CHAPTER 7

Diagnostic management of solitary pulmonary nodule

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Solitary pulmonary nodule (SPN) is defined as a single, approximately round and well-circumscribed radiographic opacity ≤ 3 cm in diameter which is completely surrounded by normal aerated lung parenchyma, without other abnormalities such as lymph node enlargement, atelectasis or pleural effusion [1].

The diagnosis of an SPN is a very common clinical problem and several pathological processes, both benign and malignant, may determine a solitary nodular lesion in the lung (table 1) [2].

Optimal management of SPN should allow the resection of all malignant nodules without delay and avoid useless surgery of benign nodules. How to reach this goal is an age old problem [3] and still remains today. Despite huge technological advancements in this diagnostic field, no widely accepted evidence-based guidelines completely address the approach to SPN [4]. In the last few years some new developments have changed the concept of managing SPN [5].

The widespread use of computed tomography (CT), the introduction of spiral and multi-detector row CT and the performance of CT-based screening programmes have greatly increased the identification of small subcentimetric nodules. The results from lung cancer screening projects show that noncalcified nodules are found in 20–50% of asymptomatic smokers or ex-smokers [6, 7]. The clinical meaning of these small lesions is different from the nodules detected by chest radiographs, generally >1 cm, for which the probability of malignancy is very high (64–82% for SPN >2 cm) [8] and for which the assumption that they should be considered malignant until proved otherwise is widely accepted. On the contrary, <1% of nodules <5 mm are malignant in patients without any previous history of cancer [9]. The likelihood of malignancy increases with the nodule size, being 0.2% for nodules <3 mm, 0.9% for those 4–7 mm, 18% for those 8–20 mm [10] and ~80% for nodules >20 mm [11]. The differences in epidemiology, clinical meaning and prognosis of subcentimetric nodules in comparison to nodules >1 cm prompt us to propose a separate specific management for these kinds of lesions. Scientific societies should probably also review the terminology for SPNs, taking into account that there should be a distinction between small and larger nodules when defining them (fig. 1).

Furthermore, thanks to the diffusion of the CT scan, other new concepts concerning the morphology of SPNs have been introduced. The identification of nodules with a pure ground-glass attenuation pattern (ground-glass opacity) (fig. 1) or with a mixed solid component and ground-glass opacity, may have a different meaning in comparison with solid SPNs. In fact, nodules with ground-glass opacity pattern, even if they could represent conditions such as focal fibrosis, haemorrhage, inflammation and atypical adenomatous hyperplasia [12], are more likely to be malignant (70–100%) than solid

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Table 1. – Possible causes of solitary pulmonary nodule

Malignant	Benign
Primary lung cancer	Benign tumours: hamartoma, lipoma, fibroma
Metastases	Granulomas: tuberculosis, histoplasmosis, coccidioidomycosis, criptococcosis, wegener, rheumatoid nodule, sarcoidosis
Carcinoid	Abscess, pneumonitis, septic embolus
Sarcoma	Fibrotic nodule
Others (lymphoma, plasmocytoma)	Cryptogenic organising pneumonia
	Silicosis
	Pulmonary infarction
	Mucocele
	Haematoma
	Arteriovenous malformation
	Intrapulmonary lymph node
	Bronchogenic cyst
	Echinococcus cyst
	Amyloidoma

nodules [8, 13–15]. The histotype that is more frequently responsible for ground-glass opacity is the bronchioloalveolar carcinoma [8, 16]. The growth rate of ground-glass nodules may be slower than solid nodules and the mean volume doubling time has been evaluated at 813 ± 375 days, which means >3 yrs [13]. This factor limits the value of the old assumption that 2 yrs of stability is a criterion to classify an SPN as benign and supports the need for an extended follow-up period for ground-glass nodules. Furthermore, the high incidence of malignancy among ground-glass opacity could suggest a more aggressive management of this type of lesion.

