

# Extrapulmonary neoplasms in lung cancer screening

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**Abstract:** A significant reduction in lung cancer specific mortality rate was demonstrated by the National Lung Screening Trial (NLST) in participants who had annual low-dose computed tomography (LDCT) screening. In addition to early detection of lung cancer, lung cancer screening (LCS) provides an opportunity to detect cardiovascular disease, pulmonary disease (such as chronic obstructive pulmonary disease and interstitial lung disease), and extrapulmonary neoplasms, such as thyroid, breast, kidney, liver, esophageal, pancreatic and mediastinal tumors. Considering the fact that 22.3% of the certified deaths in the computed tomography (CT) arm of the NLST trial were due to extrapulmonary malignancies, compared to 22.9% of deaths from lung cancer, it is possible that early diagnosis and treatment of clinically significant incidental findings may further decrease morbidity and mortality in screening participants. In this article we review prevalence, clinical relevance and management of incidentally detected extrapulmonary malignancies.

**Keywords:** Lung cancer; screening; incidental findings (IFs); neoplasm; computed tomography (CT); low-dose computed tomography (LDCT)

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## Introduction

The National Lung Screening Trial (NLST) showed that low-dose computed tomography (LDCT) screening reduced lung cancer specific mortality rate in high-risk patients by 20% compared with chest radiography, with a 6.7% reduction in all-cause mortality (1). Besides early detection of lung cancer, LDCT screening provides an opportunity for detection and early treatment of significant and potentially significant incidental findings (IF), defined as actionable abnormalities seen on LDCTs that are outside the screening purview of the study, including extrapulmonary neoplasms. Unlike other screening tests such as mammography that focus on imaging a single organ, lung cancer screening (LCS) cross-sectional

images are acquired from the lower neck to the upper abdomen including multiple organs, allowing detection of a significant number of IF.

## IFs on lung LCS

Extrapulmonary findings on LCS are very common. A study by Nguyen and colleagues that reviewed prospectively acquired data on 17,309 NLST participants showed that extrapulmonary findings were noted in 58.7% of the CT-screened participants, and 19.6% had findings coded as potentially significant (2). The impact of IFs was also evaluated by Kucharczyk and colleagues (3) who evaluated 4,073 LDCTs from LCS participants in Canada and found similar results: a total of 880 IFs described in 782 study

participants from 807 different scans (19%). Of these, 689 were considered non-cardiovascular (78%). The majority of the IFs were identified at baseline imaging (80%). There was a correlation between IF prevalence and age and pack-years of smoking; pack-years were significantly higher in the group with IFs ( $P=0.04$ ). The reported frequency of clinically significant extrapulmonary IFs (other than coronary artery calcification) in other screening studies ranges from 7% to 27% (4-7); this variation is at least in part due to inconsistent definition of what constitutes an actionable IF and different methodology for recording IFs in the different studies.

LDCT lacks the accuracy required for making a definitive diagnosis for most potentially significant IFs outside of the lung parenchyma. As a result, further diagnostic workup of the IFs is frequently recommended by the radiologist. The clinical relevance of these IFs is still controversial. Considering the fact that 22.3% of the certified deaths (416 of 1,865) in the CT arm of the NLST trial were due to extrapulmonary malignancies, compared to 22.9% of deaths from lung cancer (427 of 1,865) (1), it is possible that early diagnosis and treatment of clinically significant IF may further decrease morbidity and mortality in screening participants. However, the potential for harm includes anxiety, cost and morbidity related to additional workup of findings that may prove to be of no clinical relevance. These potential consequences of detection of IF should be discussed with patients during the shared decision-making visit. In addition, the cost-effectiveness of LCS could be negatively impacted by the detection of a large number of IF, particularly if subsequent workup is not performed appropriately, so standardization of management is critical.

### Prevalence of extrapulmonary malignancy

The prevalence of extrapulmonary malignancies presenting as IF in LDCT LCS participants published in the literature varies from 0–1.6% (1,3,4,6-10). This range can be explained by differences in the number of participants enrolled, variations in CT scanning protocol, including scanning range, differences in duration of surveillance and potential inclusion of additional imaging modalities, particularly PET/CT, in national and international LDCT screening studies. This variability also results in a significant variation in the type of reported extrapulmonary neoplasms in each study.

