incidence because we expected it to be lower in this series compared with the incidence in previous reports because of the improvement in imaging technology. We also anticipated a lower incidence for several other reasons: the study was prospective, the CT used 5-mm cuts with intravenous contrast, the scans were read by chest radiologists, the vast majority of patients had their scan performed at our institution, which is a specialized tertiary center with four radiologists who specialize in chest radiology, and all outside films were interpreted at UAB. In addition, we also review all scans before resection. Finally patients received an integrated PET/CT scan. However, the scanner for integrated PET/CT in our and most institutions only offers 16- instead of 64-slice technology and nodules 6 to 8 mm or smaller are not PET-visible. Finally, we believed that because this study was performed on patients with NSCLC and not hematogenously disseminated metastases, the incidence of other malignant pulmonary nodules would be lower.

Because of these findings, we retrospectively re-reviewed all of the CT scans in these 37 patients to evaluate whether the “nonimaged but bimanually palpable” pulmonary nodule really was “imaged” but just not described on the chest CT scan report and was also missed by our inspection of the chest CT scan before the operation. We used our intraoperative findings to help guide our retrospective review. We also looked for a “reason” why the nodules may have been missed (eg, atelectasis). Using this technique, we found that in 17 (46%) of the 37 patients and in 6 (43%) of the 14 with malignant nodules, the nodules in retrospect may have

been imaged. It is not uncommon for patients to have small 2 to 6 mm–sized nodules that are not described by the radiologist or by our review on the scan report. We also found other additional nodules as well that may have been missed but were not palpated.

In this study, we generously assumed that if a patient were to undergo a VATS lobectomy, all the mediastinal N2 lymph nodes would be completely removed as we do during an open thoracotomy and lobectomy. This assumption is of course not true for all surgeons who perform VATS lobectomy, nor is it true for all or most surgeons who perform open lobectomy as well.¹⁵ We found that 12 patients also had unsuspected N2 disease, and this again argues for mediastinal lymph node removal or at least biopsy of all assessable N2 stations at the time of resection to prevent stage migration irrespective of whether the surgical approach is VATS or open.

We found that 14 nonimaged (or perhaps we should more accurately describe them as nondescribed) pulmonary nodules were malignant and 23 were benign. Of concern is the fact that the majority of the patients who had malignant unsuspected pulmonary nodules had a T1 lesion (64%). One might expect the patients with the larger T2 tumors to have been more likely to have had an unimaged M1 nodule in another lobe, but that was not our finding. As expected, those patients with squamous cell were more likely to have a nonimaged malignant nodule than those with adenocarcinoma. If one considers the maxSUV of the known imaged NSCLC, it was predictive. The median maxSUV of the known cancer in the 14 patients with nonimaged malignant nodules was 5.0

GTS

compared with 4.1 for the 152 who did not have a nonimaged malignant nodule ($P = .045$).

An initially suggested design for this study was to start off all procedures with a VATS and then perform finger palpation over the surface of the lung and have the findings recorded. Then a thoracotomy could have been performed and bimanual palpation carried out. This design was not chosen because of institutional review board concern that this design may have altered the standard of care that we currently use for those patients with NSCLC, which is thoracotomy without the added operative time and cost of first performing a VATS. However, despite the design chosen, it is highly unlikely that any of these relatively deep 6 mm or smaller nodules would have been palpable via VATS since all nodules were only discovered by careful bimanual palpation.

Interestingly, of the 14 patients with malignant nodules, 9 had M1 lesions and 5 had small second primary tumors. By definition, the 9 patients' nodules that are labeled M1 lesions could represent second primary tumors of the same histologic classification and have a more favorable prognosis. We treated the 5 patients' nodules that had different histologic characteristics only with a segment. No patients in this series received a pneumonectomy for the unsuspected nonimaged findings. Thus the question should also be raised whether we adequately treated these unsuspected nodules that were not M1 lesions but were new T1 lesions? If not, does the potential increased morbidity of performing an open procedure outweigh the potential benefits of better intraoperative staging if unsuspected findings are not adequately treated? Moreover, does the added morbidity or performing a wedge resection in the lobe that is not removed for a nodule that turns out to be benign nodule add morbidity as well? The answers to these questions remain unknown. Recently, we have conducted four randomized prospective studies (three published)¹⁶ to find ways to reduce the pain of open thoracotomy. We believe that the difference between open thoracotomy and lobectomy compared with VATS lobectomy has been significantly reduced with some of these techniques. The pain of thoracotomy has been drastically reduced by three measures: by avoiding the lower intercostal nerve by drilling holes in the inferior rib and using intracostal sutures instead of pericostal sutures,¹⁷ by harvesting an intercostal muscle flap before chest retraction to avoid retractor injury to the intercostal nerve of the space over which the chest is entered,¹⁸ and by injecting a local anesthetic for pre-emptive analgesia in several intercostal nerves before chest retraction.¹⁹ Our patients are encouraged to return to full activity 3 weeks after thoracotomy.

