The Solitary Pulmonary Nodule

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More than 150,00 patients a year present to their physicians with the diagnostic dilemma of a solitary pulmonary nodule (SPN) found either on chest radiography or chest CT. A thoughtful and timely workup of this finding is essential if lung cancer is to be recognized early and the chance for cure optimized. Based on the literature to date, recommendations are made for appropriate imaging modalities and diagnostic testing, as well as indications for obtaining preoperative tissue diagnosis for the patient with an SPN. ***(CHEST 2003; 123:89S–96S)***

Key words: diagnostic workup; lung cancer; malignancy; solitary pulmonary nodule

Abbreviations: CXR = chest radiograph; FDG = 18-fluorodeoxyglucose; NSCLC = non-small cell lung cancer; PET = positron emission tomography; SPN = solitary pulmonary nodule; TTNA = transthoracic needle aspiration

A solitary pulmonary nodule (SPN) is radiologically defined as an intraparenchymal lung lesion that is < 3 cm in diameter and is not associated with atelectasis or adenopathy.[1] Lung lesions > 3 cm in size are defined as lung masses. One of 500 chest radiographs (CXRs) demonstrates a lung nodule. Ninety percent of these are incidental radiologic findings, found unexpectedly in radiographs obtained for unrelated diagnostic workups. More than 150,000 patients per year in the United States present their physicians with the diagnostic dilemma of an SPN. This number has increased even further due to incidental findings of lung nodules on chest CT.[2]

The tragedy of lung cancer is directly associated with its delayed presentation. Signs and symptoms are rarely present until the malignancy has become advanced and possibly unresectable. Patients with the best prognosis are those found to have stage IA (T1N0M0) disease. These patients have a 61 to 75% 5-year survival following surgical resection.[3,4] Unfortunately, approximately one half of all lung cancers have extrapulmonary spread at the time of diagnosis. As a result, the average patient with a diagnosis of lung cancer has a 5-year survival of only 10 to 15%.[5]

Therefore, a timely and accurate diagnosis of the etiology of an SPN is essential to providing the patient with malignancy a potential for cancer cure. The occult nature of a lung nodule with its few symptoms and inability to be detected on physical examination does not lend itself to the sense of immediacy prompted by the discovery of other potential malignancies, such as a breast mass.

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Differential Diagnosis

The differential diagnosis of an SPN includes neoplastic, infectious, inflammatory, vascular, traumatic, and congenital lesions.[2] Other benign etiologies for SPNs are rheumatoid nodules, intrapulmonary lymph nodes, plasma cell granulomas, and sarcoidosis. Although most SPNs are benign,[2,5] primary malignancy may be found in approximately 35% of SPNs, and solitary metastases can account for another 23%.[6–8] Clinical characteristics such as older age, a history of cigarette smoking, and a previous history of cancer all increase the probability that an SPN is malignant.[9] Radiologic characteristics (discussed below) can also influence the probability of malignancy. Bayes theorem, logistic regression models, and neural network analysis have all been developed in an attempt to use both patient history and nodule appearance to accurately predict the likelihood of malignancy.[9–12] While these represent laudable efforts, they have proven to be cumbersome and of little practical use to the clinician evaluating a patient with an SPN. In general, all SPNs should be considered malignant until proven otherwise.[13]

Radiologic Diagnostics: CXRs

Since the SPN is by definition a radiographic finding, radiologic imaging is intrinsic to the diagnostic workup. Essentially all SPN are found on

CXRs or incidentally on CT. The CXR is an excellent initial imaging study for patients with symptoms, or as routine follow-up for patients with known pulmonary lesions. The indications and efficacy of CXRs for routine cancer surveillance are beyond the scope of this chapter and are discussed in the chapter on "Follow-up and Surveillance" in these guidelines. CXRs are inexpensive, readily available, quickly obtained, and can be read by both the clinician and the radiologist.

