Thoracic surgical operations in patients enrolled in a computed tomographic screening trial

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Objective: Screening for lung cancer with computed tomography may detect cancers at an earlier stage but may also result in overdiagnosis. We reviewed the thoracic surgical operations performed on patients enrolled in our computed tomographic screening program.

Methods: From January 1999 through December 2002, screening computed tomography for lung cancer was performed annually on 1520 participants. All participants were at least 50 years old and smoked more than 20 pack/y. We found 3130 indeterminate pulmonary nodules in 1112 participants (73%). Fifty-five participants (3.6%) underwent 60 thoracic operations for a variety of indications. The medical records of these 55 patients were reviewed.

Results: Indications for operation included suspicious pulmonary nodules, mediastinal adenopathy, and a spontaneous pneumothorax. Operations performed included a lobectomy in 37 cases, wedge resection in 11, segmentectomy in 6, video-assisted thoracoscopic surgical talc pleurodesis in 1, bilobectomy in 2, mediastinoscopy in 2, and anterior mediastinotomy in 1. Benign disease was found in 10 patients (18.1%), and lung cancer was found in 45 (81.9%), 2 of whom had metachronous lung cancers. Cell types were adenocarcinoma in 15 cancers, bronchioloalveolar cell carcinoma in 13, squamous cell in 13, carcinoid in 2, small cell in 2, and large cell and undifferentiated non–small cell in 1 case each. Twenty-eight cancers were classified as stage IA, 4 as IB, 4 as IIA, 1 as IIB, 4 as IIIA, 3 as IIIB, 1 as IV, and 2 as limited small cell carcinoma. Complications occurred in 27% of patients. Operative mortality was 1.7%.

Conclusion: Computed tomographic screening finds a large number of indeterminate pulmonary nodules in smokers 50 years old or older, most of which are observed and not operated on. Although 47 cancers were detected thus far in this highly selected group of patients, this represents only 1.5% of the pulmonary nodules identified.

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Lung cancer is the most common fatal malignancy in both men and women and is usually diagnosed at an advanced stage. Fewer than 25% of the patients have localized disease that is potentially curable by surgical resection at the time of diagnosis.[1] Previous attempts to screen large populations of high-risk patients for early lung cancer with chest radiographs and sputum cytologic examination have not decreased mortality from this disease.[2-6] Recently, low-dose chest computed tomographic (CT) screening has been shown to detect lung cancer at an earlier stage and thus may have an impact on lung cancer mortality.[7-9] In 1999, the Mayo Clinic in Rochester, Minnesota, enrolled 1520 participants who underwent low-dose spiral CT screening. All participants were symptom-free men and women 50 years old or older who had a 20 pack-year history of smoking within the previous 10 years. The prevalences of lung cancer and pulmonary nodule findings and the 1- and 2-year incidences of findings from our institution have previously been reported.[10,11] Little information, however, is available about the type and number of thoracic surgical procedures that occur as a result of CT screening. The purpose of this report is to update our incidence findings and to review our early operative experience after CT screening for lung cancer.

Methods

The protocol for all participants in the Mayo Clinic low-dose spiral CT screening program for lung cancer has previously been reported elsewhere.[10,11] One thousand five hundred twenty participants underwent a baseline prevalence CT examination and three subsequent annual incidence examinations. The medical records of those participants who underwent a thoracic surgical procedure were reviewed for surgical indications, preoperative evaluation, surgical procedure, pathologic diagnosis, perioperative morbidity and mortality, and follow-up. Operative mortality included all patients who died within 30 days of operation and those patients who died later but during the same hospitalization. This study was approved by the Mayo Foundation institutional review board. Informed consent was obtained in all cases.

Results

As of November 2002, a total of 3130 indeterminate pulmonary nodules had been identified in 1112 (73%) of the 1520 participants (Table 1). Further evaluation of these nodules was obtained at the discretion of the participants' individual physicians. Additional studies most commonly obtained included thin-section chest CT, nodule-enhancement CT, positron-emission tomography (PET), and occasionally, bronchoscopy and transthoracic needle aspiration.

