

An approach to the solitary pulmonary nodule

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Solitary pulmonary nodules may represent early lung cancer, which is potentially curable. The advent of improved imaging techniques, together with the worldwide implementation of screening programmes, has intensified the need for a structured approach to the management of pulmonary nodules. We present an overview of the current literature on risk stratification, characteristics and management of pulmonary nodules that are relevant to practitioners in South Africa.

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In clinical practice, solitary pulmonary nodules (SPNs) represent a common challenge, as they may be indicative of early cancer that is curable; however, after extensive investigation the vast majority are found to be of benign aetiology. While advanced lung cancer survival rates remain low – 17% at 5 years – the diagnosis of early lung cancer (stage 1A) can be associated with a 5-year survival rate of 70 - 80%.^[1] The best possibility for cure in potentially malignant SPNs is prompt diagnosis and surgery, while at the same time trying to avoid unnecessary intervention and surgery in patients with benign disease processes.^[2]

Traditionally an SPN is defined as a single, usually well-circumscribed spherical opacity of ≤ 3 cm, completely surrounded by pulmonary parenchyma and not associated with lymphadenopathy, atelectasis or pleural effusion.^[3] The new British Thoracic Society (BTS) guideline^[4] extends the definition to include nodules in contact with the pleura. Most SPNs are asymptomatic and discovered incidentally. The incidence of SPNs ranges from 0.2% in older radiographic studies to 40 - 60% in lung screening studies.^[2] Lesions > 3 cm are considered as masses and have a high likelihood of malignancy, requiring prompt diagnosis and management.

The differential diagnosis of SPNs (Table 1) is broad, with a variety of aetiologies, which include malignancies such as bronchogenic carcinoma, carcinoid tumours, lymphoma, and solitary pulmonary metastasis, and benign aetiologies such as granulomas and hamartomas^[2] – the most common benign causes.

Low-dose computed tomography screening

With the increasing use of computed tomography (CT) of the chest, the detection of SPNs has become common.^[5] The implementation of low-dose CT lung cancer screening is expected to increase the detection of SPNs. Several studies, including lung screening trials in smokers, suggest that the majority of nodules identified on CT are benign.^[2,6-10] In the Pan-Canadian Early Detection of Lung Cancer and the British Columbia Cancer Agency studies, among the 7 008 and 5 021 nodules detected, respectively, only a total of 144 (1%) were

malignant.^[7] The false-positive rate in the National Lung Screening Trial (NLST) was 96%.^[10]

General evaluation of an SPN

The assessment of an SPN involves risk stratification of the individual patient, performing further imaging studies (if available), and formulating a management plan after taking into consideration the risks associated with various treatment strategies and individual patient preferences.

Risk stratification

Principles

Estimation of the pretest probability of cancer in an SPN includes clinical assessment of individual risk, evaluation of radiological features to differentiate between benign and malignant nodules, and use of models using logistic regression. Logistic regression models use both clinical and radiological parameters to assess the pretest risk of malignancy. This risk assessment determines further management steps, which may include CT surveillance, further investigation (e.g. positron emission tomography (PET)-CT) and/or biopsy (non-surgical or surgical).

Clinical assessment

Clinical risk stratification considers individual demographics and medical history and assesses the patient's risk. Risk factors associated with a higher likelihood of malignancy include advanced age, current or ever smokers, time from smoking cessation, number of pack-years, emphysema, asbestos exposure, history of previous extrapulmonary malignancy, radiation therapy, idiopathic pulmonary fibrosis and HIV.^[2,4]

Chest radiography

SPNs (Fig. 1) are still commonly first detected on chest radiographs, and a diameter of 8 - 10 mm is usually required before they are visible. Certain patterns of calcification may point to a benign cause (discussed below).

Table 1. The differential diagnosis of a solitary pulmonary nodule**Neoplastic****Malignant**

Bronchogenic carcinoma
 Adenocarcinoma (including adenocarcinoma in situ (previously bronchoalveolar carcinoma))
 Squamous cell carcinoma
 Large-cell lung carcinoma
 Small-cell lung cancer
 Metastasis
 Colon, breast, kidney, prostate, testicular cancer
 Extranodal lymphoma
 Pulmonary carcinoid

Benign

Pulmonary hamartoma
 Connective tissue and neural tumours
 Fibroma, neurofibroma, blastoma, sarcoma, lipoma, angioma