Finally, the clinical impact of this study's findings is unknown. VATS lobectomy is performed well by many surgeons, and the long-term survival of several VATS lobectomy series for NSCLC is comparable with those of open series. Walker in 2003²⁰ reported a 5-year survival of 77.9% for patients with stage I NSCLC who underwent

VATS. Similarly, Roviato and associates²¹ in 2004 reported a 5-year survival in patients with T1 N0 NSCLC of 70% and a survival of 56% in patients with T2 N0 NSCLC. Recently, Shigemura and coworkers²² from Japan reported an incredible 96.7% 5-year survival for patients with clinically staged IA NSCLC. McKenna and colleagues,²³ the true pioneers of VATS lobectomy, reported in 1998 a Kaplan-Meier 4-year survival for stage I NSCLC of 70%. If one argues that these palpated lesions are not clinically significant and that they will be identified later in the patient's follow-up studies and will be resected, then the cost of the second operation, the restaging tests, and the risk assessment studies needed before that reoperation occur all need to be considered. In addition, the added stress to the patient should be considered.

In conclusion, this prospective study finds that open lobectomy that affords bimanual palpation of the rest of the lung and not just digital palpation over the surface of the lung may discover nonimaged malignant pulmonary nodules in different lobes other than the one to be resected in 8.4% of patients with NSCLC. This finding is true despite the use of preoperative fine-cut 64-slice chest CT scan with 5-mm slices and intravenous contrast and integrated FDG-PET/CT scan. However, the clinical impact of these findings and of these small malignant pulmonary nodules is unknown.

References

1. D'Amico TA. Thoracoscopic lobectomy: evolving and improving. *J Thorac Cardiovasc Surg.* 2006;132:464-5.
2. McKenna RJ, Houck W, Fuller CB. Video-assisted thoracic surgery: lobectomy experience with 1,100 cases. *Ann Thorac Surg.* 2006;81:421-6.
3. Cerfolio RJ, Bryant AS, Ojha B, Eloubeidi M. Improving the inaccuracies of the clinical staging of patients with NSCLC: a prospective trial. *Ann Thorac Surg.* 2005;80:1207-13.
4. Cerfolio RJ, Allen MS, Deschamps C, Daly RC, Wallrichs SL, Trastek VF, et al. Pulmonary resection of renal cell carcinoma. *Ann Thorac Surg.* 1994;57:339-44.
5. Parsons AM, Detterbeck FC, Parker LA. Accuracy of helical CT in the detection of pulmonary metastases: is intraoperative palpation still necessary? *Ann Thorac Surg.* 2004;78:1910-6.
6. Kayton ML, Huvo AG, Casher J, Abramson SJ, Rosen NS, Wexler LH, et al. Computed tomographic scan of the chest underestimates the number of metastatic lesions in osteosarcoma. *J Pediatr Surg.* 2006;41:200-6.
7. Margaritora S, Porziella V, D'Andrilli A, Cesario A, Galetta D, Macis G, et al. Pulmonary metastases: can accurate radiological evaluation avoid thoracotomy approach? *Eur J Cardiothorac Surg.* 2002;21:1111-4.
8. Rena O, Papalia E, Ruffini E, Filosso PL, Oliaro A, Maggi G, et al. The role of surgery in the management of solitary pulmonary nodule in breast cancer patients. *Eur J Surg Oncol.* 2007;33:546-50.
9. McCormack RM, Bains MS, Begg CB, Burt ME, Downey RJ, Panicek DM, et al. Role of video-assisted thoracic surgery in the treatment of pulmonary metastases: results of a prospective trial. *Ann Thorac Surg.* 1996;62:213-7.
10. Rusch VW. Pulmonary metastasectomy. Current indications. *Chest.* 1995;107:322S-31.
11. Cerfolio RJ, Bryant AS, Ojha B, et al. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. *J Thorac Cardiovasc Surg.* 2005;129:1232-41.
12. Cerfolio RJ, Bryant AS, Ojha B, Bartolucci AA, Eloubeidi MA. The maximum standardized uptake values on positron emission tomography