Sixty thoracic surgical procedures were performed on 55 participants (33 women and 22 men). Age was a median of 62 years and ranged from 52 to 80 years. Fifty patients underwent a single procedure and 5 underwent two. Indication for the initial procedure was a pulmonary nodule with a high index of suspicion for cancer in 53 patients, mediastinal adenopathy in 1, and spontaneous pneumothorax in 1. Specific indications for pulmonary nodule resection included nodule enlargement on serial CTs in 32 patients, a new nodule in 12, nodule enhancement in 5, and morphologic appearance worrisome for malignancy in 4 (Table 2).

TABLE 1. Pulmonary nodules found on screening CT

	Participants	Nodules
Baseline CT	1520	1646
First annual incidence CT	1478	837
Second annual incidence CT	1441	382
Third annual incidence CT	1358	265
Total		3130

TABLE 2. Indication for initial surgical procedure

Indication	No. of patients
Enlarging nodule	32
New incidence of nodule	12
Positive CT nodule enhancement	5
Morphologic appearance worrisome for cancer	4
Enlarged mediastinal lymph nodes	1
Spontaneous pneumothorax	1

The number of pulmonary nodules detected by CT in these 53 patients ranged from 1 to 7 (median 3). A single nodule was observed in 15 patients, 2 nodules were observed in 7, 3 nodules were observed in 6, 4 nodules were observed in 11, 5 nodules were observed in 8, 6 nodules were observed in 5, and 7 nodules were observed in 1. These nodules were followed up for a median of 4.3 months before surgical intervention (range 21 days–31 months). Preoperative evaluation included thin-section CT in 25 cases (13 patients had 1 examination, 8 had 2, 3 had 3, and 1 had 4), CT nodule enhancement in 14 cases (13 patients had 1 examination and 1 had 2), and PET scan in 16 cases. Preoperative bronchoscopy was performed in 5 patients. Results were normal in 3 cases and identified an endobronchial squamous cell carcinoma in 2 patients. Transthoracic needle aspiration was done in 5 patients; it demonstrated lung cancer in 4 cases and was nondiagnostic in the other.

The surgical procedure was performed in the 53 patients with a pulmonary nodule after the prevalence CT in 22 patients, after the first annual incidence CT in 9, after the second annual incidence CT in 15, and after the third annual incidence CT in 7. The procedures performed on these 53 patients are shown in Table 3. The 44 patients with lung cancer underwent a lobectomy in 35 cases, bilobectomy in 2, segmentectomy in 3, and wedge resection in 4. The limited resections were performed because of poor pulmonary function in 6 cases and for advanced stage disease in 1.

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TABLE 3. Initial operations performed for pulmonary nodules

Operation type	No. of patients
Lobectomy	36
Right upper	9
Right middle	3
Right lower	8
Left upper	10
Left lower	6
Bilobectomy	2
Segmentectomy	6
Wedge resection	9
Single wedge resection	7
Multiple wedge resections	2

TABLE 4. Diameters of pulmonary nodules resected

Diameter (cm)	Malignant nodules	Benign nodules*	Total nodules
≤0.5	2	7	9
0.6–1	17	11	28
1.1–2	24	5	29
2.1–3	3	1	4
3.1–4	1	0	1
>4	1	0	1

*No size data were available for 7 benign nodules.

TABLE 5. Diameters of malignant pulmonary nodules

Stage of carcinoma	Size of nodule (cm, median and range)
IA	1.1 (0.5–3.0)
IB	1.1 (0.7–2.0)
IIA	1.5 (1.0–1.8)
IIB	6.0*
IIIA	2.4 (1.3–3.5)
IIIB	1.5 (1.0–1.6)
IV	1.2*

*Only 1 patient.

All 44 patients with lung cancer underwent concomitant mediastinal lymphadenectomy, 19 had preliminary video-assisted thoracoscopic surgery (VATS), and 3 had preliminary mediastinoscopy. The 9 patients with benign pulmonary nodules all underwent a limited pulmonary resection, except 1 who underwent a lobectomy for a centrally located nodule that was not amenable to wedge excision. These resections were performed through a thoracotomy in 6 cases and by VATS in 3 cases.

Lymph node enlargement in the single patient with mediastinal adenopathy was detected after the third annual incidence CT and this patient underwent a left anterior mediastinotomy that demonstrated metastatic pulmonary adenocarcinoma. The single patient with a spontaneous pneumothorax had it diagnosed between the prevalence and first annual incidence CTs and underwent bilateral bleb resections with pleurodesis by VATS.