Infectious**Granulomas**

Tuberculosis
 Fungal (histoplasmosis, coccidioidomycosis, blastomycosis, cryptococcosis)
 Atypical mycobacteria
 Bacterial (nocardiosis)
 Parasitic (*Dirofilaria immitis*)

Lung abscess**Round pneumonia****Hydatid cyst****Inflammatory****Rheumatoid arthritis****Sarcoidosis****Granulomatosis with polyangitis****Lipoid pneumonia****Congenital****Pulmonary sequestration****Bronchogenic cyst****Arteriovenous malformation****Miscellaneous****Pulmonary infarct****Rounded atelectasis****Mucoid impaction****Progressive massive fibrosis**

Fig. 1. An example of an SPN seen on chest radiography. A nodule was noted in the right lower zone of a 50-year-old female smoker. A CT and an integrated PET-CT were done on the patient (Figs 2 and 4).

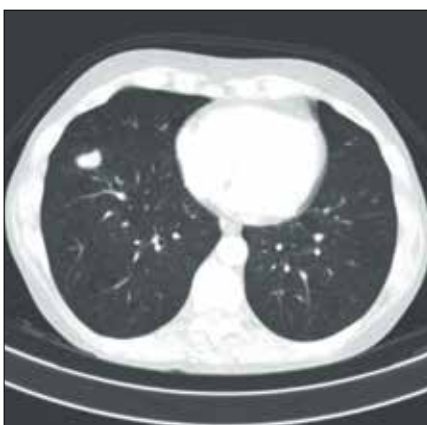


Fig. 2. A CT scan of the chest of the same patient as in Fig. 1, showing a 19 × 12 mm SPN in the right lower lobe.

Chest CT

In a patient with an indeterminate nodule identified by chest radiography, it is recommended that CT of the chest should be performed (preferably with thin sections through the nodule). The predictors on CT (Fig. 2) that could assist with the likelihood of malignancy in SPNs include: the nodule size, border, density (calcification, fat), growth rate or volume-doubling time (VDT), nodule attenuation and location.

Data from clinical trials indicate that the risk of malignancy rises with increasing nodule size.^[6,7,11,12] More than 90% of nodules <2 cm in diameter are benign. However, subcentimeter nodules may represent an early stage of lung cancer. Data from the NLST suggested that the likelihood of malignancy increased

significantly from 1.7% for nodules 7 - 10 mm in diameter to 11.9%, 29.7% and 41.3% for nodules with a diameter of 11 - 20 mm, 21 - 30 mm and >30 mm, respectively.^[10]

Nodules with irregular, lobulated or spiculated (corona radiata) borders are associated with a progressively higher probability of malignancy than those with smooth borders.^[6,13] The corona radiata sign consists of very fine linear strands extending 4 - 5 mm outward from the nodule. Nevertheless, malignant SPNs may also present with a smooth border.

Certain types of calcification in SPNs indicate benign disease processes. There are six different patterns of calcification: central dense nidus; diffuse solid; laminated; popcorn; punctate; and dendriform.^[14] Diffuse, central, laminated and popcorn calcification are considered to be benign^[3,4,13,15,16] – the first three types are associated with granulomatous processes, with popcorn calcification typically occurring in a pulmonary hamartoma. The presence of intranodal fat density and popcorn calcification is specific for pulmonary hamartoma. All other patterns of calcification are suspicious of malignancy. Stippled and eccentric calcification patterns are seen in malignant nodules and warrant further evaluation and workup.^[17]

Lung nodules containing fat include pulmonary hamartoma, lipoma and lipoid pneumonia.

Calcific metastases may occur in primary sarcomas, such as osteosarcoma, chondrosarcoma and synovial sarcoma.^[14] Primary carcinomas associated with metastases that may calcify include papillary and mucinous adenocarcinomas, and medullary carcinoma of the thyroid.^[14]

Studies have shown that 70% of lung cancers are located in the upper lobes.^[4,6,7] As benign nodules can occur in the upper and lower lobes, location is not a good independent predictor of malignancy. Tuberculosis (TB) is common in the South African (SA) setting and classically affects the upper lobes. Perifissural and subpleural solid nodules are likely to be benign if they are homogeneous, have a lentiform or triangular shape, measure <10 mm in size, and are within 1 cm of the fissure or the pleural surface.^[18]

Based on nodule attenuation on CT, SPNs can be classified as non-solid (ground glass), partly solid, or solid. Non-solid nodules have underlying bronchovascular structures visible

through them, while a partly solid nodule also contains solid regions that will mask visibility of the underlying bronchovascular structures.^[19] New nomenclature for SPNs has been adopted by the BTS guideline,^[4] with classification of nodules into solid and subsolid; additionally, there is subclassification of subsolid nodules into part-solid and pure ground-glass nodules (pGGNs) (Fig. 3).

