ORIGINAL ARTICLE

Surgical Resection of Benign Nodules in Lung Cancer Screening: Incidence and Features

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ABSTRACT

Introduction: Interventions and surgical procedures are common for nonmalignant lung lesions detected on lung cancer screening (LCS). Inadvertent surgical resection of benign nodules with a clinical suspicion of lung cancer can occur, can be associated with complications, and adds to the cost of screening. The objective of this study is to assess the characteristics of surgically resected benign nodules detected on LCS computed tomography which were presumed to be lung cancers.

Methods: This retrospective study included 4798 patients who underwent LCS between June 2014 and January 2021. The benign lung nodules, surgically resected with a presumed cancer diagnosis, were identified from the LCS registry. Patient demographics, imaging characteristics, and pathologic diagnoses of benign nodules were analyzed.

Results: Of the 4798 patients who underwent LCS, 148 (3.1%) underwent surgical resection of a lung nodule, and of those who had a resection, 19 of 148 (12.8%) had a benign diagnosis (median age = 64 y, range: 56–77 y; F = 12 of 19, 63.2%; M = seven of 19, 36.8%). The median nodule size was 10 mm (range: 6–31 mm). Most nodules were solid (15 of 19, 78.9%), located in the upper lobes (11 of 19; 57.9%), and were peripheral (17 of 19, 89.5%). Most nodules (13 of 17; 76.5%) had interval growth, and four of 17 (23.5%) had increased fluorodeoxyglucose uptake. Of the 19 patients, 17 (89.5%) underwent sublobar resection (16 wedge resection and one segmentectomy), whereas two central nodules (10.5%) had lobectomies. Pathologies identified included focal areas of fibrosis or scarring (n = 8), necrotizing granulomatous inflammation (n = 3), other nonspecific inflammatory focus (n = 3), benign tumors (n = 3), reactive lymphoid hyperplasia (n = 1), and organizing pneumonia (n = 1).

Conclusions: Surgical resections of benign nodules that were presumed malignant are infrequent and may be unavoidable given overlapping imaging features of benign and malignant nodules. Knowledge of benign pathologies that can mimic malignancy may help reduce the incidence of unnecessary surgeries.

Keywords: Lung cancer screening; Chest CT; Radiology; Thoracic surgery

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Drs. Archer and Mendoza contributed equally to this work.

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Introduction

Despite modern advances in lung cancer treatment, lung cancer remains the leading cause of cancer-related deaths in the United States.[1,2] Lung cancer screening (LCS) with low-dose chest computed tomography (CT) can diagnose lung cancer at earlier stages and reduces lung cancer-specific and all-cause mortality in select at-risk populations in the setting of clinical trials[3–6] and clinical implementation.[7] Adults aged 50 to 80 years with at least 20 pack-years of smoking history who are current smokers or quit within the past 15 years are eligible for LCS.[7]

Despite the proven benefits of LCS, concerns still need to be addressed regarding its potential drawbacks, including overdiagnosis and false-positive lung cancer diagnosis. Initial estimates for overdiagnosis in the National Lung Screening Trial and the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) were 18.5% and 19.7%, respectively, in their initial years but dropped to 3% and 8.9% with long-term follow-up.[3,6] The reported false positivity rates vary widely across studies, with reported rates of 7.9% to 49.3% for baseline screening and 0.6% to 28.6% for subsequent screening rounds. This variation is likely because of differences in how a false-positive result is defined.