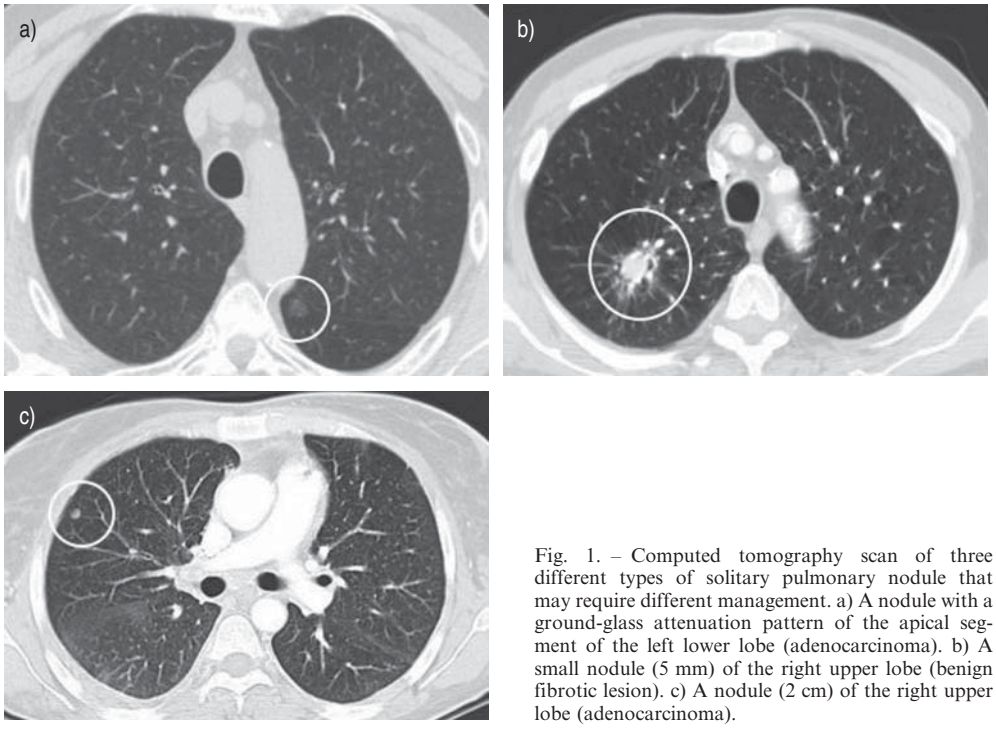

Fig. 1. – Computed tomography scan of three different types of solitary pulmonary nodule that may require different management. a) A nodule with a ground-glass attenuation pattern of the apical segment of the left lower lobe (adenocarcinoma). b) A small nodule (5 mm) of the right upper lobe (benign fibrotic lesion). c) A nodule (2 cm) of the right upper lobe (adenocarcinoma).

Management of small subcentimetric nodules

Since the prevalence of cancer is low and the diagnostic value of bioptic techniques is small in SPNs <1 cm, the management of subcentimetric nodules is mainly based on CT follow-up. Recently, the Fleischner Society proposed an algorithm for nodules <8 mm in patients aged >35 yrs (table 2) [9], which has been shared by the American College of Chest Physicians (ACCP) guidelines for the diagnosis and management of lung cancer [17]. The follow-up period is determined on the basis of SPN size and of patients' risk for malignancy: low-risk patients are considered those with minimal or absent history of smoking or other known risk factors, while high-risk patients are considered as those with a history of smoking or with other known risk factors. For nodules ≤4 mm detected in low-risk patients, no further follow-up is required, while for high-risk patients or in selected cases with suspicious morphology a single follow-up CT should be performed at 12 months without any further check up to verify whether the lesion has changed or not. For nodules >4 mm and ≤6 mm, a single follow-up at 12 months is recommended for low-risk patients, while for high-risk patients a CT scan should be repeated at 6–12 months and, if unchanged, at 18–24 months. Nodules >6 mm and ≤8 mm should be followed in low-risk patients at 6–12 months and then at 18–24 months if unchanged. In high-risk patients a CT scan should be performed at 3–6 months, then at 9–12 months and 24 months, if stable [9].