However, the diagnosis of lung cancer from CXRs alone can be quite difficult. The failure to recognize lung cancer on the CXR is one of the most frequent causes of missed diagnosis in radiology.[14] The rate of failure to diagnose lung cancer from CXRs varies from 25 to 90% in a number of different studies with differing study designs.[15–17] In the radiologic literature, an error rate of 20 to 50% for radiologic detection of lung cancer is generally accepted.[18] If an SPN is missed on the CXR, the delay in diagnosis can be substantial. Quekel et al[19] looked at CXRs retrospectively in 259 patients with proven non-small cell lung cancer (NSCLC) and found a 19% incidence of missed diagnoses. Those patients with missed lesions had significantly smaller nodules (median diameter 16 mm), more superimposing structures, and more indistinct border edges on CXRs than those SPNs that were correctly identified. The delay in diagnosis from the time of initial radiologic appearance was also significant at 472 days vs 29 days. This resulted in 43% of lesions being upstaged from T1 to T2 lesions during the delay period.[19]

Traditionally the presence of "benign" calcification or the absence of growth over a 2-year time period has been believed to be reliable indicators of benign disease. These criteria have been known since the 1950s.[20,21] In the 50 years since, we have learned that there are really no other characteristics that can consistently differentiate a benign nodule from a malignant nodule based on appearance on the CXR. Therefore, for patients with an SPN that is visible on the CXR, all previous CXRs should be reviewed. For all patients with previous CXRs, an SPN that is unchanged for > 2 years does not require further diagnostic evaluation.

Benign calcification refers to central, diffuse, laminar, or popcorn patterns.[2] Other types of calcifications such as eccentric or stippled calcifications are radiologically "indeterminant" and are seen in both benign and malignant lesions. CXRs may also falsely suggest that calcium is present, leading the clinician and patient to have false confidence that the nodule is benign. In a recent series by Berger et al,[22] 7% of nodules that were believed to be "definitely calcified" by the CXR lacked calcium on the CT scan.

The growth rate of a lesion may also be an unreliable predictor of a benign nodule. Benign lesions typically have a doubling time of either < 1 month or > 16 months.[23] Malignant nodules have a doubling time from anywhere from 40 to 360 days.[24] The CXR is also less sensitive than CT for detecting changes in size of an SPN, as a doubling in spherical tumor volume may result in a change in diameter of only a few millimeters.

The morphology of a nodule that is spherical with rounded edges is associated with benign disease. However, 20 to 34% of SPNs with this appearance are malignant, most notably those nodules that represent metastatic disease.[25,26]

Recommendations

1. For patients with an SPN that is visible on the CXR, all previous CXRs should be reviewed. Level of evidence, poor; benefit, substantial; grade of recommendation, C
2. For all patients with previous CXRs, an SPN that is unchanged for > 2 years does not require further diagnostic evaluation. Level of evidence, fair; benefit, substantial; grade of recommendation, B
3. For patients with an SPN visible on the CXR in which benign central calcification is present, no further diagnostic evaluation is necessary. Level of evidence, good; benefit, substantial; grade of recommendation, A

Radiographic Diagnostics: Chest CT

Spiral CT with IV contrast enhancement is the imaging modality of choice for the SPN and should be obtained on all newly diagnosed SPNs. CT provides ideal imaging for characterizing the nodule and its location. The CT scan can also be used to identify synchronous lung lesions or metastatic liver or adrenal lesions or mediastinal lymph nodes. Chest CT is also helpful for assessment of chest wall, mediastinal, or diaphragmatic invasion or for evaluation of superior sulcus (Pancoast) tumors. Of course, by strict definition the SPN does not invade the chest wall, mediastinum, or superior sulcus.

CT has a 50% sensitivity and 89% specificity for detecting mediastinal invasion and 14% sensitivity and 99% specificity for identifying chest wall invasion,[27] and it is well demonstrated to be more sensitive than the CXR in characterization of the nodule and the mediastinum. Studies demonstrate that MRI has a similar sensitivity and specificity for evaluation of the mediastinum and chest wall.[28,29] CT evaluation of mediastinal adenopathy has a wide range of reported sensitivities and specificities in the

literature. Shea and Lillington[29] of the Lung Cancer Study Group reviewed this literature on CT and MRI mediastinal evaluation and found a CT sensitivity of 70 to 90% and a specificity of 60 to 90%. If mediastinal adenopathy was not appreciated on CT, there was only a 15% chance of finding positive N2 disease at the time of surgery. Mediastinal detection of N2 disease was similar for CT and MRI. If mediastinal adenopathy is visualized radiographically, the most important role of CT is to provide a road map for further procedures that will give a tissue diagnosis.[28]

A number of benign etiologies for SPNs have a characteristic appearance on CT. The nodule containing a fat density can be classified as a hamartoma with confidence. Arteriovenous fistulas demonstrate presence of a feeding artery and a draining vein as well as contrast enhancement on CT. Rounded atelectasis is associated with a dense "comet tail" sign on CT. A fungus ball can be identified as an SPN within a cavity. Pulmonary infarcts may be characterized on CT as a wedge shape abutting the pleura with air bronchograms.