To standardize the reporting and management of lung nodules identified during LCS, the American College of Radiology introduced Lung-RADS.[8] In this system, identified nodules are categorized on the basis of the probability of lung malignancy, relying on nodule characteristics such as size, density, stability or growth over time, and other features that may increase suspicion for malignancy such as spiculations and locoregional lymphadenopathy. These categories and corresponding malignancy probability determine the identified nodule's management.[8] Retroactive application of Lung-RADS to the National Lung Screening Trial database revealed a reduction in false-positive result.[9,10] Retroactive application of Lung-RADS to clinical data in an LCS program also yielded similar results.[11] Nodules reported to be "suspicious" or "very suspicious" using Lung-RADS have a high likelihood of malignancy.[12]

Nonetheless, false-positive results are not uncommon as most nodules identified on LCS are benign. Many false-positive examinations detected infectious or inflammatory nodules that eventually resolve on follow-up.[12–14] There are, however, limited data on surgically resected benign nodules considered malignant before surgery. The objectives of our study are to determine the rate of resections for benign nodules that were presumed malignant in a large established LCS program and determine the imaging and pathologic features of these nodules.

Materials and Methods

Patients and Review of Medical Records

Written informed consent was waived for this HIPAA-compliant, institutional review board-approved (IRB2019P003363) retrospective study conducted in a large quaternary medical center with an established LCS program.

The patients who underwent surgical resection of benign nodules with a presumed cancer diagnosis were identified from the institutional LCS registry database between June 2014 and January 2021 maintained by the radiology department as per American College of Radiology requirements.

The patient characteristics, radiology reports, surgical procedures, and pathologic diagnosis of resected nodules were collected from electronic medical records (EPIC, Verona, WI). The Lung-RADS category of the nodule at the time of detection was extracted from the LCS CT report. The number of days from detection to resection, type of surgery (wedge, segmentectomy, or lobectomy), and surgical complications were captured.

Review of Imaging

The first LCS study of resected lung nodules was selected for image analysis. A board-certified radiologist specializing in lung cancer imaging (DPM) and a thoracic imaging fellow (JMA) reviewed images concurrently on our institutional PACS (Visage 7, PRO Medicus Ltd., Richmond, Australia). Imaging findings were determined and recorded by consensus. Imaging features included for the nodule were size, lobe, axial location (central for inner third versus peripheral for outer two-thirds), density (solid, ground-glass, or part-solid), and mediastinal or hilar lymphadenopathy (a lymph node larger than 10 mm in the short axis). On follow-up CT, when performed, the evolution of the nodule was determined as stable or enlarged (increase in diameter by at least 1.5 mm). When performed, the standardized uptake value for the nodule on fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT was classified as negative (standardized uptake value [SUV] < 2), mild (SUV of 2–4), moderate (SUV of 4–8), or intense (SUV > 8).

Results

Patient Sample

A total of 4798 patients underwent 9148 low-dose chest CT for LCS during the study period. Of these, 148 (3.1%) underwent surgical resection of their nodule, and 19 of 148 (12.8%) had a benign diagnosis. The median age of the patients was 64 years old (range: 56–77 y), and most were female (F = 12 of 19, 63.2%; M = seven of 19, 36.8%). See Table 1 for patient characteristics, nodule characteristics, and final pathologic diagnoses.

Imaging Characteristics

There were 11 nodules identified during the baseline LCS CT, whereas the remaining eight were identified during the annual screening. At the time of detection, the nodules had a median size of 10 mm (range 6–31 mm; Table 1). Most (15 of 19) were solid in density (78.9%), three (15.8%) were part-solid, and one (5.3%) was ground-glass. The lobar distribution was as follows: right upper lobe = 6; left upper lobe = 5; right lower lobe = 4; left lower lobe = 3; right middle lobe = 1. Most were peripheral in location: peripheral = 17; central = 2.

All but two patients (17 of 19) had follow-up CT (range 1–6 mo) after the initial detection of the nodule. Of these, 13 (76.5%) had interval increase in size (Fig. 1*A*–*D*), whereas four (23.5%) were stable. Thirteen nodules were further evaluated with FDG-PET/CT (SUV range: 0.5–10.7). Most nodules had no significant (nine of 13; 69.2%) or mild (two of 13; 15.4%) FDG uptake (Fig. 1*A*–*D*). Two nodules (15.4%) had intense FDG uptake (Fig. 2*A*–*D*). Those with reported enlarged lymph nodes (n = 3) only had mild nodal FDG uptake.

