Management of the Solitary Pulmonary Nodule

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Context.—Optimal management of the patient with a solitary pulmonary nodule entails early diagnosis and appropriate treatment for patients with malignant tumors, and minimization of unnecessary interventions and procedures for those with ultimately benign nodules. With the growing number of high-resolution imaging modalities and studies available, incidentally found solitary pulmonary nodules are an increasingly common occurrence.

Objective.—To provide guidance to clinicians involved in the management of patients with a solitary pulmonary nodule, including aspects of risk stratification, workup, diagnosis, and management.

Data Sources.—Data for this review were gathered from an extensive literature review on the topic.

Conclusions.—Logical evaluation and management pathways for a patient with a solitary pulmonary nodule will allow providers to diagnose and treat individuals with early stage lung cancer and minimize morbidity from invasive procedures for patients with benign lesions.

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A solitary pulmonary nodule (SPN) is defined as a single, well-circumscribed lesion evident on radiographic imaging and surrounded by lung parenchyma that measures 3 cm or less.1–3 A similar lesion that measures greater than 3 cm is classified as a lung mass. Although they are entities along the same spectrum, the SPN presents a unique set of challenges that will be the focus of this review. Once identified, a lung nodule must be evaluated to determine the likelihood of malignancy using a number of diagnostic criteria. Optimal management of the patient with an SPN entails early diagnosis and appropriate treatment for patients with malignant tumors and minimization of unnecessary interventions and procedures for those with ultimately benign nodules. With the growing number of high-resolution imaging modalities and studies available, incidentally found SPNs are an increasingly common occurrence, with the prevalence of nodules detected on computed tomography (CT) at 31%. That number is as high as 50% in high-risk patients.4 The National Lung Screening Trial recently demonstrated a decrease in lung cancer–specific mortality to 247 deaths per 100 000 person-years from 309 deaths per 100 000 person-years, a 20% decrease in mortality by implementing CT screening in a high-risk population.5 A cohort of nearly 55 000 patients was studied at 33 medical centers in the United States. All patients were between 55 and 74 years old, with at least a 30-pack-year smoking history and a history of smoking within the past 15 years. With Medicare approval in February 2015 for lung cancer screening with low-dose CT scans in a similar population, the incidence of SPNs is certain to rise in coming years.

The etiology of an SPN can be a number of benign or malignant processes. Benign diagnoses include granulomas, hamartomas, organizing pneumonia, abscess or fungal infections, tuberculosis, chondromas, Wegener granulomatoses, arteriovenous malformations, sarcoidoses, hematomas, rounded atelectases, and bronchopulmonary sequestration. Malignant etiologies include primary lung cancer, metastatic disease from another organ, and carcinoid tumors.6

EVALUATION OF MALIGNANT RISK

Both clinical and radiographic features must be assessed in determining a patient’s risk of malignancy. Further steps in management are based on that initial evaluation.

Clinical Features

Although smoking history, older age, exposures, and certain risk factors in the history increase the likelihood an SPN is malignant, the absence of risk factors does not preclude a malignant diagnosis.7 Smoking is the single most important risk factor in the development of lung cancer, with a lifetime risk of lung cancer of 30% in heavy smokers. In contrast, never-smokers have a lifetime risk of less than 1%.8,9 Patients who actively smoke more than 1 pack/day are at greater risk than those who smoke fewer cigarettes and those who are never smokers.10 Former smokers have a lower risk of lung cancer after 5 years of abstinence, with progressively declining rates with time.11 Increasing patient age corresponds to a greater risk of malignancy, with more
than 50% of nodules proving to be malignant in patients older than 60 years, compared with only 3% in patients younger than 40 years old. Other individual patient risk factors that increase the likelihood of an SPN being malignant include chronic obstructive pulmonary disease, asbestos exposure, a history of prior lung cancer, and a history of extrathoracic cancer.

**Radiographic Features**

Incidentally found SPNs are most commonly discovered on CT scans. Although some may be seen on chest radiographs, a CT scan affords superior detail for evaluating specific characteristics of the nodule. Of particular importance is a thorough review of all previous imaging to assess both changes in size and the rate of change over time. Nodule size is consistently and independently predictive of a risk of malignancy. Numerous studies have demonstrated that increasing nodule size corresponds with increasing risk of malignancy. A nodule smaller than 5 mm, less than 1% malignancy risk; a nodule of 5 to 9 mm, 2% to 6% malignancy risk; a nodule of 10 to 20 mm, 18% malignancy risk; a nodule 20 mm or larger, more than 50% malignancy risk.