The patient with a new finding of an SPN and a recent history of pneumonia or pulmonary symptoms may warrant following the lesion for 4 to 6 weeks to rule out an infectious etiology. However, persistence of the nodule in such a patient should not further delay the diagnostic workup. In a 3-year retrospective study, $< 1\%$ of all SPNs were found to have an infectious etiology.[30] This incidence may be somewhat higher in regions endemic for fungal infections or tuberculosis.

Malignant pulmonary nodules may be ill defined with irregular margins and spiculated borders. In fact, 84 to 90% of spiculated nodules are malignant.[25,26] The size of a lung nodule is also a good indicator of the likelihood of malignancy. The vast majority of nodules > 2 cm in size are malignant, compared to a 50% rate of malignancy in all nodules < 2 cm in size.[31] The incidence of malignancy in a lung lesion > 3 cm is so great that all these lesions should be surgically resected unless medically contraindicated. Air bronchograms and pseudocavitation are characteristics seen on CT imaging that are more common in malignant (30%) than benign (5%) lesions.[25] Cavitation of a nodule is also indicative of malignancy, but inflammatory and infectious disease may also present with this morphology. In these situations, wall thickness can further aid in determining the probability that an SPN is benign or malignant. Woodring and Fried[32] found that 95% of all nodules with a wall < 5 mm were benign in origin, 84% of all cavitated lesions with a wall > 15 mm in thickness were malignant, and 73% of nodules with a wall thickness of 5 to 15 mm were benign.

For those SPNs with indeterminant morphology, IV contrast enhancement with helical CT imaging may be a helpful adjunct. Swenson et al[33] found nodules enhancing to > 20 Hounsfield units to be a predictive feature of malignancy while contrast enhancement < 15 Hounsfield units was characteristic of benignancy with a sensitivity of 98%, specificity of 73%, and 85% accuracy.

Recommendation

4. For patients with an SPN, spiral CT of the chest with contrast is indicated to better characterize the nodule, parenchyma, and mediastinum. CT can be useful in identifying nodules more likely to be benign and obviate the need for further diagnostic evaluation. Additionally, chest CT plays an important role in staging (as delineated in the chapter on Noninvasive Staging elsewhere in these guidelines). Level of evidence, good; benefit, moderate; grade of recommendation, B

Radiologic Diagnostics: MRI

MRI has a very limited role in the evaluation of the SPN. It may be beneficial in the patient who cannot tolerate IV contrast. MRI may also allow better anatomic evaluation of the lung apices, thoracic inlet, chest wall, or diaphragm due to its ability to provide sagittal, coronal, and oblique images. In general, the cost of MRI is not worth the lower risk of contrast-induced toxicity for most patients, as the imaging accuracy of CT is as good for most locations of SPNs. With the exception of special instances, MRI is not indicated for the routine workup of the SPN. Additionally, the cost of MRI is not worth the lower risk of contrast-induced toxicity for most patients because the imaging accuracy is at least as good as CT for most locations of lesions.

Recommendation

5. For patients with an SPN, MRI is not indicated except in these special instances. Level of evidence, good; benefit, none; grade of recommendation, D

Radiologic Diagnostics: Positron Emission Tomography

Positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG) has proven to be an excellent mode of tumor imaging. FDG is taken up by cells in glycolysis but is bound within these cells and cannot enter the normal glycolytic pathway.