Surgical Resection and Pathologic Diagnosis

Of the 19 patients with nodules, 17 underwent sublobar resection (16 wedge resections and one segmentectomy) and two had lobectomies. Two patients with wedge resections had CT-guided fiducial placements to guide the surgery. One patient underwent a diagnostic CT-guided biopsy that was inconclusive on pathology. None of the other 18 patients had preoperative biopsy attempted. Diagnostic lobectomy was performed on two patients because of central location of the tumor, and one of the nodules at the time of surgery was adherent to lobar bronchus. A bronchopleural fistula and a prolonged air leak complicated one of the lobectomies. The remainder had no complications.

Benign pathologies identified were focal areas of fibrosis or scarring (n = 8), necrotizing granulomatous inflammation (n = 3), other nonspecific inflammatory focus (n = 3), and organizing pneumonia (n = 1). Three were benign tumors, as follows: (1) ciliated muconodular papillary tumor, (2) sclerosing pneumocytoma, and (3) chondroid hamartoma. Finally, one nodule represented reactive lymphoid hyperplasia.

Table 1. Clinical, Imaging, and Pathologic Features of Patients Who Underwent Resection for Benign Nodule After Lung Cancer Screening

Age, y	n (%)
Median	64
Range	56-77
Sex, n (%)	
Female	12 (63.2)
Male	7 (36.8)
Lung-RADS designation, n (%)	
Lung-RADS 3	6 (31.6)
Lung-RADS 4A	9 (46.4)
Lung-RADS 4B	3 (15.8)
Lung-RADS 4X	1 (5.3)
Nodule location, n (%)	
RUL	6 (31.6)
RML	1 (5.3)
RLL	4 (21.1)
LUL	5 (26.3)
LLL	3 (15.8)
Nodule density, n (%)	
Solid	15 (78.9)
Part-solid	3 (15.8)
Ground-glass	1 (5.3)
Nodule size, mm	
Median	10
Range	6-31
Nodule FDG-PET uptake, n (%)	
Negative	9 (47.4)
Mild	2 (10.5)
Intense	2 (10.5)
N/A	6 (31.6)
Type of surgery, n (%)	
Wedge resection	16 (84.2)
Segmentectomy	1 (5.3)
Lobectomy	2 (10.5)
Pathology, n (%)	
Focal fibrosis/scar	8 (42.1)
Necrotizing granuloma	3 (15.8)
Other nonspecific inflammation	3 (15.8)
Organizing pneumonia	1 (5.3)
Reactive hyperplasia	1 (5.3)
Hamartoma	1 (5.3)
Ciliated muconodular papillary tumor	1 (5.3)
Sclerosing pneumocytoma	1 (5.3)

FDG-PET, fluorodeoxyglucose-positron emission tomography; LLL, left lower lobe; LUL, left upper lobe; N/A,; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

Discussion

The incidence of surgical resection of benign nodules that were presumed malignant is low, accounting for less than 13% of lung resections and less than 0.4% among all screened patients and was associated with a low complication rate. The surgical resection of benign nodules occurred despite selection on the basis of higher Lung-RADS categories (Lung-RADS 3 and 4), follow-up CT to assess change to exclude infection and inflammatory process, and PET imaging. Our study is the first to describe the features of benign nodules mistaken as cancers on LCS CTs after adopting updated Lung-RADS categories and follow-up guidelines.