Signs of growth on serial imaging are highly suggestive of malignancy. The growth rate of an SPN is also used to evaluate the potential for malignancy, with most malignancies doubling in volume between 20 and 400 days. Those doubling in a shorter time are likely to be infectious, whereas stability for a longer period usually suggests a benign process. Although these guidelines are generally applicable to solid nodules, subsolid nodules are more likely to harbor early or lower-grade adenocarcinomas, which grow more slowly. A solid SPN that has been stable for more than 2 years is likely to be benign, as is a subsolid nodule that has been stable for more than 3 years.

Attenuation of the nodule on CT imaging may be characterized as solid or subsolid, with subsolid lesions further divided as pure subsolid and part solid. Although solid lesions are more common, subsolid lesions are more likely to be malignant. Solid nodules smaller than 8 mm are less likely malignant and may be followed with serial imaging. Subsolid nodules are challenging because they are difficult to biopsy and are not reliably characterized on functional imaging. Although pure ground-glass lesions smaller than 10 mm are unlikely to be malignant, the incidence of malignancy increases with increasing size and with the development of a solid component. The presence of a part-solid nodule was found to be independently associated with malignancy in CT screening trials.

Certain characteristics of an SPN may be more suggestive of malignancy. Irregular borders are more likely to be malignant compared with smooth borders. However, if the patient has a known history of extrathoracic cancer, an SPN with round, smooth borders may be a pulmonary metastasis from the primary tumor via a hematogenous route. Eccentric or stippled calcifications are more likely to be malignant, whereas diffuse, central, laminated or “popcorn” calcifications are more likely to be benign, typically granulomas or hamartomas.

**MANAGEMENT**

A combination of factors should be assessed in determining the risk of malignancy for each patient, and management recommendations must be personalized to individual cases. An absence of rigid, evidence-based guidelines dictates that decision making should be done in conjunction with individual patient preferences and risk tolerance. Although an aggressive approach to resection will identify and treat more early stage cancers, it can also subject patients to the inherent risks of potentially unnecessary, invasive surgical procedures. Similarly, a conservative approach of watchful waiting may result in the interval progression of otherwise curable malignancies. As previously mentioned, every effort should be made on initial evaluation to obtain and evaluate any previous imaging to evaluate interval change in size and character of the SPN.

**Low-Risk Patients**

A patient with a small nodule and few risk factors may be followed with serial imaging. The Fleischner Society has published recommended intervals for follow-up of solid and subsolid nodules based on size and risk stratification. (Tables 1 and 2). Small nodules may be imaged less frequently, whereas larger nodules require shorter follow-up intervals. If the SPN is stable on serial imaging, imaging may be stopped after 2 years for solid nodules and 3 years for subsolid nodules. Growth during the surveillance period should prompt functional imaging or biopsy given the increased risk of malignancy.

**Intermediate-Risk Patients**

Patients at intermediate risk for malignancy based on clinical and radiologic factors should undergo functional imaging with 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan and possibly tissue sampling. **Functional Imaging**—Functional imaging is most commonly performed with FDG-PET scan, a nuclear medicine study that uses FDG uptake as a marker for glucose metabolism. Although cancers are more likely to be metabolically active, false-positive findings may be found with infection or inflammation, as well. In nodules larger than 8 mm, PET is highly sensitive for malignancy (72%–94%). In addition, PET can provide staging information regarding mediastinal lymph nodes and distant sites of metastases. False-negatives may be found with cancers that...
are less metabolically active (carcinoids, minimally invasive adenocarcinomas, adenocarcinomas in situ). Smaller SPNs and subsolid nodules are less reliably evaluated with PET.

The degree of FDG avidity is measured by the standardized uptake value (SUV), with a correlation between higher SUVs and an increased chance of malignancy. Although no specific value determines the boundary between malignant and benign, most studies cite SUVs greater than 2.5 as having the highest probability of malignancy, with more than 80% of lesions with SUVs between 2.6 and 4.0 being malignant and more than 95% of lesions with SUVs greater than 4 demonstrating malignancy.

### Tissue Sampling

Many techniques are available for obtaining tissue diagnoses and may be tailored to the individual patient’s anatomy and the location of the SPN.

#### Central Lesions

Bronchoscopy can be used with bronchial washing, brushing, and transbronchial needle biopsy, producing a diagnostic yield of 65% to 88%. Bronchoscopy is a technique ideally suited to large, central lesions, with yield dropping to 30% to 40% in SPNs without an endobronchial component. Bronchoscopy with biopsy offers the advantage of being able to be performed in an awake patient with minimal morbidity.

Endobronchial ultrasound can be used in central lesions located near the distal trachea, mainstem bronchus, or proximal lower lobes, particularly if the clinician uses a central endobronchial ultrasound probe. By combining direct bronchoscopic airway visualization with ultrasound-guided biopsy of the lesion, endobronchial ultrasound provides a diagnostic yield of 75% to 85% in large, centrally located lesions. Additionally, if the biopsy results in a malignant diagnosis, endobronchial ultrasound can also be used to stage the mediastinal lymph nodes in the same setting.