Increased activity is demonstrated in cells with high metabolic rates, as is seen in tumors and areas of inflammation. Gould et al[34] performed a meta-analysis of the literature on pulmonary nodules and masses and PET scanning and found 40 good studies with an overall sensitivity of 96.8% and specificity of 77.8% for detecting malignancy. PET scans also have a 96% sensitivity and 88% specificity with 94% accuracy in the diagnosis of benign nodules. High diagnostic accuracy for detecting tumor also makes PET more accurate than CT for detecting mediastinal lymph node metastases and distant metastases. Indeed, T1 lung cancer may have up to a 21% incidence of regional lymph node metastases.[35,36]

The spatial resolution of PET is currently 7 to 8 mm, and so the imaging of SPNs < 1 cm is unreliable with the current generation of PET scanners and should not be performed. PET with FDG may also give false-negative results for nodules that are carcinoid tumors or bronchoalveolar carcinomas, as these tumors may not have high FDG uptake.[37] False-positive results may be seen in lung lesions with an infectious or inflammatory etiology, such as tuberculosis, histoplasmosis, or rheumatoid nodules. PET had been available only in large academic centers but is now becoming much more accessible. PET scans are more expensive than other imaging modalities, with Medicare reimbursement of $1,912 compared to $276 reimbursement for chest CT or $560 reimbursement for transthoracic needle aspiration (TTNA).[38]

PET scan is not only an excellent imaging study for tumor, but it can potentially change patient management by detecting unsuspected nodal and metastatic disease. Therefore, the question regarding when to include PET scans as part of the workup of the SPN is not one of diagnostic accuracy but of when clinical decision making will be changed by its findings and warrants the cost of the study. For low-risk patients with a pretest likelihood of malignancy of only 20%, the posttest likelihood of malignancy with a negative finding PET is 1%.[34] The high negative predictive value of PET in this patient population would support observation for the SPN with a negative PET finding. However, high-risk patients with a pretest likelihood of malignancy of 80% still have a 14% posttest likelihood of malignancy with a negative PET finding.[34] The patient with high risk of malignancy should have a tissue diagnosis of the SPN, and the only question should be the most efficient means of obtaining this tissue diagnosis. There is no indication for PET in the workup of an SPN with a negative mediastinal evaluation on CT if operative intervention is definitely planned or if it will otherwise not change patient management. Likewise, there is no indication for PET in a patient with a known malignancy who has a questionable pulmonary metastasis vs lung cancer primary tumor.

Recommendations

6. For patients with an SPN < 1 cm in size, PET scanning is not currently recommended. Level of evidence, good; benefit, none/negative; grade of recommendation, D
7. For patients with an SPN who are surgical candidates and have a negative mediastinal evaluation on CT, PET scanning with FDG as an investigational tool, where available, may be warranted. Level of evidence, fair; benefit, moderate; grade of recommendation, B
8. For patients with an SPN who are marginal surgical candidates, if PET with FDG results are negative, a repeat CT scan is required at least once in 3 months. Level of evidence, good; benefit, substantial; grade of recommendation, A
9: For patients with an SPN who are marginal surgical candidates, if there are unchanged results from prior CXRs and negative PET scan findings, serial follow-up is recommended, consisting of an initial CXR, and CT scanning at 3, 6, 12, and 24 months. Level of evidence, fair; benefit, substantial; grade of recommendation, B

Tissue Diagnosis: TTNA

Obtaining a tissue diagnosis via TTNA is somewhat less invasive than bronchoscopy and Wang needle biopsy and does not require IV sedation. Certainly, it is much less invasive than surgery, but a nonmalignant diagnosis may not be believed and TTNA and bronchoscopy can at best only be diagnostic, not therapeutic. The sensitivity for malignancy is 64 to 100%.[39,40] Unfortunately, the sensitivity of TTNA for a specific benign diagnosis is 12 to 68% but only 12% in a number of studies.[41] Adding automated cutting (core needle biopsy) to TTNA may increase the yield of a specific diagnosis of benign disease from 12 to 75%.[42] Yield is also increased by having an on-site pathologist to assess the quality of biopsy samples at the time of the procedure.[43] TTNA is contraindicated in the patient with a single lung. Relative contraindications to this procedure are the patient with pulmonary hypertension, coagulopathy or a bleeding diathesis, severe COPD, or vascular malformations. The most frequent complication of TTNA is pneumothorax in 25 to 30% of patients, with 5 to 10% of these patients requiring a chest tube. Pneumothorax is decreased by avoiding crossing pulmonary fissures and multiple

punctures of the lung parenchyma. There can be up to a 10% incidence of hemoptysis and hemorrhage, which is increased by the use of cutting needles. Air embolus and tumor seeding are rare, 0.1% and 0.05% respectively.[44]