In our patient population, the most common pathologies were focal areas of fibrosis or scarring (eight of 19; 42.1%) and necrotizing granulomatous inflammation (three of 19; 15.8%). Causes of benign nodules depend on geographic and population factors, particularly endemic fungal or mycobacterial infections. Smith et al.[15]

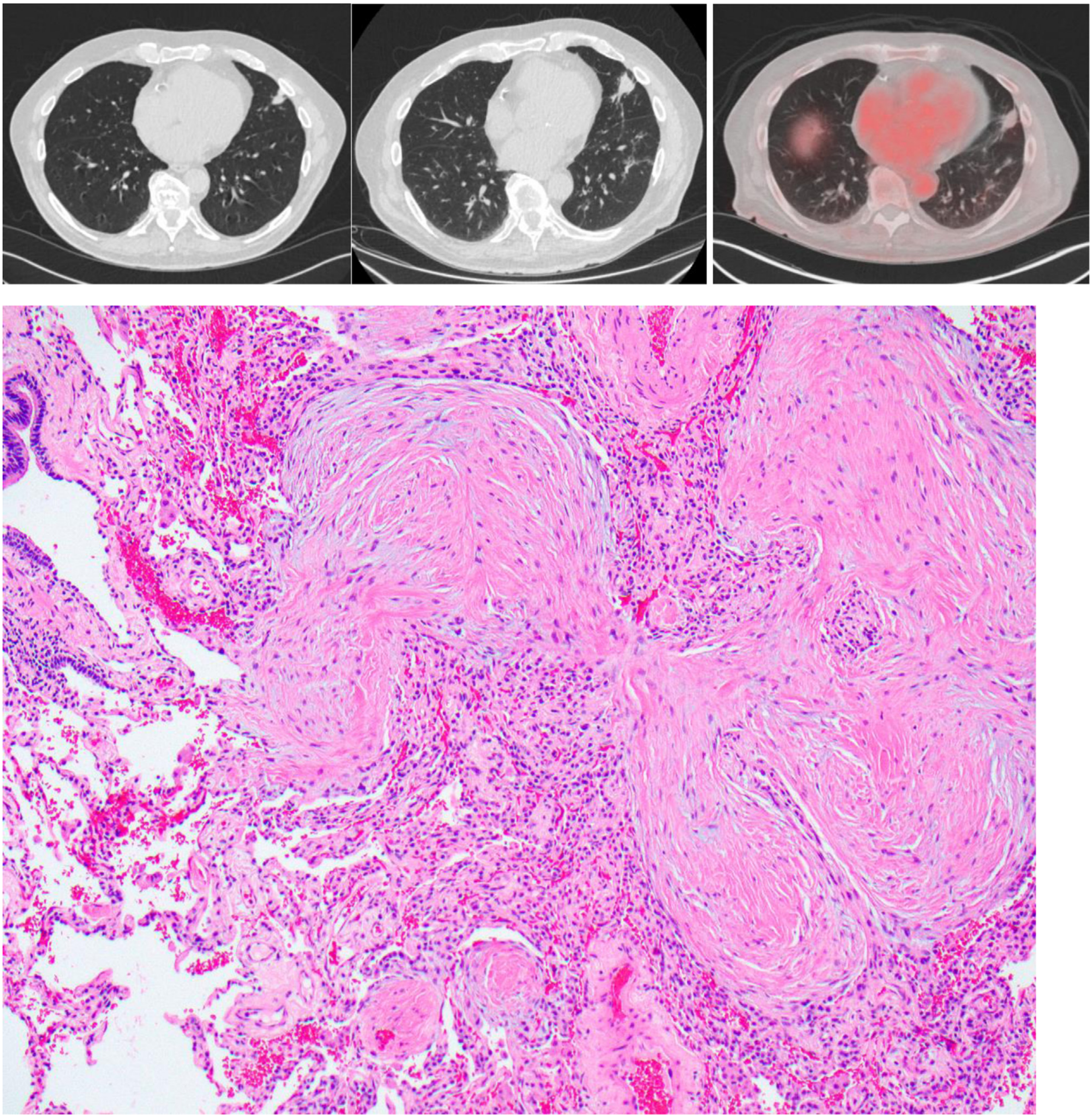

Figure 1. A 74-year-old man with resected focal organizing pneumonia. (*A*) Baseline LDCT reveals a 7-mm nodule in the lingula. (*B*) Follow-up CT 6 months after reveals increased size of the nodule to 13 mm. (*C*) Subsequent PET/CT revealed no significant FDG uptake (maximum SUV of 1.1). (*D*) Hematoxylin and eosin-stain image (100× magnification) after wedge resection revealed focal organizing pneumonia. CT, computed tomography; LDCT, low-dose CT; PET/CT, positron emission tomography/CT.