These recommendations should not be applied for patients with a previous history of cancer, in whom the likelihood for an SPN to be malignant is high and, consequently, a more careful evaluation is required.

Management of nodules >8 mm

Imaging

A solid SPN >8 mm has a high probability of being malignant, and this probability is ~80% for nodules >20 mm [11]. Generally, most patients with SPNs are asymptomatic and the lesion is detected by a chest radiograph or a CT scan performed for other reasons. There are only two imaging criteria that can be used to safely differentiate between malignant and benign nodules. The first is the stability of the nodule over time. The assumption that a solid nodule which has been stable for 2 yrs is a reliable indicator of benignity has been accepted for a long time [18], even if a recently published article [19] raises serious doubts on it and recommends caution in applying this rule, suggesting a longer follow-up period. However, there is no evidence that a follow-up longer than 2 yrs is able to identify more malignant nodules or to improve the patient's outcome [17]. Careful research to obtain previous chest radiographs of the patients

Table 2. – Guidelines for management of nodules ≤8 mm according to the Fleischner Society [9]

Nodule size mm	Low-risk patients	High-risk patients[#]
≤4	No follow-up	CT scan at 12 months. If stable, no further follow-up
>4–≤6	CT scan at 12 months. If stable, no further follow-up	CT scan at 6–12 months, then at 18–24 months if stable
>6–≤8	CT scan at 6–12 months, then at 18–24 months if stable	CT scan at 3–6 months, then at 9–12 months and at 24 months if stable

CT: computed tomography. [#]: or suspicious morphology on CT scan.

should, in any case, be the first step in the management of an SPN. The second imaging criterion that can be used to define a nodule as benign is the presence of calcification in a benign pattern (diffuse, central, lamellar or popcorn) or of fat (diagnostic for hamartoma). On the contrary, eccentric and amorphous calcifications can also be present in malignant nodules [17, 20]. Other imaging criteria, such as margin of the nodules and cavitation, can not be assumed as absolutely predictive for malignancy. Even if a nodule with spiculated margins has a high probability of being malignant (~90%) [21], spiculations can also be observed in benign processes such as lipoid pneumonia, organising pneumonia, tuberculoma and fibrosis [20]. Smooth margins do not indicate a benign nodule with certainty, as ~21% of malignant lesions may have smooth borders [22]. The presence of cavitation can occur in malignant SPNs as a result of necrosis and in benign lesions due to granulomas, abscess and pulmonary infarcts. An analysis of the wall thickness may help, since benign SPNs with cavitation generally have thin walls (<4 mm), while cavitate SPNs with a wall thickness >16 mm have an 84.2% probability of being malignant [23, 24]. However, there is a significant overlap of this pattern (fig. 2) [18] and the characteristics of cavitation cannot be used to define the nature of an SPN. The measurement of the attenuation value of the nodule using CT densitometry has also been used, in addition to the nodule morphology, in order to evaluate the nature of SPNs. In a study in a large series of patients, using a density of 264 Hounsfield units as a cut-off point and considering all the nodules with greater density to be benign, only one nodule defined as benign was found to be malignant [25]. However, this technique is subordinate to the local expertise and has not been widely used [26].

Positron emission tomography

In the last few years, the use of positron emission tomography (PET) to evaluate an SPN has become widely diffused. This technique is based on the use of a radionuclide glucose analogue (fluoro-2-deoxy-D-glucose) which, because of the increased glucose metabolism of malignant lesions, is taken up and accumulates in neoplastic cells. The diagnostic value of PET to distinguish between benign and malignant SPNs was assessed in recent meta-analyses [8, 17]. The sensitivity for malignancy ranged 80–100% with a pooled value of 87%. The specificity value was lower, ranging 40–100% with a mean of