Recommendations

10. For patients with an SPN who are operable candidates, TTNA is not indicated. Level of evidence, good; benefit, none; grade of recommendation: D
11. For operable patients with an SPN who decline surgical intervention, TTNA or transbronchial needle biopsy is the preferred procedure for establishing a diagnosis. Level of evidence, fair; benefit, substantial; grade of recommendation, B
12. For patients with an SPN who are not operable candidates, or are at high risk, TTNA may be helpful to establish tissue diagnosis. Level of evidence, good; benefit, moderate; grade of recommendation, B

Tissue Diagnosis: Bronchoscopy

Bronchoscopy may be an good approach for obtaining a tissue diagnosis in the large, central lung mass or in those with endobronchial encroachment, as diagnostic yield is 70% and 90%, respectively.[45–49] The best application of bronchoscopy and TBNA is for staging of NSCLC by aspirating enlarged mediastinal lymph nodes. The discovery of metastatic disease will change patient management and obviates any further surgical staging. However, for the patient with a peripheral lung nodule, there is little role for bronchoscopy. Although the reported diagnostic yield of 40 to 80% for peripheral lesions is surprisingly high, these reports are primarily from centers that employ routine use of fluoroscopy and multiple sampling methods.[46] Bronchoscopic diagnostic yield is proportional to the size of the lung lesion. In the evaluation of the SPN, bronchoscopy has been shown to provide no measurable preoperative benefit to the patient, as it does not obviate the need for surgery.[49]

Recommendation

13. In patients with an SPN, bronchoscopy is usually not indicated. Level of evidence, good; benefit, none; grade of recommendation, D

Surgery

The patient with an SPN that is new and does not have benign appearing calcifications should be considered to have a malignancy until proven otherwise. Surgical resection is the ideal approach, as it is both diagnostic and therapeutic. If it is believed that based on patient history that the SPN may not be NSCLC but rather metastatic disease, then thoracoscopy and wedge resection is an accepted initial surgical approach. The specimen should be sent for frozen section, so that conversion to a thoracotomy and lobectomy can be performed in the same setting should the nodule prove to be NSCLC. Localization techniques such as methylene blue dye injection and wire localization may assist thoracoscopic resection of small nodules or those not in the lung periphery.[50,51] Suzuki et al[52] suggest that nodules < 1 cm or > 5 mm from the nearest pleural surface should have preoperative localization to optimize thoracoscopic resection. For the surgical candidate with an SPN proven to be NSCLC, lobectomy and systematic mediastinal lymph node dissection is the standard of care for complete oncologic resection and staging.[53] Five-year survival following complete resection of stage 1A or 1B NSCLC is 65 to 80% and 50 to 60%, respectively. For the patient who is a marginal surgical candidate and whose pulmonary or cardiac status would benefit from a limited resection, wedge resection or segmentectomy is acceptable for treatment of NSCLC. Warren and Faber[54] demonstrated similar long-term survival for patients who had segmentectomy vs lobectomy for stage I NSCLC, but overall local recurrence was 23% vs 5%. In the only prospective trial, performed by the Lung Cancer Study Group, Ginsberg and Rubinstein[55] reported a local recurrence rate for segmentectomy or wedge resection of T1N0 NSCLC three times greater than that for lobectomy, but long-term survival was not as impressively decreased. Because of the greatly increased rate of recurrence, patients who have a limited resection require close postoperative surveillance.

Recommendations

14. In operable patients with an SPN, if the lesion is amenable to a wedge resection, then a wedge resection is the procedure of choice followed by a lobectomy if the pathologic finding is positive for cancer. Level of evidence, fair; benefit, substantial; grade of recommendation, B
15. In operable patients with an SPN, if the lesion is not amenable to a wedge resection, a diagnostic lobectomy is acceptable. Level of evidence, good; benefit, substantial; grade of recommendation, A
16. All pulmonary resections, anatomic or nonanatomic, must include a systematic lymph

node dissection. Level of evidence, good; benefit, substantial; grade of recommendation, A

17. For patients with an SPN who are marginal surgical candidates, a wedge resection or segmentectomy is acceptable. Level of evidence, fair; benefit, substantial; grade of recommendation, B

Follow-up

The patient with an SPN who does not have a tissue diagnosis and who is deemed acceptable for observation should be followed up closely for a minimum of 2 years. This should include an initial CXR, and CT scanning at 3, 6, 12, and 24 months for best monitoring for nodule growth. There is very little objective evidence for frequency of surveillance monitoring.