reported granuloma to be the most common benign pathology, found in 91 of 140 patients (65.0%), followed by hamartoma (17 of 140 patients; 12.1%).

There is no clear consensus on false-positive screening results, variably defined as Lung-RADS categories 3 and 4 and no lung cancer diagnosis within one year[16] or any result leading to additional evaluation that did not result in a cancer diagnosis.[17] In a single-center, retrospective study among patients selected from LCS, Ho et al.[18] found that benign nodules accounted for 14 of 83 (16.9%) resections for Lung-RADS 4 nodules and 0.43% (14 of 3280) of total patients screened for lung cancer and comparable to our results. In a study by Rzyman et al.[19] of surgical resections of lung nodules detected during LCS, they found a much higher incidence of surgical resections of benign nodules at 36% (37 of

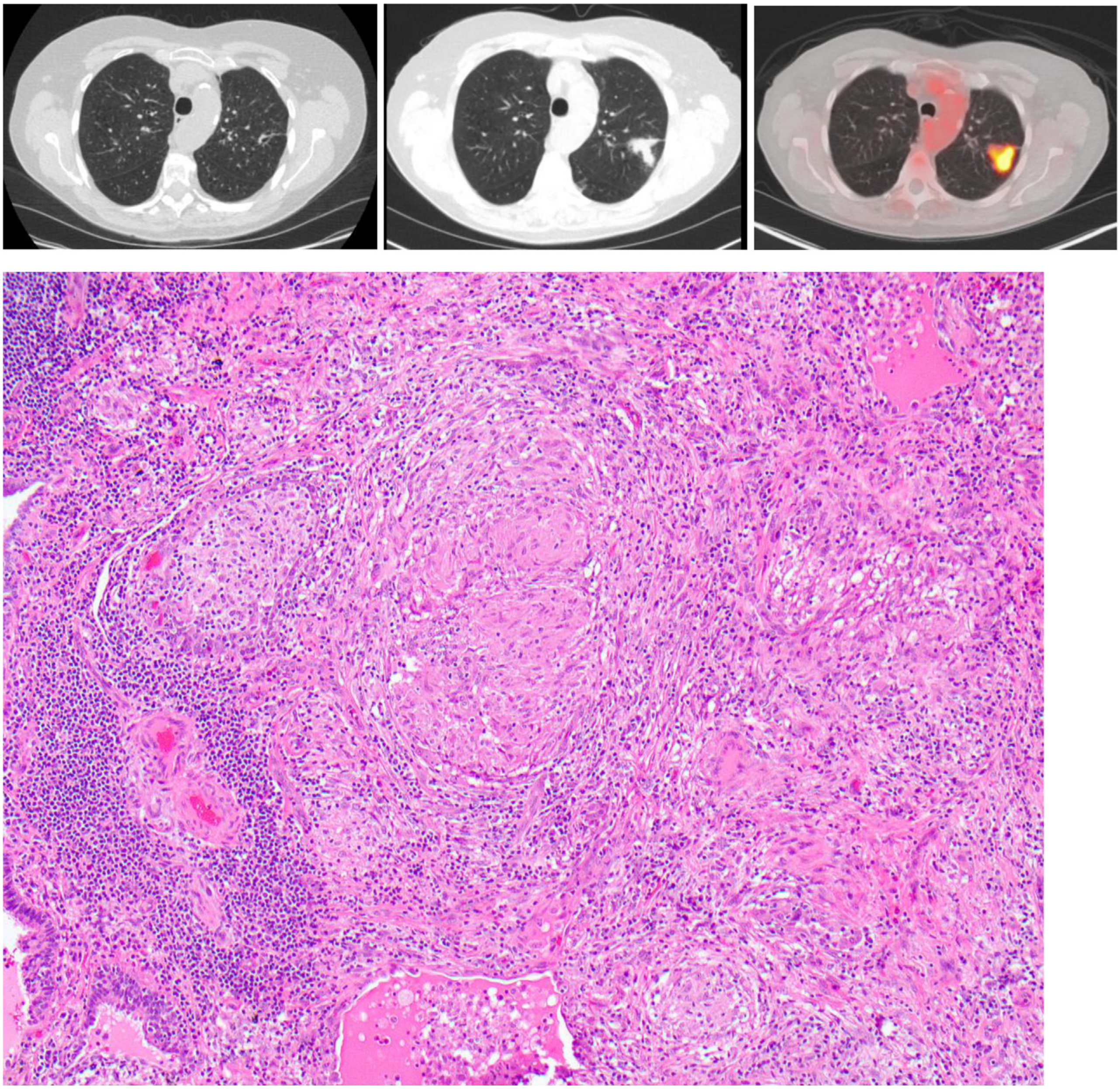

Figure 2. A 77-year-old woman with resected necrotizing granuloma. (*A*) Baseline LDCT reveals a left upper lobe 5-mm solid nodule with an adjacent cystic airspace. (*B*) Routine annual follow-up LDCT revealed significant enlargement of the nodule. (*C*) Subsequent PET/CT revealed focal intense FDG uptake (maximum SUV of 10.7). Percutaneous biopsy was performed but was nondiagnostic (not illustrated). (*D*) Hematoxylin and eosin-stain image (100× magnification) after wedge resection revealed necrotizing granulomatous inflammation with rare acid-fast bacilli (not illustrated). Cultures ultimately yielded atypical mycobacteria (mycobacterium avium complex). CT, computed tomography; FDG, fluorodeoxyglucose; LDCT, low-dose CT; PET/CT, positron emission tomography/CT.