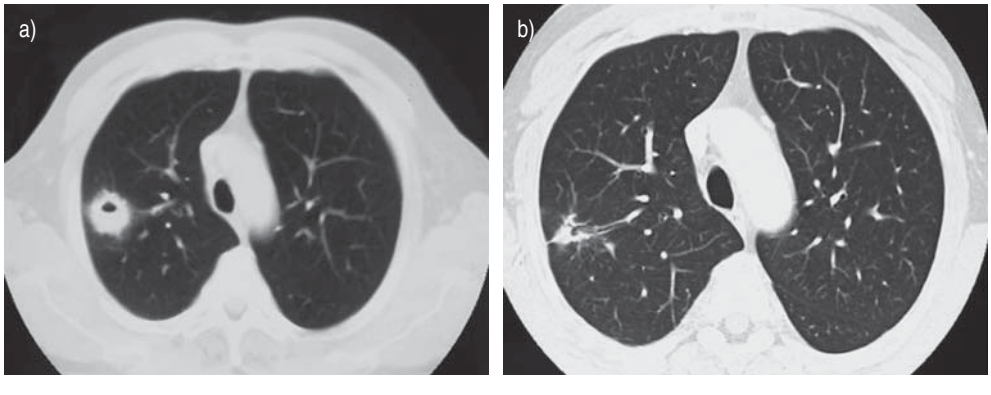

Fig. 2. – a) Computed tomography scan of a nodule (2.3 cm) with spiculated margins and eccentric cavitation with thick walls of the right upper lobe. Transbronchial needle aspiration showed purulent material with identification of *Staphylococcus aureus* (abscess). b) A computed tomography scan showing regression of the lesion after 15 days of antibiotic therapy.

83% [8]. PET is considered less sensitive for SPNs <1 cm [17], even though one study reports a 93% sensitivity for malignancy with a negative predictive value of 94% in 36 SPNs <1 cm [27]. In the same study, the specificity of PET for small nodules was 77% with a positive predictive value of 72%. The PET false-negative results are generally related to cases of bronchioloalveolar carcinoma, carcinoids and mucinous adenocarcinomas [28]. False-positive cases are usually seen in infections or granulomatous inflammatory conditions such as tuberculosis, mycoses, rheumatoid nodules and sarcoidosis [17]. Another PET advantage is the possibility to detect occult distant metastases in cases of malignant SPNs. In a study on 156 patients with SPN, occult metastases were present in 10 (6%) cases and PET was able to identify eight such cases [29].

The role of PET in the management of SPN is still under debate. The good accuracy of PET may help to decide whether or not to send the patients for surgery in case of indeterminate SPNs on CT evaluation. In the recent ACCP guidelines on the diagnosis and management of lung cancer, PET is strongly recommended (grade IB) in patients with an undetermined SPN >1 cm and a low-to-moderate clinical pre-test probability of malignancy, while it is not recommended for patients with a clinical high probability of cancer, who should be directly proposed for surgical resection [17]. It should be observed that PET may also be useful in patients with a high probability of cancer for staging purposes before surgery [29]. However, patients with an SPN referred for surgery on the basis of PET scan positivity should be informed that there is ~20% probability of the lesion not being malignant and that the risk of unnecessary surgery is possible.

Biopsy techniques

The ACCP guidelines on diagnosis and management of lung cancer suggest to prefer an immediate surgical resection in patients who are good candidates for surgery, affected by SPN with a moderate to high clinical probability of malignancy or when the nodule is hypermetabolic by PET [17]. In the clinical practice, most of the patients referred for SPN are poor candidates for surgery or can not be operated on at all due to age, comorbidities and respiratory failure. In a revision of our experience on 1,432 patients with an SPN who were referred to the Pulmonary Diseases Unit of Ancona Hospital (Ancona, Italy), only 382 (27%) were good candidates for surgery, 19% were a contraindication for surgery (age and cardiorespiratory impairment) and in 32% surgery was considered as high risk. Furthermore, 4.3% of patients refused surgery without a definitive diagnosis [30]. In this context, in most SPN cases, a bioptic approach with subsequent cytohistological definition of the lesion is necessary.

An SPN may be approached, for bioptic purposes, both transbronchially and percutaneously. Percutaneous fine needle aspiration is the bioptic technique that provides the best sensitivity in the diagnosis of SPNs and it will be described in detail in another chapter of this *European Respiratory Monograph* (*ERM*). Herein, the bronchoscopic techniques used to approach an SPN will be described and the possibility of integrating the transbronchial approach with the transthoracic approach will also be evaluated.