#### Mid to Peripheral Lesions

Transbronchial needle biopsy involves percutaneous fine-needle aspiration and/or core biopsy of the SPN, passing a needle through the parenchyma under imaging guidance (typically CT) with a patient who remains awake with local anesthetic and conscious sedation. Needle biopsy has the advantages of a diagnostic accuracy of more than 88% yield, a sensitivity of 90%, and a false-negative rate of 22%. When compared with fine-needle aspiration, core biopsy allows for larger tissue samples with improved histologic evaluation of nodule architecture for genetic and immunohistochemical testing. The most significant disadvantage of transthoracic needle biopsy is a procedural risk of pneumothorax ranging from 17% to 50%, with one-half of cases of pneumothorax requiring chest tube placement and hospitalization. This risk increases in older patients and in patients with emphysematous lungs, with increasing numbers of pleural transgressions, and with increasing distance between the chest wall and the lesion.

Guided transbronchial biopsy allows for localization of the SPN, introduction of a sheath up to the nodule, and tissue sampling involving needle biopsy, brushing, and forceps biopsy. Different systems are currently available, with electromagnetic navigational bronchoscopy (superDimension, Medtronic, Minneapolis, Minnesota) one of the most popular options. By converting a thin-slice chest CT into a 3-dimensional rendering of the lung and airways, electromagnetic navigational bronchoscopy uses an electromagnetic field in the operating room to merge live bronchoscopy images with real-time computer-generated images. This allows for guided direction of a sheath to the SPN beyond the reach of bronchoscopy alone. Larger nodule size and proximity of the SPN to an airway on CT imaging both increase the diagnostic yield. The technique can also be used to place fiducial markers in patients with lung cancer who are marginal surgical candidates to undergo sublobar resection or stereotactic radiation.

### Cytology Adequacy Check: Technical Approaches and Considerations

In the era of precision medicine, obtaining adequate tissue samples is critical to ensure accurate morphologic diagnosis and to detect targetable genetic abnormalities. Specimen adequacy checks during procedures (rapid on-site evaluation by cytology) and communication between pathologists and procedure performers become increasingly important for adequate sampling. Immediate, intraprocedural feedback from pathologists may provide valuable information for procedure performers regarding the quality

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**Table 2. Recommendations for the Management of Subsolid Pulmonary Nodules Detected at Computed Tomography (CT): A Statement From the Fleischner Society**

<table>
<thead>
<tr>
<th>Nodule Type, mm</th>
<th>Management Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary, pure GGNs</td>
<td>No CT follow-up required</td>
</tr>
<tr>
<td>≤5</td>
<td>Initial follow-up CT at 3 mo to confirm persistence, then annual surveillance CT for a minimum of 3 y</td>
</tr>
<tr>
<td>&gt;5</td>
<td>Initial follow-up CT at 3 mo to confirm persistence. If persistent and solid component ≤5 mm, then yearly surveillance CTs for a minimum of 3 y. If persistent and solid component ≥5 mm, then biopsy or surgical resection</td>
</tr>
<tr>
<td>Solitary, part-solid nodules</td>
<td>Initial follow-up CT at 3 mo to confirm persistence. If persistent and solid component ≤5 mm, then biopsy or surgical resection.</td>
</tr>
<tr>
<td>Multiple, subsolid nodules</td>
<td>Obtain follow-up CT at 2 and 4 y</td>
</tr>
<tr>
<td>Pure GGNs ≤5</td>
<td>Initial follow-up CT at 3 mo to confirm persistence, then annual surveillance CT for a minimum of 3 y.</td>
</tr>
<tr>
<td>Pure GGNs &gt;5 without a dominant lesion</td>
<td>Initial follow-up CT at 3 mo to confirm persistence. If persistent, biopsy or surgical resection is recommended, especially for lesions with &gt;5 mm solid component</td>
</tr>
<tr>
<td>Dominant nodules with part-solid or solid component</td>
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</table>

Abbreviation: GGN, ground-glass nodule.

and quantity of a sample, which will help to determine whether additional sampling from the same or different areas is needed. In addition, intraprocedural adequacy checks may serve as triaging processes to direct the specimen immediately for microbiology cultures, flow cytometry, or other appropriate studies based on the initial assessment.

By assessing the initial specimen, pathologists can provide the following critical information:

1. Is the specimen lesional and viable? If not, sampling a different area of the lesion is recommended.
2. If viable lesional tissue is obtained, pathologists need to determine whether cultures (suspicion of infection) or flow cytometry (suspicion of lymphoma) are needed.
3. If neoplasms are considered, the specimen should contain sufficient tumor cells for morphologic diagnosis and potential molecular tests. If not sufficient, additional sampling from the lesion is recommended.