TABLE 6. Pathologic classification of resected pulmonary nodules

Pathologic type	No. of nodules
Benign nodules	31
Granuloma	12
Intrapulmonary lymph node	5
Lung scar or fibrosis	4
Bleb or bullae	3
Pneumocystic hyperplasia	2
Visceral pleural thickening	2
Hamartoma	1
Pulmonary embolism	1
Bronchoalveolar cell hyperplasia	1
Malignant nodules	48
Squamous cell carcinoma	15
Bronchoalveolar carcinoma	15
Adenocarcinoma	12
Carcinoid	3
Small cell carcinoma	2
Large cell carcinoma	1

Postoperative complications occurred in 27% of cases and included prolonged air leak in 6 patients, atrial arrhythmias in 4, pneumonia in 4, and ileus, cerebral vascular accident, depression, and temporary vocal cord paralysis in 1 each. There was 1 operative death (operative mortality 1.7%) from an intracerebral hemorrhage 14 days after a left lower lobectomy for a stage IIIA (T3 N1 M0) adenocarcinoma.

Seventy-nine pulmonary nodules (31 benign and 48 malignant) were resected in the 53 patients whose indication for operation was a suspicious pulmonary nodule. A single nodule was resected in 33 patients, 2 were resected in 15, 3 were resected in 4, and 4 were resected in 1. The diameters of the resected nodules are described in Tables 4 and 5. Nine patients had only benign nodules resected; the remaining 44 all had lung cancer. Cancer cell types in these 44 patients were squamous cell in 13 patients, adenocarcinoma in 13, bronchioloalveolar cell in 13, carcinoid in 2, small cell in 2, and large cell in 1 (Table 6). Twenty-seven patients had disease classified as stage IA, 3 as IB, 4 as IIA, 1 as IIB, 3 as IIIA, 3 as IIIB, and 1 as IV. In the group of 7 patients with advanced stage cancer (IIIA, IIIB, or IV), 3 had their cancer operated on within 2 months of detection on screening CT and 4 were observed for a median of 18.2 months (range 6-26.8 months) before resection. The 2 patients with small cell carcinoma had disease classified as limited small cell carcinoma. The T classifications in patients with non–small cell carcinoma were T1 in 33 cases, T2 in 4, T3 in 1, and T4 in 4. The N classifications were N0 in 32 cases, N1 in 8, and N2 in 2.

Follow-up was complete for all 54 surviving patients and ranged from 0.1 to 41 months (median, 19 months). Five patients have died, all from lung cancer. Forty-nine patients are currently alive, 3 with recurrent lung cancer. The initial site of recurrent cancer was locoregional in 2 cases, systemic in 2 cases, and both in 4 cases.

Five patients had a subsequent thoracic operation. One patient initially had a left lower lobectomy for a T2 N0 M0 adenocarcinoma with bronchioloalveolar features and underwent a subsequent right upper lobectomy for a T2 N0 M0 adenocarcinoma 11 months later. This patient is currently alive with no evidence of disease 14 months after the second operation. Two patients had mediastinal lymphadenopathy develop 6 and 12 months after curative pulmonary resection for stage IA and IIA lung cancer, respectively. Mediastinoscopy revealed recurrent cancer in both patients. Both were treated with radiation and chemotherapy and are alive 25 and 41 months after the initial resection, respectively. The fourth patient had a right middle lobectomy for stage IA typical carcinoid and underwent a right upper lobe wedge resection for an undifferentiated non–small cell carcinoma (T1 N0 M0) 22 months later. This patient died of disseminated non–small cell carcinoma 11 months after the second operation. The fifth patient had a malignant pleural effusion develop 10 months after wedge resection for extensive stage IIIA adenocarcinoma. A VATS talc pleurodesis was performed, and this patient died 5 months after the original surgery.

Discussion

Screening a high-risk population for lung cancer with low-dose spiral CT results in the detection of multiple pulmonary nodules, most of which are benign.[7-11] Management of these nodules poses significant diagnostic and therapeutic challenges, and few guidelines have emerged as to how these patients should be evaluated.[12,13] Options available include either further evaluation at the time of discovery with thin-section CT, CT enhancement, PET scan, biopsy (transbronchial or transthoracic), VATS resection, and thoracotomy or surveillance with high-resolution CT every 3 to 6 months. Evaluation and management of the individual participant after detection of the pulmonary nodule were not part of our CT screening trial protocol. Instead, all patients were subsequently evaluated by their personal physicians with a combination of the management options mentioned here.