The role of bronchoscopy in SPN

Bronchoscopy and SPN

The first question that should be discussed is whether bronchoscopy is indicated in patients with SPN. The ACCP guidelines for the diagnosis and management of lung

cancer, both in the first and second edition, report that bronchoscopy is not recommended in patients with SPN because it has rarely been shown to change the stage and, as such, obviates the need for surgery [17, 31]. However, it must be observed that this recommendation is based on the results of an old retrospective study in 91 patients [32] with a pulmonary lesion $\leq$6 cm, in which a pre-operative bronchoscopy did not obviate the need for surgery or alter the stage of cancer. The ACCP guidelines [17] did not mention a recent study in 64 patients with peripheral bronchogenic carcinoma, in which bronchoscopy detected unsuspected endobronchial lesions on CT scans in 17% of the cases and three of these patients had a nodule with a diameter $<$3 cm [33]. The authors of this paper concluded that more studies are necessary before abandoning pre-operative staging bronchoscopy [33]. Furthermore, other studies have disagreed with the concept of not performing bronchoscopy in patients with SPNs because of the possibility of: 1) detecting subclinical disorders in vocal cords; 2) detecting unexpected variations in bronchial anatomy, the knowledge of which could be useful for the surgical strategy; 3) identifying simultaneous central endobronchial lesions; and 4) obtaining information for localising the segment where the SPN is located by using the fluoroscopic guided approach [34]. In effect, in a study of 1,024 patients with peripheral pulmonary nodules and masses who were referred to our institution (Pulmonary Diseases Unit, Azienda Ospedali Riuniti, Ancona) [35], we found endoscopically visible lesions that remained unsuspected by imaging techniques in 12.6% of cases. This value is probably overestimated because patients with lesions $>$3 cm were also included in this study. In any case, there is still no evidence that pre-operative bronchoscopy is useless in patients with SPN and in many institutions the endoscopic evaluation is routinely performed before surgery. It must also be emphasised that bronchoscopy has a great role in staging when hilar mediastinal lymph node enlargement is evident on a CT scan. Transbronchial needle aspiration (TBNA) of lymph nodes may provide an opportunity to stage lung cancer during the first diagnostic bronchoscopy and, even if the definition of SPN excludes the presence of lymph nodes enlargement [1], it is not rare to see cases with a small nodular lesion and metastatic lymph node involvement.

Bronchoscopic bioptic techniques

It is well known that sampling instruments can be pushed through the airways in the lung periphery to subpleural regions for the diagnosis of peripheral pulmonary lesions. This diagnostic technique can be performed under the guidance of systems, such as fluoroscopy, that are able to localise the position of the sampling instruments. While the guidance systems are not necessary in cases of diffuse lung diseases, in patients with localised lesions such as SPN the use of a guidance technique is mandatory [36]. The transbronchial approach to SPN was first described by TSUBOI *et al.* [37], prior to the advent of the bronchofibrescope, employing a curette introduced through a Metras catheter. With the advent of the flexible bronchoscope, several sampling instruments, such as washing, curette, biopsy forceps, brushing and transbronchial needles, have been used alone or in association through the working channel of the fiberscope in this diagnostic setting [35, 38–50]. The guidance system traditionally employed in the transbronchial approach to SPN is fluoroscopy. A rotating C-arm fluoroscope should be available to allow the operator to assess the correct position of the sampling instrument both in the antero-posterior and lateral view. If the fluoroscope is not available in the bronchoscopic room, it is possible to organise this type of diagnostic procedure in a radiological suite equipped with a rotating fluoroscope, as we have done for a long time [35].

Table 3 shows the diagnostic sensitivity of the transbronchial approach under fluoroscopic guidance in peripheral pulmonary lesions. The studies performed in series with patients affected by lesions >3 cm are considered. The different sensitivity of each study in relationship to the lesion size is reported, when available.