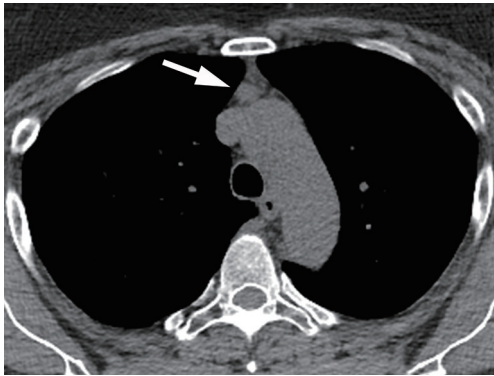
According to Nguyen *et al.* (2), the prevalence of potentially significant abnormalities in CT-screened NLST participants

was highest for cardiovascular findings (8.5%), followed by renal (2.4%), hepatobiliary (2.1%), adrenal (1.2%), and thyroid (0.6%) findings. Sixty-seven of 17,309 participants (0.39%) had primary extrathoracic cancers diagnosed during screening. The prevalence of cancers among screened participants was 0.26% (45 cases) for kidney, 0.08% (14 cases) for thyroid, and 0.05% (8 cases) for liver cancers. There were no adrenal malignancies.

In another study, Rampinelli *et al.* (7) identified 27 extrapulmonary malignancies among 5,201 participants (0.5%) undergoing 5 years of LDCT screening in the COSMOS (Continuous Observation of Smoking Subjects) study. Eight malignancies were diagnosed in the 1st year of screening, 9 in the 2nd year, 4 in the 3rd year, 2 in the 4th year, and 4 in the 5th year. The most commonly diagnosed malignancies (44%) were renal cell carcinoma (7) and lymphoma (5). Other tumor types included thyroid cancer (3), thymoma (2), pancreatic neoplasm (2), schwannoma (1), hepatocellular carcinoma (1), gastrointestinal stromal tumor (1), prostate cancer (1), breast cancer (1), adrenal gland neoplasm (1) and ovarian cancer (1). Importantly, the extrapulmonary neoplasms were overlooked by the initial readers in five participants, but could be retrospectively detected (7). Although lymphoma was the second most common malignancy in this study, most incidentally detected enlarged mediastinal nodes in chest CT have proven to be benign, most commonly reactive to an infectious process, pulmonary edema, and diffuse lung disease, such as fibrosis or sarcoidosis. Less frequently, incidentally detected enlarged mediastinal nodes represent metastatic disease, small cell lung cancer or lymphoma. In a study that investigated incidental mediastinal lymphadenopathy with positron emission tomography, endoscopic ultrasound (EUS)- or endobronchial ultrasound-guided biopsies, and had clinical follow-up in 83 patients, 66% of the nodes were reactive and 22% represented sarcoidosis; only one case of metastatic disease was seen in a patient with known breast cancer (11).

Historically, the frequency of incidental breast findings on diagnostic chest CT has been reported as 1.1% and the frequency of malignant findings as 0.3–0.4%, i.e., 1 out of 250 women undergoing chest CT will show a malignant incidental breast lesion (12,13). Concordantly, in the study by Kucharczyk and colleagues (3), of the 7 incidentally detected malignancies (0.8%), 4 were breast cancers and the remainder were 2 plasmacytomas of the rib and 1 thyroid cancer.

In the Early Lung Cancer Action Project (ELCAP), Henschke and colleagues (14) evaluated the frequency and temporal evolution of mediastinal masses found in screening participants. Of the 9,263 study participants, 71



**Figure 1** Mediastinal incidentaloma. LDCT shows a 2-cm mediastinal soft-tissue nodule suspicious for thymic neoplasm (arrow). The lesion was stable at 3-month follow-up LDCT (not shown) and subsequently managed with annual LDCT follow-up. LDCT, low-dose computed tomography.

had a mediastinal mass at baseline screening (prevalence of 0.77%). Of the 71 masses, 41 were thymic, 16 were thyroidal, 2 were esophageal cancers, 6 were tracheal-esophageal diverticula, and 6 were other masses, including cystic lesions. Among the 11,126 annual repeat screenings, only one new mediastinal mass was identified (incidence of 0.01%). This suggests a long average duration for mediastinal masses in asymptomatic individuals. Among the 41 thymic masses, five were larger than 3.0 cm in diameter, and all five were resected; of these 5, 1 was a thymic carcinoma and 4 were noninvasive thymomas. Of the remaining 36 thymic masses, 25 were evaluated at follow-up CT 1 year later: 5 had increased in diameter, 2 had decreased, and 18 remained unchanged (14).