Solid lesions are more common in practice, but subsolid lesions have a higher likelihood of being malignant, with CT screening studies showing that the identification of a solid component in a partly solid nodule was an independent predictor of malignancy.^[20] Pure ground-glass SPNs typically represent adenocarcinoma in situ, atypical adenomatous hyperplasia or minimally invasive adenocarcinoma.^[4] Increased growth or development of a solid component in a GGN is strongly associated with transformation to invasive adenocarcinoma.^[2]

The VDT for malignant bronchogenic tumours is rarely <1 month or >1 year.^[21] The average doubling time for a malignant tumour is 120 days (range 7 - 590 days). The exception would be indolent tumours, such as adenocarcinoma in situ, which has a doubling time of up to 900 days. Doubling times <1 month may indicate infection, infarction, a lymphoma, or fast-growing metastases.^[22,23]

Data from the Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym: NELSON) found that VDT in SPNs <400 days, 400 - 600 days, and >600 days at 3- and 12-month screening had 2-year cancer probabilities of 9.7%, 4.1% and 0.8% respectively.^[24]

Other characteristics suggestive of malignancy on CT include: vascular convergence, dilated bronchus leading to the nodule, presence of pseudocavitation or true cavitation.^[16] Benign lesions usually have thinner, smoother walls <4 mm, thicker irregular walls >15 mm being suggestive of malignancy.^[19,25,26] Nevertheless, there is overlap between the two, with thick-walled cavities also seen in benign infectious processes such as TB, fungal infections and rheumatoid nodules.^[27]

Pretest probability testing with a logistic model

There are various validated prediction models that use a combination of clinical and radiological features to assess the probability

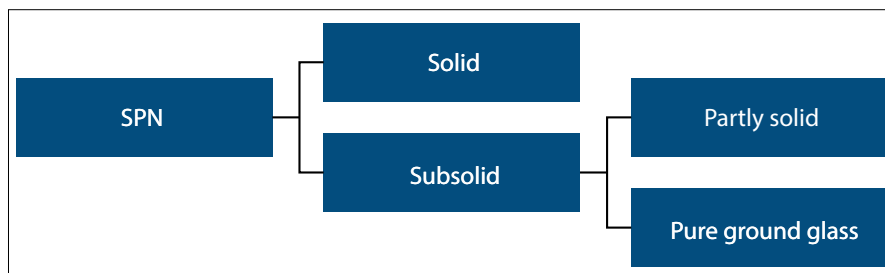


Fig. 3. A general classification of SPNs.



Fig. 4. The corresponding PET-CT of the patient in Fig. 2, showing a mass with FDG uptake. The standardised uptake value was 7.06. A surgical biopsy was done, which revealed a poorly differentiated neuro-endocrine tumour.

of malignancy. Prediction calculators are available online and also via medical applications for downloading on mobile devices. Current guidelines recommend their use in risk assessment.^[4,16] The newest of these guidelines is the BTS guideline (2015), which recommends the use of the Brock and Herder models in its management algorithms.

The Bayesian model^[12] uses the most important predictors of malignancy, i.e. spiculation, diameter and cavity wall thickness. Predictors of a benign aetiology are VDT >465 days and calcification. The Mayo Clinic model^[6] uses six independent

predictors of malignancy, including three clinical risk factors (age, smoking status, history of cancer >5 years previously), and three radiological features (diameter, spiculation and upper-lobe location). The Veterans Administration model^[11] uses independent predictors of positive smoking history, older age, larger nodule diameter and time since quitting smoking. The Brock University model^[7] is based on the predictors of cancer, including older age, female sex, family history of lung cancer, emphysema, larger nodule size, location of the nodule in the upper lobe, SPN type, lower nodule count

and spiculation. Lastly, the Herder model^[28] uses the addition of PET-CT and a 4-point intensity score to the Mayo Clinic model to improve its accuracy.