On the basis of the different results reported in table 3, several considerations can be made. First, it should be noted that the sensitivity of the transbronchial approach to peripheral pulmonary lesions varies greatly in the literature. The reasons for the differing results may be linked to several factors, such as the size of the lesion, the sampling instrument used, the relationship between the nodule and the airways, and the operator's experience and ability.

In all these studies, the diagnostic yield was highly related to the size of the lesion, ranging 5–64% for nodules <2 cm to 30–75% for lesions >2 cm. The diagnostic sensitivity may increase to over 80% for lesions with a diameter >4 cm. Only one study [48] reports a very high value of sensitivity for nodules <2 cm (83.5%); however, in this study a very complex approach was employed using a selective bronchography to localise the nodule before transbronchial curettage.

The sampling instrument utilised may also influence the sensitivity of the technique. In most of the studies reported in table 3, the use of washing alone provides very poor results (9–40%), which were generally lower than those obtained from other sampling instruments. In addition, bronchoalveolar lavage (BAL) has been used for diagnosing peripheral lung tumours, by employing a greater amount of fluid (150 mL) introduced through the segmental bronchus leading to the lesion. In a study on 55 patients with peripheral tumour, BAL showed the same low diagnostic yield as that in washing in cases of peripheral nodules (20% for washing and 28.5% for BAL), while sensitivity was higher (40%) in cases with an infiltrative pattern [58]. Washing or BAL have the advantage that they can be performed even if fluoroscopy is not available, but the low diagnostic yield in cases of localised peripheral lesions does not support their routine use as the only means of sampling. In most studies in which TBNA was utilised as a sampling instrument, this tool provided better sensitivity in comparison to that obtained with forceps and brushing [35, 47, 49–52, 55, 56]. The better results obtained by TBNA are probably due to the ability of the needle to penetrate the lesion even if it does not involve the mucosal surface or if it is located adjacent to a bronchiolar spur that can be perforated by the needle (fig. 3). In only one study did TBNA not show a better sensitivity in comparison with forceps [53]; however, in this study, conducted in a small series of 49 patients, the approach with the needle was attempted after having utilised brushing and performing four biopsies. In our experience [35, 51], the performance of brushing or biopsies may induce perilesional bleeding that could make the fluoroscopic visualisation of the nodule more difficult, increase the amount of blood sampled with the following needle aspiration and thus reduce the diagnostic yield of TBNA. Analysing the results of table 3, it should also be remarked that all the studies show higher diagnostic yield if the results obtained with the association of more than one sampling instrument are considered. Since it is not recommended to use all sampling instruments in all patients, we think that the most appropriate association is the employment of TBNA, which provides the best sensitivity for malignant nodules, with forceps biopsy, which is able to provide a better yield on benign nodules (45.8% for biopsy *versus* 17.4% for TBNA) (fig. 4) [35].

Another factor that may determine the success of a transbronchial approach to SPNs is the relationship of the lesion with the bronchial tree. In this regard, NAIDICH *et al.* [59] suggested that a criterion for using a transbronchial approach to SPNs could be a positive ''bronchus sign'' (*i.e.* a bronchus leading to or contained within an SPN as seen by a thin-section CT scan). This suggestion was based on a study of 65 patients, 51 of whom had peripheral lesion and whose transbronchial biopsy showed 55% sensitivity

Table 3. – Diagnostic yield of transbronchial approach under fluoroscopic guidance in peripheral pulmonary lesions