- of a non-small cell lung cancer predict stage, recurrence, and survival. *J Thorac Cardiovasc Surg.* 2005;130:151-9.
13. Mountain CF. The international system for staging lung cancer. *Semin Surg Oncol.* 2000;18:106-15.
 14. Pogrebnjak HW, Pass HI. Initial and reoperative pulmonary metastasectomy: indications, technique and results. *Semin Surg Oncol.* 1993;9:142-9.
 15. Little AG, Rusch VW, Bonner JA, Gaspar LE, Green MR, Webb WR, et al. Patterns of surgical care of lung cancer patients. *Ann Thorac Surg.* 2005;80:2051-6.
 16. Cerfolio RJ, Bryant AS, Bass CS, Bartolucci AA. A prospective, double-blinded, randomized trial evaluating the use of preemptive analgesia of the skin before thoracotomy. *Ann Thorac Surg.* 2003;76:1055-8.
 17. Cerfolio RJ, Price TN, Bryant AS, Sale Bass C, Bartolucci AA. Intracostal sutures decrease the pain of thoracotomy. *Ann Thorac Surg.* 2003;76:407-11.
 18. Cerfolio RJ, Bryant AS, Patel B, Bartolucci AA. Intercostal muscle flap reduces the pain of thoracotomy: a prospective randomized trial. *J Thorac Cardiovasc Surg.* 2005;130:987-93.
 19. D'Andrilli A, Ibrahim M, Ciccone AM, Venuta F, De Giacomo T, Massullo D, et al. Intrapleural intercostal nerve block associated with mini-thoracotomy improves pain control after major lung resection. *Eur J Cardiothorac Surg.* 2006;29:790-4.
 20. Walker WS, Codispoti M, Soon SY, Stamenkovic S, Carnochan F, Pugh G. Long-term outcomes following VATS lobectomy for non-small cell bronchogenic carcinoma. *Eur J Cardiothorac Surg.* 2003;23:397-402.
 21. Roviato G, Varoli F, Vergani C, Nucca O, Maciocco M, Grignani F. Long-term survival after videothoracoscopic lobectomy for stage I lung cancer. *Chest.* 2004;126:725-32.
 22. Shigemura N, Akashi A, Funaki S, Nakagiri T, Inoue M, Sawabata N, et al. Long-term outcomes after a variety of video-assisted thoracoscopic lobectomy approaches for clinical stage IA lung cancer: a multi-institutional study. *J Thorac Cardiovasc Surg.* 2006;132:507-12.
 23. McKenna RJ, Wolf RK, Brenner M, Fischel RJ, Wurnig P. Is lobectomy by video-assisted thoracic surgery: an adequate cancer operation? *Ann Thorac Surg.* 1998;66:1903-8.

Discussion

Dr Thomas A. D'Amico (Durham, NC). I congratulate both authors for this thoughtful study that describes the incidence of nodules that may have been missed at resection for lung cancer, a concept derived from experience with thoracoscopic metastasectomy.

Just as with metastasectomy, it is possible that thoracoscopic exploration for resection of lung cancer will miss nodules, some of which may be malignant. However, in this study, as in others, the majority of missed nodules are benign. Regarding the malignant nodules, the presence has been demonstrated, but the significance, as you said, has not. I and others, I'm sure, are surprised that so many of the nodules missed were 6 mm or larger, including all 3 of the noncarcinoid second primary lesions. One would expect a 64-slice scanner to perform better.

Future studies are required to elucidate the significance of these missed nodules in patients with both benign and secondary pulmonary malignancy. It is possible that sequential thoracoscopic procedures have a better outcome than thoracotomy in some patients, depending on the biology of the tumor.

In light of your study and these comments, I have four questions. What percentage of your patients underwent mediastinoscopy? You found many more patients with N2 disease than with second primary lesions.

Second, why did you not include thoracoscopic exploration as part of your study to determine the true incidence of the missed nod-

ules? Thoracoscopic exploration may have found pleural or other disease that would preclude thoracotomy.

Third, in this study, 14 of 166 patients had missed malignant nodules. Of these 14, 9 of 14, or 5%, were thought to have M1 lesions. Five of those 9 already met criteria for adjuvant chemotherapy. Thus only 4 patients, or 2%, had nodules that were found that changed their therapy.

As well, 5 of 166 patients were thought to have second primary tumors. Two of these 5 tumors were carcinoids, and although you refute that they are tumorlets, by definition they are. Tumorlets are carcinoids 5 mm or less that do not show up on CT scan, so by definition these are tumorlets. One of the 5 was a pleura-based nodule that you would have thought could have been found thoracoscopically. One of the 5 that you resected was actually N2. Therefore, there is only 1 patient left with a second primary that definitely can be said to have benefited, and it is not certain that a second thoracoscopic procedure would have been less effective than that.

Finally, you found many more benign lesions than malignant ones. Do you completely discount the potential negative effects of these added resections?