With systematic collaboration and constant communication between pathologists and procedure performers, diagnostic yields will be significantly greater than with blind biopsies.

Technically, the adequacy check is relatively easy to set up and can be performed in a bronchoscopy suite, operating room, or the cytology laboratory. The turnaround time is short, and the adequacy check can be performed within about 3 to 5 minutes with well-trained personnel. Every effort should be made to ensure most of the valuable tissue goes to the paraffin block for potential immunohistochemical or molecular tests. A quick, light touch of the biopsy tissue to a slide (touch preparation) is used for intra-procedural adequacy checks. The biopsy tissue should be allowed to touch the slide briefly, then be dropped into formalin immediately thereafter. The most common mistake is overtouching or even rolling the biopsy tissue on the slide, which will extract most of the tumor cells on the positively charged slide and leave a fibrous core in the paraffin block. As soon as the initial assessment is completed, all tissue should go directly to formalin without wasting tissue on touch preparations. In addition, the cell block should be made from needle rinse or residual fixative of the biopsy tissue, which can be a valuable substitute for immunohistochemical or molecular studies if the biopsy tissue runs out.

As discussed earlier in this review, a biopsy of lung nodules carries significant risk, and the samples are usually small and may be exhausted before molecular tests can be performed. This is an extremely challenging issue that needs awareness and preprocedural planning to maximize the utility of limited tissue. Some considerations include preordered, unstained paraffin sections to avoid repeated trimming of the tissue block, selecting only critical immunostains for diagnosis and classification, and making a cell block whenever possible. Improved technique in making touch preparation slides is often of great value.

High-Risk Patients

In patients with a high probability of having a malignant SPN, management decisions should be based on whether the patient is a suitable candidate for surgical resection. Standard preoperative workup should be obtained, including pulmonary function testing and cardiac testing, in addition to optimizing other medical comorbidities. In addition, functional imaging should be obtained, if not previously performed, and mediastinal staging should be planned as appropriate.

Patients whose preoperative testing or condition precludes them from operative resection still need a tissue diagnosis to confirm the presence of malignancy and, possibly, for molecular testing. The array of techniques and options available are outlined above, with care taken to subject the patient to the least invasive and fewest procedures possible. Mediastinal staging should be obtained as appropriate. These cases should be presented at multidisciplinary tumor boards, followed by referral of the patients to oncology and radiation oncology to evaluate appropriate treatment options.

Patients with a high probability of having a malignant SPN who are surgical candidates should undergo surgical biopsy with thoracoscopic wedge resection and intraoperative, frozen-section analysis. If the nodule is a primary lung malignancy, the patient should undergo completion lobectomy or segmentectomy, along with mediastinal lymph node dissection. If the wedge resection is consistent with a metastasis from an extrathoracic primary, the wedge is both diagnostic and therapeutic. If the result from the wedge is benign, then the patient has a definitive diagnosis without undergoing a larger, unnecessary operation and does not need further imaging follow-up. This approach is most effective in patients with peripheral nodules. In those with central nodules, localization techniques, including electromagnetic navigational bronchoscopy–guided marker placement, hook-wire placement, fluoroscopy, or ultrasound, can aid in locating the nodule and facilitating intraoperative core needle biopsy for diagnosis.

By following this path, patients with a high risk for malignancy avoid undergoing additional transthoracic or transbronchial needle biopsies and their inherent procedural risks. Given the high pretest probability that a patient has cancer, a needle biopsy demonstrating benign or nondiagnostic tissue would more likely represent a sampling error, rather than a truly benign diagnosis, thus offering little reassurance to either the physician or the patient.

Multidisciplinary Conferences

It is critically important to evaluate and discuss cases of SPN with a multidisciplinary team. Multidisciplinary tumor boards influence providers’ initial plans in 26% to 40% of cases.

CONCLUSIONS

Because incidentally detected, solitary pulmonary nodules are increasingly common, systematic evaluation of these patients is essential. Assessment of individual risk factors and thorough review of imaging characteristics and changes in nodule size and characteristics will form the basis for risk stratification. Patients at low risk for malignancy may undergo serial CT imaging until long-term stability is established. Those at intermediate risk should have further assessment with functional imaging and possible tissue sampling. Patients at high risk for malignancy should be assessed for surgical fitness, and if suitable, should undergo thoracoscopic wedge resection with intraoperative, frozen-section analysis to guide further therapy. Rapid on-site evaluation by cytology and communication between pathologists and proceduralists are essential for adequate sampling. All patients should be discussed in a multidisciplinary conference. Logical evaluation and management pathways
for SPNs allow providers to diagnose and treat individuals with early stage lung cancer and to minimize morbidity from invasive procedures for patients with benign lesions.

References