In contrast to the previous studies, van de Wiel *et al.* (6) reported that the incidental detection of extrapulmonary malignancies in the Dutch-Belgian lung cancer screening trial (NELSON) was negligible. Among the 1,929 participants, 129 (7%) had clinically significant IFs of which only one was a malignancy. Furthermore, detection of this metastatic pancreatic malignancy was not associated with clinical benefit since no curative treatment was possible.

### Proposed guidelines for management of extrapulmonary IFs in LCS

Currently, there are no specific recommendations to determine which IFs should be considered relevant in LCS, although future editions of American College of Radiology (ACR) Lung-RADS (Lung CT Screening

Reporting and Data System), used to standardize LDCT screening interpretation, reporting and recommendations for management of identified lesions, may address this issue. In this regard, Lung-RADS version 1.0 classification leaves the relevance of detected IFs to the discretion of the reader and simply provides a category S modifier for screening participants who have a clinically significant or potentially clinically significant non-lung cancer finding.

While IFs should be evaluated on a case-by-case basis, there are general guidelines available for the management of incidentally detected lesions in the thyroid, liver, kidney, pancreas and adrenal glands (15-18). These guidelines are important to ensure patients receive appropriate medical care and to minimize unnecessary diagnostic workup that can decrease the cost-effectiveness of LCS and add to the overall health care economic burden.

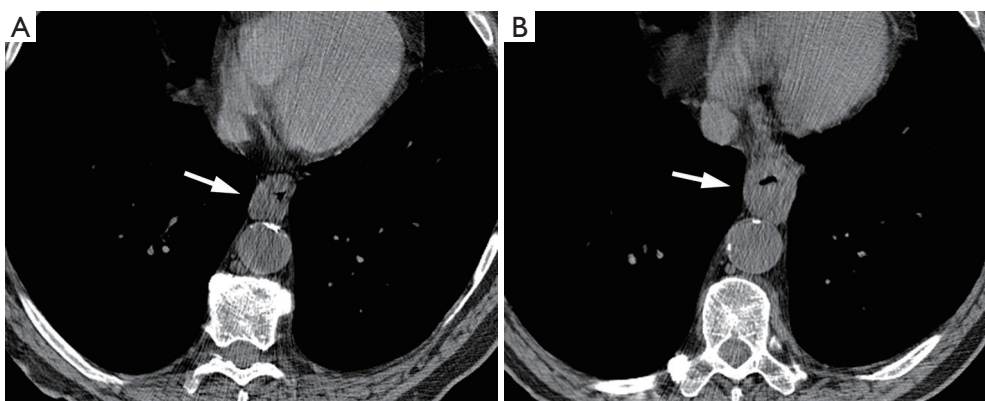
### Thyroid gland

The incidental thyroid nodule is one of the most common IFs on imaging studies that include the neck. A white paper on the management of IFs in the thyroid gland recommends evaluation with thyroid ultrasound, and possibly fine needle aspiration (FNA) depending on ultrasound findings, in patients with nodules >1.5 cm (for patients age  $\geq 35$  years, which includes LCS participants) and/or nodules with findings suspicious for malignancy including microcalcifications, mixed solid/cystic attenuation, local invasion as well as associated lymphadenopathy and/or nodules that are fluorodeoxyglucose (FDG) avid on PET/CT imaging (15).

### Mediastinum

There is little literature regarding the importance of incidentally detected mediastinal findings. According to available data, most mediastinal masses found in the context of CT screening for lung cancer in asymptomatic people can be approached in a “conservative” manner; this includes thymic masses smaller than 3 cm in diameter, as most of these remain unchanged or even decrease in size (14). In these cases, a short-term follow-up LDCT or PET/CT imaging may be considered to exclude active malignancy, followed by continued follow-up at annual LDCT screening if stable (*Figure 1*). Mediastinal lesions  $\geq 3$  cm may require further investigation with contrast-enhanced chest CT or MRI, except those with a typical benign cystic appearance.

Esophageal cancer is not a common IF, but the presence of focal esophageal wall thickening or esophageal mass



**Figure 2** Esophageal tumor. Screening LDCT at baseline (A) and year 1 (B) shows focal circumferential wall thickening in the distal esophagus (arrows) which has increased. Biopsy confirmed esophageal adenocarcinoma. LDCT, low-dose computed tomography.

should prompt further investigation with endoscopic evaluation (*Figure 2*).