Recommendation

18. For patients with an SPN without a definitive tissue diagnosis, a minimum follow-up of 2 years is recommended. This should include an initial CXR, and CT scanning at 3, 6, 12, and 24 months. Level of evidence, poor; benefit, moderate; grade of recommendation, C

Summary of Recommendations

1. For patients with an SPN that is visible on CXR, all previous CXRs should be reviewed. Level of evidence, poor; benefit, substantial; grade of recommendation, C
2. For all patients with previous CXRs, an SPN that is unchanged for >2 years does not require further diagnostic evaluation. Level of evidence, fair; benefit, substantial; grade of recommendation, B
3. For patients with an SPN visible on CXR in which benign central calcification is present, no further diagnostic evaluation is necessary. Level of evidence, good; benefit, substantial; grade of recommendation, A
4. For patients with an SPN, a spiral CT of the chest with contrast is indicated to better characterize the nodule, parenchyma, and mediastinum. CT can be useful in identifying nodules more likely to be benign and obviate the need for further diagnostic evaluation. Additionally, chest CT plays an important role in staging (as delineated in the chapter on noninvasive staging elsewhere in these guidelines). Level of evidence, good; benefit, moderate; grade of recommendation, B
5. For patients with an SPN, MRI is not indicated except in these special instances. Level of evidence, good; benefit, none; grade of recommendation, D
6. For patient with an SPN <1 cm in size, PET scanning is not currently recommended. Level of evidence, good; benefit, none/negative; grade of recommendation, D
7. For patients with an SPN who are surgical candidates and have a negative mediastinal evaluation on CT, PET scanning with FDG as an investigational tool, where available, may be warranted. Level of evidence, fair; benefit, moderate; grade of recommendation, B
8. For patients with an SPN who are marginal surgical candidates, if PET scanning with FDG results are negative, a repeat CT scan is required at least once in 3 months. Level of evidence, poor; benefit, substantial; grade of recommendation, C
9. For patients with an SPN who are marginal surgical candidates, if there are unchanged results from prior CXR and negative PET scan findings, serial follow-up is recommended, consisting of an initial CXR, and CT scanning at 3, 6, 12, and 24 months. Level of evidence, fair; benefit, substantial; grade of recommendation, B
10. For the patients with an SPN who are operable candidates, TTNA is not indicated. Level of evidence, good; benefit, none; grade of recommendation, D
11. For operable patients with an SPN who decline surgical intervention, TTNA or transbronchial needle biopsy is the preferred procedure for establishing a diagnosis. Level of evidence, fair; benefit, substantial; grade of recommendation, B
12. For patients with an SPN who are not operable candidates, or are at high risk, TTNA may be helpful to establish tissue diagnosis. Level of evidence, good; benefit, moderate; grade of recommendation, B
13. For patients with an SPN, bronchoscopy is usually not indicated. Level of evidence, good; benefit, none; grade of recommendation, D
14. For operable patients with an SPN, if the lesion is amenable to a wedge resection, then a wedge resection is the procedure of choice followed by a lobectomy if the pathologic finding is positive for cancer. Level of evidence, fair; benefit, substantial; grade of recommendation, B
15. For operable patients with an SPN, if the lesion is not amenable to a wedge resection, a

diagnostic lobectomy is acceptable. Level of evidence, good; benefit, substantial; grade of recommendation, A

16. All pulmonary resections, anatomic or nonanatomic, must include a systematic lymph node dissection. Level of evidence, good; benefit, substantial; grade of recommendation, A
17. For patients with an SPN who are marginal surgical candidates, a wedge resection or segmentectomy is acceptable. Level of evidence, fair; benefit, substantial; grade of recommendation, B
18. For patients with an SPN without a definitive tissue diagnosis, a minimum follow-up of 2 years is recommended. This should include an initial CXR, and CT scanning at 3, 6, 12, and 24 months. Level of evidence, poor; benefit, moderate; grade of recommendation, C

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