In our experience, the small diameter of most of these pulmonary nodules limits the usefulness of some diagnostic imaging modalities. Imaging with PET or CT enhancement is limited to nodules that are 1 cm or more in diameter.[14] This size limitation would exclude 25% of all nodules and 16% of the malignant nodules found in our series from noninvasive evaluation. Invasive diagnostic procedures, whether by needle aspiration, bronchoscopy, or VATS, are also limited by both the size of the nodule and the anatomic location.[15,16] Preoperative localization with methylene blue injection and wire placement may be of some value in patients considered for VATS or thoracotomy.[16,17] In our series, preoperative CT wire localization was used in 2 cases. With this stepwise, gradual approach, the number of explorations for benign disease was minimized to fewer than 1% of the participants.

Controversy exists regarding the extent of pulmonary resection necessary for cure and the need for lymphadenectomy in these small cancers.[18-20] Formal resection of the tumor by lobectomy and complete mediastinal lymphadenectomy has been the standard of care practiced by most thoracic surgeons.[21] Limited resection, in contrast, appears to increase local recurrence and may compromise survival.[22,23] Also, in one series 7% of patients with lung cancers smaller than 1 cm in diameter were demonstrated to have N1 or N2 lymph node metastases.[24] In our series 15.7% of patients with lung cancer 1 cm or less in diameter had N1 lymph node involvement. Currently, few data are available to indicate the effect of limited pulmonary resection on survival and local recurrence with these small cancers.[22,23] Thus we continue to recommend a formal anatomic pulmonary resection with mediastinal lymphadenectomy for patients with lung cancer of any size who otherwise are in good health. A randomized trial comparing these two options is necessary to determine the proper treatment of small lung cancers.

CT screening results in the detection of smaller pulmonary nodules than those detected by screening chest radiography.[7] Some of these nodules are, of course, malignant. Whether earlier detection of lung cancer by CT screening will alter the natural history of this disease has not yet been determined. However, reported survival rates of 80% after pulmonary resection for stage IA lung cancer detected by CT are encouraging.[25] Follow-up in our series is too short to evaluate of the impact of CT screening on survival. Some authors are doubtful of a survival benefit because of the tendency of some lung cancers to metastasize even at an apparently localized stage.[26,27] Currently, there is no proof that CT screening will improve overall mortality from lung cancer.

Unfortunately, CT screening also detects advanced cancers. Eight of our patients who had surgery were at stage IIIA or higher, and there were 3 other participants with advanced cancer in our CT screening trial who did not undergo any surgical intervention. These advanced cancers, as well as some of the small cell cancers detected, suggest that CT screening may not have as significant an impact on mortality as initially suggested. We await the findings of the National Lung Cancer Screening Trial by the American

College of Radiology Imaging Network that is currently underway.

Mortality associated with surgical resection was low (1.7%), and fortunately no deaths occurred among the patients found to have only benign disease. Morbidity was significant, indicating that pulmonary resection should not be undertaken lightly. For the present, careful patient selection and surgical judgment are critical in determining who should undergo surgical intervention. Observing small, potential curable lung cancers may allow cells to metastasize, negating the value of CT screening. Conversely, if too many benign nodules are resected, patients and their physicians will not want to consider CT screening. Perhaps in the future an appropriate percentage of "negative" or benign pulmonary resections will be established

In conclusion, low-dose CT screening for lung cancer detects a large number of indeterminate pulmonary nodules. Although most of these nodules are benign, a significant number of early lung cancers are detected in this selected group of patients. Although the mortality associated with surgery in these patients is low, careful patient selection is necessary to avoid the performance of unnecessary procedures for benign disease. Whether early detection of lung cancer by CT screening followed by pulmonary resection decreases cancer mortality remains unknown.

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Discussion

Dr John D. Mitchell *(Denver, Colo).* Epidemiologists will tell you that for a screening test implemented on a large scale to be effective, it must provide benefit to the targeted population, usually through improved survival with respect to the disease in question. At the same time, the screening process should not impose undue harm on the population by way of numerous false-positive results or needless follow-up tests, nor should it place a disproportionate burden on society, typically through excessive costs. Low-dose CT is the most promising technology used to date to screen for lung cancer in high-risk populations, although questions persist regarding actual survival benefit, the so-called overdiagnosis of indolent tumors, and cost.