### **Lymphadenopathy**

According to ACR recommendations for the management of incidentally detected mediastinal lymph nodes, depending on size, texture, and distribution of the nodes, options include reporting as probably benign needing no follow-up, or indeterminate and recommending follow-up with CT, PET/CT and/or biopsy (19). Incidentally detected mediastinal lymph nodes <15 mm (in short axis) in patients with no other findings do not require further evaluation (19). Mildly enlarged mediastinal and hilar nodes are also frequently seen in association with pulmonary findings suggestive of pulmonary edema, fibrosis, infection, collagen vascular disease, or sarcoidosis, and generally require no additional workup. Consideration for short-term follow-up CT or other diagnostic procedures is made in cases of isolated, significantly enlarged lymph nodes (*Figure 3*) (20). The lack of benign lymph node features, such as smooth and well-defined borders, uniform attenuation, and central fatty hilum, or the loss of these features since the previous examination, should raise suspicion of a clinically significant condition and require further investigation (19).

### **Breast**

Breast incidentalomas without the pathognomonic appearance of fibroadenomas (coarse calcifications) may require further work-up with mammography and/or dedicated ultrasound (*Figure 4*). If available, correlation with mammography

or previous chest CT examinations should be obtained. If the lesion is confirmed to be new or shows increase in size, it should be regarded as a finding suspicious for breast malignancy (21).

### **Upper abdomen**

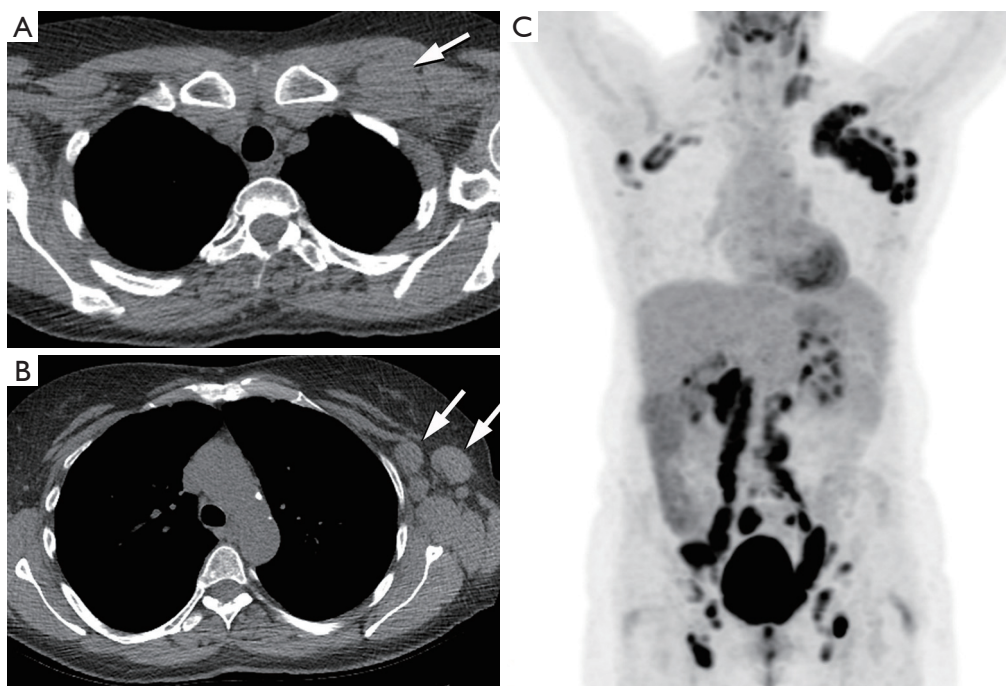
Recently the ACR updated recommendations for the management of abdominal IFs detected on diagnostic imaging studies (16-18). These recommendations can, to a large part, be adapted to manage incidentally detected abdominal findings in the LCS population.

Liver lesions <1 cm in low-risk patients and lesions with benign features (sharply marginated with homogeneous low attenuation 0–20 HU) require no additional workup. For liver lesions  $\geq 1$  cm without distinctly benign features and liver lesions in high risk patients (with known primary malignancy with a propensity to metastasize to the liver, cirrhosis, and/or other hepatic risk factors), liver MRI is recommended (16).