I appreciate the authors for investigating these difficult issues.

Dr Cerfolio. Dr D'Amico, thank you very much. Four questions but actually six sentences that require my comment. First of all, all nodules were 6 mm or less, not 6 mm or greater. All nodules were 6 mm or less.

Second, you said that more patients had N2 disease. That is not true. Twelve patients had N2. That's 7%. That's less than 14 patients who had malignant disease.

Dr D'Amico. According to the manuscript, the majority were 6 mm or larger.

Dr Cerfolio. No, they were not. You can go back and look at Table 2.

Dr D'Amico. I have your manuscript.

Dr Cerfolio. No, I'm talking about the nodules that we found at the time of surgery. They were all 6 mm or less.

Dr D'Amico. As to the second issue, I said there were more with N2 disease than second primary lesions. We would all argue that it is important prognostically to find M1 disease, and no one would argue that it is not, but we are probably not going to affect the survival of those patients, and, in fact, the original thoracotomy was a negative effect. However, more N2 disease was found than second primary disease.

Dr Cerfolio. There were more N2 lesions found than second primary lesions, that's true, but I do not know the clinical significance of that. However, there were more patients who had malignant pulmonary nodules than had unsuspected N2. You asked me when we do mediastinoscopy. Well, as you know, any time a CT scan questions an N2 or an integrated PET/CT scan questions an N2, we do mediastinoscopies. In this series, I think 38 or 40 patients got mediastinoscopy. If any of them were positive, they were eliminated from this study. All these were mediastinoscopy-negative. Actually, 1 of them had a positive 4R, so it was a falsely negative mediastinoscopic result. All the rest of them were in endoscopic ultrasound range. We did not routinely use endoscopic ultrasound because of the prospective study we published in *Chest* in December 2006 (130:1791-5).

Your next question was about, by definition, what is a tumorlet. By definition, a carcinoid tumorlet is a carcinoid not seen by CT scan, less than 5 mm. Go back and look at the size in the table of the carcinoids that were removed.

Finally, you asked about the morbidity of removing benign nodules. That is a very good question. I do think that because you are using a Bovie electrocautery device (Bovie Medical Corporation, St Petersburg, Fla), you are using a stapler, you are getting inflammation in the part of the lung that you want to leave, and I do think that there is morbidity in that. I think it is a very good point.

Dr D'Amico, we are on the same page. I think your comments are great.

Dr Raja M. Flores (*New York, NY*). I think this is a very interesting paper, but I would be very cautious about how you incorporate these data into your clinical practice. The implications are that you should not be doing a VATS lobectomy because you would miss lesions that you would otherwise find at thoracotomy. Then you need to take it one step further: Do we do a sternotomy or bilateral thoracotomy to palpate the contralateral lung? I think these data, while interesting, need to be looked at a little more in depth.

Dr Cerfolio. That is the same comment that we hear all the time about metastasectomies. If you believe that you are going to find more nodules at the time of thoracotomy, why not explore both sides? I would caution you and say that those data are looking at the nodules in the same lung. We have no data that the incidence is as high in the other lung, especially if the scan shows no nodules there. So be careful not to assume that just because we find more nodules when the CT scan shows 1 or more, we will find 1 nodule when the CT shows none. I do not know of any data that would suggest to just randomly explore a chest that has no evidence of a nodule.

Dr Nasser K. Altorki (*New York, NY*). You may have mentioned it already, but was there a correlation between the size of the index lesion and the presence of these secondary nodules?

Dr Cerfolio. I tried to show that in one pie graph. I figured most of these patients would have T2, larger lesions. They did not. Most were T1. So 9 of these patients had T1 lesions, less than 3 cm, and yet they had unsuspected malignant nodules.

Dr. Altorki. This is a pretty broad category. A 3-cm tumor and a 1-cm tumor are clearly different.

Dr Cerfolio. You are right. I would have to go back and see the exact size.

Dr Steven D. Herman (*Brooklyn, NY*). What do you think the impact on the study outcome and conclusions would be of doing the CT scans at 1-mm cut slices as opposed to 5-mm cuts, providing higher resolutions of small lesions, or by repeating studies closer to the surgery date if the studies are aged? Given the fast speed of CT scanning available in 64-slice machines, this may offer more accurate imaging.

Dr Cerfolio. Without studying it, I do not know the answer, but my guess is that we would find more of these nodules. As Dr D'Amico said, we are going to find a lot more benign nodules as well. Then we are going to go to the operating room and do a right thoracotomy. I will say in the operative note that there's a 2-mm nodule in the left upper lobe or 1-mm nodule in the left lower lobe that I am assuming is benign, but I proceeded with resection. I think we are going to see more of these.