Functional imaging and PET-CT

Various functional imaging modalities have been studied in patients with SPNs to distinguish malignant from benign nodules. These include PET-CT, dynamic CT, dynamic magnetic resonance imaging (MRI) and dynamic single photon emission CT (SPECT). Studies have shown similar sensitivities between these different modalities for the detection of malignancy.^[29]

18-Fluorodeoxyglucose (FDG) PET-CT is, however, the preferred functional imaging modality, as it is more widely available and assists in clinical lung cancer staging (Fig. 4).

False-positive PET findings with standard uptake values >2.5 are often seen in infectious or inflammatory conditions, including TB, endemic mycoses (histoplasmosis), rheumatoid nodules, sarcoidosis and pneumonia.^[30-32] False-negative results are seen in subcentimeter (<1 cm) nodules, subsolid nodules, malignancies with low metabolic activity (e.g. adenocarcinoma in situ, carcinoid) and hyperglycaemia.^[33] False-negative results in the first three reflect the low mass of metabolically active malignant cells.

Biomarkers

Although some biomarkers have shown early interesting results, none has been validated for clinical use and none is currently recommended for use.^[4]

General management of SPNs

Principles

Most guideline recommendations on the evaluation and management of SPNs are based on low-quality evidence and expert opinion. Two of these guidelines include those by the Fleischner Society (Table 2)^[34,35] and the American College of Chest Physicians (ACCP).^[16] These guidelines use nodule size to determine further management, based on patient risk stratification. The ACCP guideline has similar recommendations as the Fleischner Society, pertaining to nodule size and further management (no follow-up, CT surveillance or biopsy). The ACCP guideline,

Table 2. Recommendations for the management of SPNs as per statements from the Fleischner Society^[34,35]

Nodule type and size	Low risk	High risk
Solid nodules		
≤ 4 mm	No follow-up	Follow-up at 12 months; if unchanged, no further follow-up
$>4 - 6$ mm	Follow-up at 12 months; if unchanged, no further follow-up	Initial follow-up CT at 6 - 12 months; then at 18 - 24 months if no change
$>6 - 8$ mm	Initial follow-up CT at 6 - 12 months; then at 18 - 24 months if no change	Initial follow-up CT at 3 - 6 months; then at 9 - 12 months and 24 months if no change
>8 mm	Follow-up CT at 3, 9 and 24 months	Same as low risk
Dynamic contrast-enhanced CT Consider PET-CT and/or biopsy		
Subsolid nodules (pGGNs)		
<5 mm	No follow-up needed	
≥ 5 mm	Initial follow-up at 3 months; if persistent, annual CT for ≥ 3 years (FDG-PET of limited value, potentially misleading and not recommended)	
Subsolid nodules (partly solid nodules)		
<5 mm	Initial follow-up at 3 months; if persistent, annual CT for ≥ 3 years	
≥ 5 mm	Initial follow-up at 3 months; if persistent, biopsy or surgical resection (consider PET-CT for partly solid nodules with a solid component >8 mm)	

however, also incorporates surgical risk in their management algorithm. The new BTS guideline is based on a comprehensive review of the current literature and includes nodule volume and VDT in addition to nodule size.^[4] Management options include serial CT surveillance, further imaging, non-surgical biopsy and surgical resection.

Decisions about further evaluation depend on clinical probability of malignancy determined by clinical, radiological and various logistic models, nodule characteristics such as size, attenuation (solid v. subsolid) and growth (VDT), as well as informed patient preference, associated risks and comorbidities that influence fitness for surgery.

The current BTS guideline recommends that the same diagnostic approach be applied to nodules that are discovered incidentally, via screening studies, in patients with a history of extrapulmonary malignancy, and in those with known lung malignancy. No consensus was reached on the risk of malignancy in SPNs in patients with a previous history of malignancy, with some studies indicating an increased risk and others showing no

difference.^[36-39] Lung nodules detected in patients considered for radical cure should be evaluated on their own and not assumed to be malignant, as the probability of these being benign is high.

The BTS 2015 guideline addresses four groups of patients: (i) requiring no further follow-up; (ii) with solid nodules $\geq 5 - <8$ mm in diameter or volume <300 m³; (iii) with solid nodules with diameter ≥ 8 mm or volume ≥ 300 m³; and (iv) with subsolid nodules.