Renal lesions that are sharply marginated with homogeneous low attenuation (0–20 HU) require no further evaluation. Renal lesions with attenuation 20–69 HU or those with thick or irregular wall, mural nodule, calcification or septa, should be further evaluated with MRI or CT without and with intravenous contrast (17).

Adrenal gland lesions that have macroscopic fat or attenuation  $\leq 10$  HU or lesions that are stable in size for 12 months require no further evaluation. In addition, an incidental adrenal lesion that is <1 cm in short axis usually does not need be further investigated. Incidental adrenal lesions measuring 1–2 cm with no prior imaging in



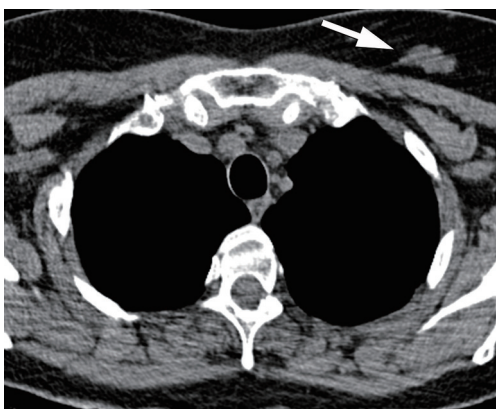


**Figure 3** Lymphoma. Baseline LDCT images (A,B) show left retropectoral and axillary lymphadenopathy (arrows) measuring up to 3.1 cm × 2.2 cm. Further investigation was performed with ultrasound and fine needle aspiration. Pathology confirmed follicular lymphoma; (C) MIP coronal PET/CT image performed for staging shows hypermetabolic multicompartmental lymphadenopathy involving the left neck and bilateral axillary, retroperitoneal, iliac, inguinal and femoral regions. MIP, intensity projection image; LDCT, low-dose computed tomography.

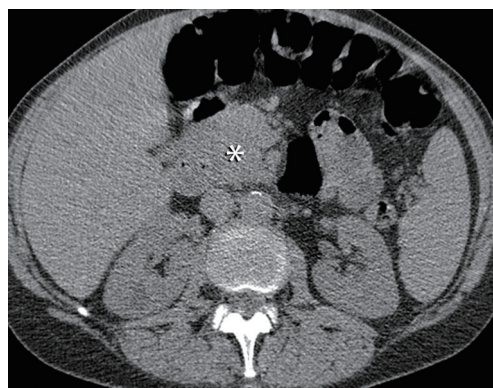
patients with no cancer history are still probably benign; follow-up adrenal protocol CT in 12 months has been recommended in the general population. However, in the LCS population undergoing annual LDCT, evaluation for lesion stability at the 12-month LDCT follow-up may be sufficient (*Figure 5*). Adrenal masses >2 cm (or ≥1 cm in patients with cancer history) and <4 cm should be evaluated with adrenal protocol CT. Adrenal masses ≥4 cm without benign features in patients without history of prior cancer will require consideration for resection (without biopsy) to treat possible primary adrenal cortical carcinoma. Correlation with clinical signs or symptoms (hypertension, Cushing's features) may suggest a biochemically active neoplasm. For adrenal masses ≥4 cm in patients with prior history of cancer, biopsy or PET/CT is recommended to exclude metastatic disease (18). Both benign and malignant adrenal masses may enlarge over time, and there is not a known growth-rate threshold to differentiate benign from malignant adrenal masses (22). New or enlarging adrenal lesions on annual LDCT should be considered for adrenal CT protocol evaluation or resection (no cancer history); or

biopsy or PET/CT evaluation (if prior cancer history) (18).