104). Nevertheless, when considering studies not confined to LCS, the incidence of benign pathology among suspected lung cancers was lower. Smith et al.[15] found benign processes in 140 of 1560 patients (9%) who underwent resection for focal pulmonary lesions, and Carillo et al.[20] reported benign disease in 12 patients (9.6%) of 125 consecutive patients who underwent surgery for pulmonary lesions suspicious of malignancy. The likely factors contributing to the slightly higher rate of resections for benign nodules in the screening population are a higher risk of cancer in heavy smokers, challenges of percutaneous CT-guided biopsy in emphysema, and adherence to the standard recommended guidelines of the LCS program.

There were no deaths from surgical resections or major complications other than a single case of bronchopleural fistula and prolonged air leak from emphysema (5.3%, one of 19). The complication rate is similar to that of Ho et al.[18] in a similar group of patients recruited from LCS, with prolonged air leaks noted in five of 83 resections (6%).

Imaging features of the resected benign nodules in our study overlap with those of malignant nodules. Interval growth and an increase in the density of a lung nodule are important predictors of nodule malignancy. They are the basis for follow-up imaging to determine the malignancy risk.[8] Most notably, in our cohort, three-fourths of the nodules with follow-up imaging increased in size, increasing suspicion of malignancy. Currently, there are no established alternatives to standard CT imaging for LCS. Although CT radiomics of lung nodules can help differentiate benign and malignant solid nodules and predict malignancy in subsolid nodules, the results need more validation[21,22] and are not currently standard of care. Conversely, many malignant nodules can exhibit long-term stability, sometimes doubling times greater than 700 days.[23]