No further follow-up

No follow-up is required in patients with solid nodules with benign patterns of calcification, nodule size <5 mm (both solid and subsolid) or a volume <80 mm³, and solid perifissural or subpleural nodules <10 mm with triangular or lentiform shape. However, caution and follow-up are advised for perifissural nodules >10 mm, especially in patients with a history of extrapulmonary cancer.^[4]

Lung screening studies have provided evidence that nodules <5 mm or <100 mm³ have a low risk of malignancy, i.e. there is no

difference compared with individuals without pulmonary nodules.^[24] However, because of lack of standardisation between volumetric determining programmes, the BTS has reduced the threshold value to 80 mm³. Studies of patients with perifissural nodes <10 mm showed that none of the nodules was malignant.^[18]

Solid nodules ≥5 - <8 mm in diameter or volume ≥80 - <300 mm³

The risk of malignancy in this group was found to be low (2.4%) in the NELSON trial, justifying conservative management with CT surveillance.

Solid nodules ≥5 - <8 mm in diameter or volume ≥300 mm³

The NELSON trial found an increased risk of 16.9% for malignancy in nodules with a volume ≥300 mm³, and 9.7% for lung nodules with a diameter >8 mm (Fig. 5).^[24]

In this group of patients with nodule size ≥8 mm and volume ≥300m³, the BTS recommendations include risk stratification using the Brock model. If the risk is low (<10%), serial CT follow-up is recommended, and if the risk is deemed to be high (>10%), further imaging with PET-CT is indicated. Additional risk stratification is then suggested with the use of the Herder model.

Using the Herder risk stratification model, suggestions are as follows: (i) low risk (<10%) – can be followed-up by CT surveillance; (ii) intermediate risk (10 - 70%) – further evaluation such as non-surgical biopsy, excision biopsy or CT surveillance should be based on patient preference and associated comorbidities; and (iii) high risk (>70%) – surgical biopsy is the best option, with non-surgical treatment for those who are poor surgical candidates.

In facilities where volumetric measurement can be done, follow-up of patients with solid nodules with interval CT and determination of VDT at 1 year for nodules 5 - 6 mm, and at 3 months and 1 year for nodules with diameter ≥6 mm and volume ≥80 mm³, is suggested. A volume change of ≥25% is defined as significant growth and requires further intervention (imaging, biopsy or surgery). Patients can be discharged if the volume change is <25% at 1 year, although if diameter is used to assess growth a 2-year follow-up