What epidemiologists do not tell you is what to do with all those tiny nodules identified on the scans. In this report Crestanello and colleagues have described their surgical experience associated with the lung cancer screening trial with CT at the Mayo Clinic. The management of these patients, with aggressive intervention in those with malignancy and minimization of invasive procedures in those with a benign process, is of practical importance to all thoracic surgeons. I have three questions for Dr Crestanello.

First, I wonder if you could discuss in greater detail from your experience with this study how these patients with a positive screening result should be evaluated. I do not mean someone with an obvious 3-cm cancer, but patients with much smaller nodules, perhaps less than 1 cm, where PET may not be helpful, or patients with multiple nodules. When should these patients be observed, and when should intervention be pursued? Have you and your colleagues devised an evaluation strategy or treatment algorithm on the basis of your findings?

Dr Crestanello. Yes, we have an algorithm recommended for patients found to have nodules on the CT. It is basically based on the size of the nodules, on the aspects of the nodules. For nodules smaller than 4 mm in diameter, it is recommended that the patient have a thin-section CT in 6 months. For nodules in which the diameter is between 4 and 8 mm, thin-section CT is recommended in 3 months. For nodules between 8 and 20 mm, thin-section CT or a nodule-enhancement CT study or a PET scan is recommended immediately. And obviously, for nodules that are bigger than 20 mm in diameter, a biopsy, surgical or transthoracic, is recommended. So how do you interpret the results of the further studies? Well, if there is any enlargement of the nodules in the subsequent studies, a surgical biopsy is recommended, as is the case if the CT enhancement study or PET results are positive.

Dr Mitchell. Second, in many CT screening studies, the percentage of stage IA cancers is often quite high, between 80% and 90%. In this study, although still high, the percentage was more around 60%. Why do you think you and your colleagues found fewer early stage tumors or, to put it another way, a higher percentage of more advanced tumors?

Dr Crestanello. That is an interesting question that also puzzled us. We compared our study with the other two large studies, which are the studies from Japan[7] and New York.[8,25] The cancers that they found, in the first study 15 in 3000 patients and in the second study 27 in 1000 patients, were IA disease in 81% and 85% of cases, respectively. Ours was 59%. The populations were different. One was in Japan, the other was in New York, and ours was in the Midwest. Also, the criteria for enrollment in the trial were different. In the trial in New York, the age was 60 years or older. In our study it was 50 years or older. The smoking criteria were also different. Ours was greater than 20 packs/y and theirs was greater than 10 packs/y. Also, the incidences of cancer in the New York study and our study were different. There were 27 cancers in 1000 patients in their study, and in our study there were 54 cancers in 1500 patients. We believe that all those factors may have contributed to this difference in the incidence of early stage cancers.

Dr Mitchell. Finally, although CT is quite good at identifying abnormalities, it is possible to miss tumors through CT screening. Were there any cases like this in your series in which a patient enrolled in the study had symptoms from lung cancer that was missed by the screening?

Dr Crestanello. No, there were no such cases of which I am aware. There was 1 patient who had cancer diagnosed on the basis of sputum cytologic examination who was enrolled in the CT scanning trial. The patient had a small cell cancer and was not operated on and is not included in this series.

Dr Douglas Wood *(Seattle, Wash).* I want to follow up Dr Mitchell's last question regarding a more advanced cancer that showed up because of symptoms. Have you looked at this in your data? Dr Mitchell rightly pointed out the most compelling aspect, which is the problem of screening false-positives, but one of the other aspects is this problem of missed cancers. You only operated on 2% of nodules, or even less than that, and the question is whether there were nodules that on follow-up 4 months later or 6 months later or a year later you found to be cancers and in retrospect wished you had operated on.

Dr Crestanello. Yes, there were some cases like that. In the CT scanning trial there were nodules that were not initially identified on the scan, and then in retrospect after reviewing the scan after the first or the second annual incidence the scan was done, they were identified in that situation. But they were all small nodules, and I do not think that early operation on those patients would have made a difference in the prognosis of these patients. There were no big nodules that were missed. Those nodules that were diagnosed in retrospect after a nodule appeared on subsequent scans were all small nodules, in the 4-mm range or smaller.