FDG-PET/CT is an indication to characterize solitary pulmonary nodules, but there is overlap in the findings of benign and malignant diseases. Lung adenocarcinoma of ground-glass attenuation and those with certain underlying genetic alterations can have low-level FDG uptake,[24,25] whereas inflammatory and infectious nodules can have high FDG uptake. Our cohort had variable FDG uptake, with no or mild uptake in 11 of 13 and intense in two of 13. Our cohort's two nodules with intense FDG uptake were necrotizing granulomas and nonspecific inflammation on histologic evaluation. In a meta-analysis of 12 studies with 1297 patients, FDG-PET/CT was found to have a sensitivity of 82% and a specificity of 81% for differentiating malignant from benign solitary pulmonary nodules.[26] The overlap in FDG-PET/CT findings between infectious or inflammatory findings and malignancy represents a considerable diagnostic challenge in patients without convincing evidence of metastatic disease.

Percutaneous CT-guided biopsy to confirm a diagnosis of malignancy before surgical resection can reduce resections of suspicious nodules found on LCS CTs. Barta et al.[27] retrospectively found a reduced rate of surgical resection for benign lesions in patients who underwent preoperative fine-needle aspiration (7.9%) compared with those without preoperative biopsy (25.9%). Obtaining a diagnosis with a preoperative biopsy may also be more cost effective. In a model-based analysis in the United Kingdom, Barnett et al.[28] estimated savings of more than £70,000 per 100 patients for percutaneous lung biopsy (also using Heimlich valve chest drains to avoid hospital admission in the vast majority) versus intraoperative frozen section. In addition, they also estimate saving 56 operative hours per 100 percutaneous biopsies as patients found to have benign disease at biopsy will not need to undergo surgery. Nevertheless, surgical resection without preoperative histopathologic is not uncommon and there are discordances in guidelines and clinical practices. In a study of 10,226 patients in Netherlands who underwent surgical resection for lung cancer, more than one-third of the patients were operated without preoperative diagnosis.[29] Not all nodules are amenable to preoperative tissue sampling, either because of size or location, and contraindications to biopsy, such as severe emphysema and pulmonary hypertension. The method and results of the percutaneous biopsy are also operator and technique dependent.[30]

Sometimes, resection of a benign nodule may be necessary and beneficial. Grogan et al.[31] found that the benign diagnosis changed treatment course and medication (most frequently initiating an antifungal) in surgically diagnosed benign disease. There are also instances wherein the patient would prefer a definitive diagnosis over continued follow-up, and diagnosis could alleviate the patient's anxiety.

Given the overlapping imaging features of benign and malignant nodules and given that definitive preoperative diagnosis is not always feasible, resection of benign nodules remains unavoidable in a LCS program. It may be possible to reduce the incidence of these resections by further refining screening and management guidelines. In addition, deep learning cancer risk models and liquid biopsy were also found to have promise in detecting early lung cancer and may be of use in the future.[32,33]

Our study has a few limitations. First, this is a retrospective study from a single quaternary care institution and can limit its generalizability to other practice settings. Second, the number of surgically resected benign nodules remains small, although it is expected for a successful screening program. Finally, we did not compare the characteristics of resected benign nodules and pathology-proven malignant nodules in patients on LCS.

Conclusion

The imaging characteristics of benign resected nodules overlap considerably with those of malignant nodules and continue to pose a challenge during LCS. Therefore, surgical resections of benign nodules that were presumed malignant are unavoidable in a lung cancer program but are infrequent and have a low complication rate.

CRediT Authorship Contribution Statement

John M. Archer: Data curation; Formal analysis; Investigation; Project administration; Roles/Writing—original draft.

Dexter P. Mendoza: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Visualization; Writing—review and editing.

Yin P. Hung: Investigation; Visualization; Writing—review and editing.

Michael Lanuti: Investigation; Visualization; Writing—review and editing.

Subba R. Digumarthy Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing—review and editing.

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