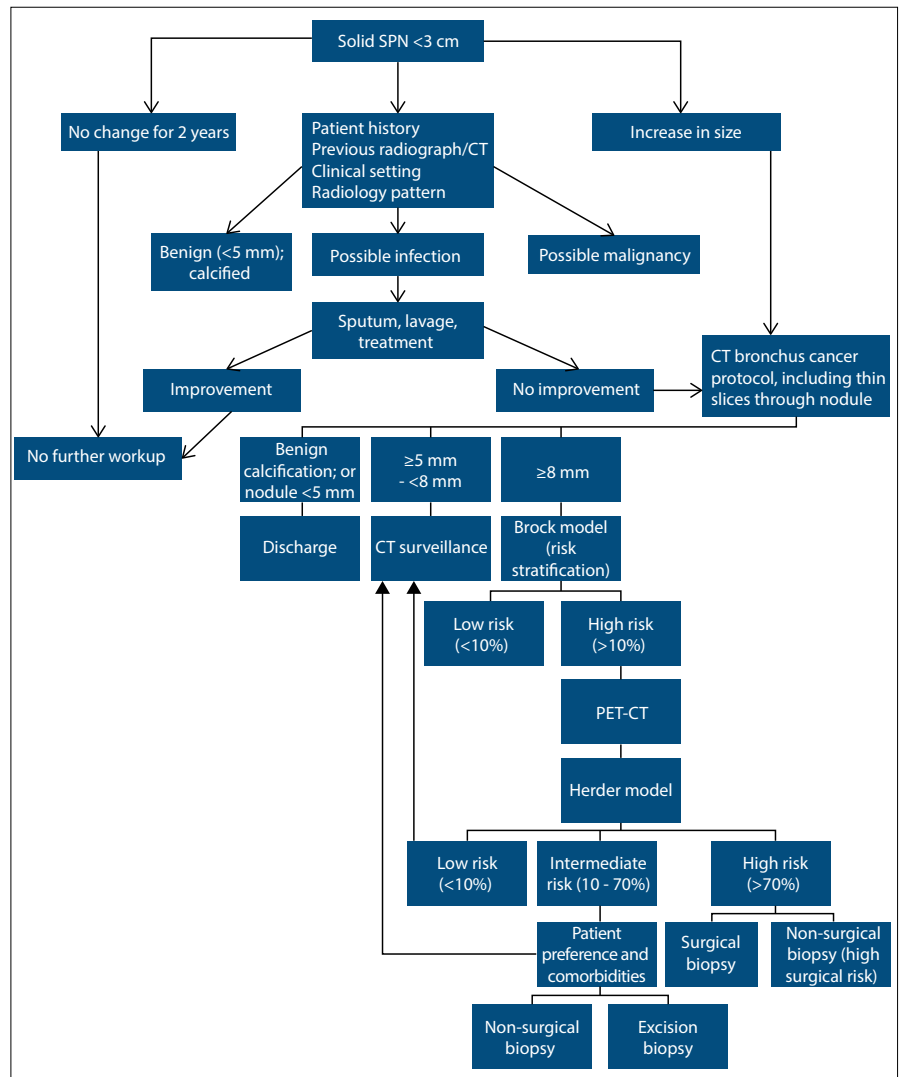


Fig. 5. A suggested approach to SPNs (adapted from BTS and Murrmann et al.^[40]).

is required. A patient with VDT >600 days could be discharged or CT surveillance could be done based on patient preference. A VDT 400 - 600 days should prompt a biopsy or surveillance based on patient preference, whereas a VDT <400 days should definitely indicate further workup and management.

Subsolid nodules

Subsolid nodules may represent slow-growing indolent tumours and further management will be dependent on size, risk stratification in persistent nodules, growth and nodule subtype. For nodules ≥5 mm, a repeat CT scan is advised in 3 months. If the nodule disappears, the patient may be discharged. CT surveillance with intervals of 1, 2 and 4 years is suggested for patients with low risk (<10%). CT surveillance, CT-guided

biopsy, or resection should be considered in patients with a high risk (>10%), taking into account patient preference and surgical risk. Resection/non-surgical treatment or observation should be considered for pGGNs that enlarge ≥2 mm, considering patient preference and surgical risk. If observation is chosen, a repeat CT at a maximum interval of 6 months should be performed. Resection/non-surgical treatment should be considered for patients with partly solid nodules that show an increase in solid component, pGGNs that develop a solid component, and pathologically proven malignancy, keeping in mind patient preference and surgical risk.

Biopsy

Non-surgical biopsy

Options for non-surgical biopsy include bronchoscopy and CT-guided transthoracic

needle aspiration (TTNA) or biopsy. The sensitivity of CT-TTNA was 90% in 11 studies, with the risk of pneumothorax between 4% and 8%.^[20] Conventional bronchoscopy has a low yield and a low sensitivity of 13.5% reported in the NELSON study and is not recommended by the current BTS guideline.^[4,24] Bronchoscopy yield can be augmented with fluoroscopy, radial endobronchial ultrasound and electromagnetic navigation bronchoscopy and is indicated if a bronchus sign is seen on CT.

Surgical biopsy

Surgical resection is the gold standard and the definitive treatment for malignant nodules. Surgical approaches include video-assisted thoracoscopic surgery (VATS) or thoracotomy. Patients fit for surgery should undergo VATS wedge resection with progression to lobectomy and systematic sampling of mediastinal lymph nodes, if malignant. Sublobar resection (wedge resection and segmentectomy) was associated with worse outcomes in cases of stage 1 cancer.^[41] Segmentectomy may be considered in patients in whom preservation of lung tissue will improve outcome. In patients who are not candidates for surgery, therapeutic alternatives include external beam radiation therapy and percutaneous radiofrequency ablation.^[4]

SPN in the SA context

The World Health Organization (WHO) has rated SA as a high-prevalence (>125/100 000) TB region, with statistics suggesting an estimated incidence of 450 000 active cases of TB in 2013. The incidence of benign granulomas is therefore exceedingly high, with incidental upper-lobe nodules being a common finding on imaging. In this setting, these findings would raise an already very high false-positive rate even further. This could lead to unnecessary investigations, high cost and associated morbidity. Even with the use of FDG-PET, the high false-positive rate would still limit accuracy, further complicating the evaluation of SPNs in our setting.^[30]

Conclusion

The SPN remains a clinical challenge, with the potential of early malignancy. The 2015 BTS guideline assists with risk stratification and appropriate management of different patient groups. Benign granulomas in a high TB-endemic area such as SA can complicate the evaluation of SPNs. Risk stratification models and management algorithms need to be validated in this setting.

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