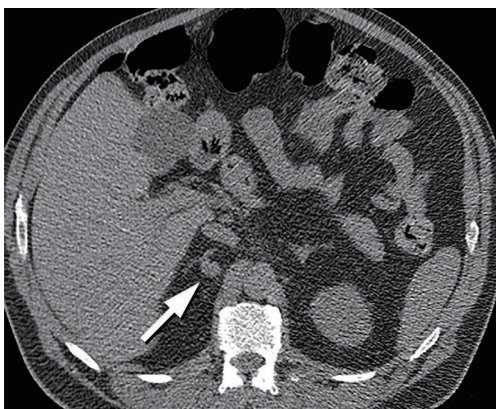
Incidentally detected solid pancreatic lesions are almost always consistent with pancreatic adenocarcinoma or neuroendocrine tumor and should be properly evaluated with pancreas protocol CT and/or MRI; they usually require an aggressive approach with biopsy and/or surgery, except in elderly patients with small neuroendocrine tumors (*Figure 6*). Incidentally detected pancreatic cysts are presumed to be mucinous unless proven otherwise. Current recommendation for pancreatic cysts <1.5 cm is evaluation with contrast-enhanced MRI or pancreas protocol CT annually for patients <65 years old and every 2 years for patients ≥65 years old for 5 years, and then annually for an additional 5 years, up to the age of 80 years (23). Cysts that demonstrate interval growth (≥20% increase in longest axis diameter) may require more frequent imaging surveillance or EUS/FNA. The evaluation of larger lesions will depend on lesion size, communication with the main pancreatic duct, presence of suspicious features, such as thickened/enhancing wall or solid component, as well as interval growth. Evaluation may require CT or MRI with magnetic



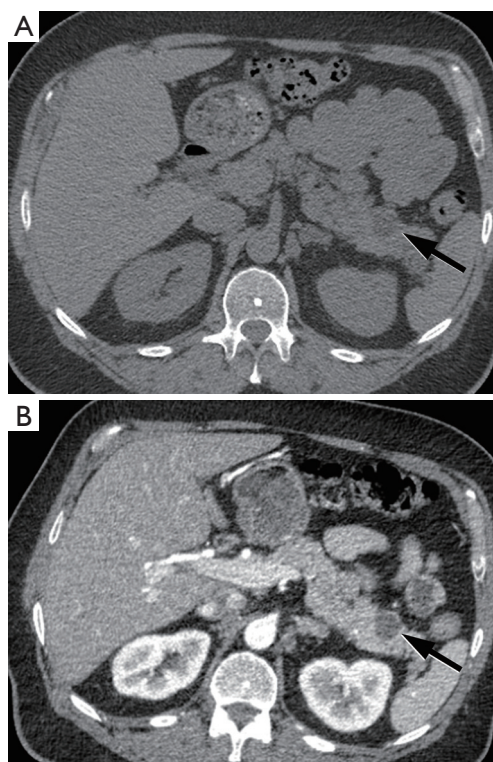
**Figure 4** Breast incidentaloma. LDCT shows a soft-tissue mass in the left breast (arrow). Management recommendation includes correlation with mammography and/or ultrasonography. Breast cancer was confirmed on pathology. LDCT, low-dose computed tomography.



**Figure 6** Solid pancreatic mass. LDCT shows a poorly-margined mass in the head of the pancreas (asterisk), consistent with pancreatic cancer. Pancreatic adenocarcinoma was confirmed on pathology. LDCT, low-dose computed tomography.



**Figure 5** Adrenal gland nodule. LDCT shows a 1.3-cm right adrenal gland nodule (arrow). Patient had no prior imaging and no history of malignancy. For incidental adrenal lesions measuring 1–2 cm with no prior imaging in patients with no cancer history, evaluation for lesion stability at the 12-month LDCT follow-up may be sufficient. Follow-up at subsequent annual LDCT screening showed no significant interval change (not shown), most consistent with an adenoma. LDCT, low-dose computed tomography.



**Figure 7** Cystic pancreatic lesion. (A) LDCT shows an indeterminate 2-cm low-attenuation lesion identified in the tail of the pancreas (arrow); (B) pancreas protocol CT imaging performed with intravenous contrast allows better characterization of the well-defined cystic lesion in the tail of the pancreas (arrow). Endoscopic ultrasound/fine needle aspiration (EUS/FNA) showed no malignant cells. The lesion remained stable on subsequent follow-up imaging (not shown). LDCT, low-dose computed tomography.

resonance cholangiopancreatography (MRCP), and possible EUS/FNA and surgical consultation (*Figure 7*) (23).

In summary, a considerable number of IF can be identified in LCS participants, including extrapulmonary malignancies in a small percentage of cases. Early detection and treatment of these neoplasms may potentially decrease mortality and morbidity in lung screening participants, but further studies are needed to evaluate the effect of

treatment intervention on patient outcome. The possible consequences related to IFs should be discussed with patients during shared decision-making visits. The use of standardized guidelines for reporting and management of IFs is warranted to avoid unnecessary workup and cost while maintaining optimal clinical care.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare

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