First author [Ref.]	Patients n	Lesion size	Sampling instrument	Diagnostic yield %
SOLOMON [39]	36	NA	Washing	22
		NA	Brushing	80
ELLIS [40]	21	>4 cm	Brushing	57
			Biopsy	81
	24	≤4 cm	Brushing	29
			Biopsy	58
KOVNAT [41]	23	NA	Brushing	56
CLARK [43]	14	All (2.2–8 cm)	Biopsy	35
CORTESE [44]	48	All	Brushing	40
			Biopsy	46
			Brushing + biopsy	60
	4	<2 cm	Brushing	0
			Biopsy	0
	17	2–3.5 cm	Brushing	25
			Biopsy	47
	21	4–6 cm	Brushing	67
			Biopsy	57
	6	>6 cm	Brushing	17
			Biopsy	33
RADKE [45]	97	All	Brushing + biopsy	63
		<2 cm	Brushing + biopsy	28
		≥2 cm	Brushing + biopsy	64
WALLACE [46]	133	All	Washing	9
			Brushing	12
			Biopsy	20
			Washing + brushing + biopsy	19
		<2 cm	Washing	2
			Brushing	2
			Biopsy	5
			Washing + brushing + biopsy	5
		2–4 cm	Washing	15
			Brushing	19
			Biopsy	28
			Washing + brushing + biopsy	30
SHURE [47]	42	All (0.8–9 cm)	Biopsy	36
			Needle (TBNA)	52
			Biopsy + brushing + washing	48
			TBNA + brushing + washing	67
			Biopsy + TBNA + brushing + washing	69
MORI [48]	85	<2 cm	Washing	42
			Curette	83
WANG [49]	20	15 patients: <3 cm	Brushing	20
		5 patients: >3 cm	Biopsy	15
			TBNA	55
			Brushing + biopsy + TBNA	55
WANG [50]	24	NA	Brushing	32
			Biopsy	18
			TBNA	36
			Needle brush	50
			Brushing + biopsy + TBNA + needle brush	55
GASPARINI [35]	570	All (0.8–8 cm)	Biopsy	54
			TBNA	69
			Biopsy + TBNA	75
GASPARINI [51]	1008	All (0.8–9 cm)	Biopsy	50
			TBNA	70
			Biopsy + TBNA	76

Table 3. – Continued

First author [Ref.]	Patients n	Lesion size	Sampling instrument	Diagnostic yield %
		≤2 cm	Biopsy	42
			TBNA	64
			Biopsy + TBNA	66
KATIS [52]	37	All (1.8–7 cm)	Washing	24
			Brushing	27
			Biopsy	38
			TBNA	62
			Washing + brushing + biopsy + TBNA	70
CHECHANI [53]	49	All	Washing	35
			Brushing	52
			Biopsy	57
			TBNA	51
			Washing + brushing + biopsy + TBNA	73
		≤2 cm	Washing + brushing + biopsy + TBNA	54
		2.1–3 cm	Washing + brushing + biopsy + TBNA	60
		3.1–4 cm	Washing + brushing + biopsy + TBNA	73
		4.1–5 cm	Washing + brushing + biopsy + TBNA	82
		>5.1 cm	Washing + brushing + biopsy + TBNA	87
LAI [54]	170	All	Brushing + biopsy	62
		<2 cm	Brushing + biopsy	35
		≥2 cm	Brushing + biopsy	64
BILACEROGLU [55]	92	2–5 cm	Washing	4
			Brushing	26
			Biopsy	49
			TBNA	57
			Washing + brushing + biopsy + TBNA	68
REICHENBERGER [56]	172	All	Washing	22
			Brushing	30
			Biopsy	17
			TBNA	35
			Washing + brushing + biopsy + TBNA	51
		<3 cm	TBNA	28
		>3 cm	TBNA	67
BAAKLINI [57]	177	All	Washing	40
			Brushing	41
			Biopsy	52
			Washing + brushing + biopsy	60
		≤2 cm	Washing + brushing + biopsy	23
		2.1–2.5 cm	Washing + brushing + biopsy	40
		2.6–4 cm	Washing + brushing + biopsy	62
		>4 cm	Washing + brushing + biopsy	83

NA: not available. TBNA: transbronchial needle aspiration.

when the bronchus sign was present and 32% when the bronchus sign was negative. These results were confirmed in a subsequent study [60]. It should be interesting to evaluate whether the bronchus sign also has some value in predicting the success of transbronchial approach using TBNA. BILACEROGLU *et al.* [55] performed a study using washing, brushing, biopsy and TBNA in 92 patients and distinguished the bronchus sign

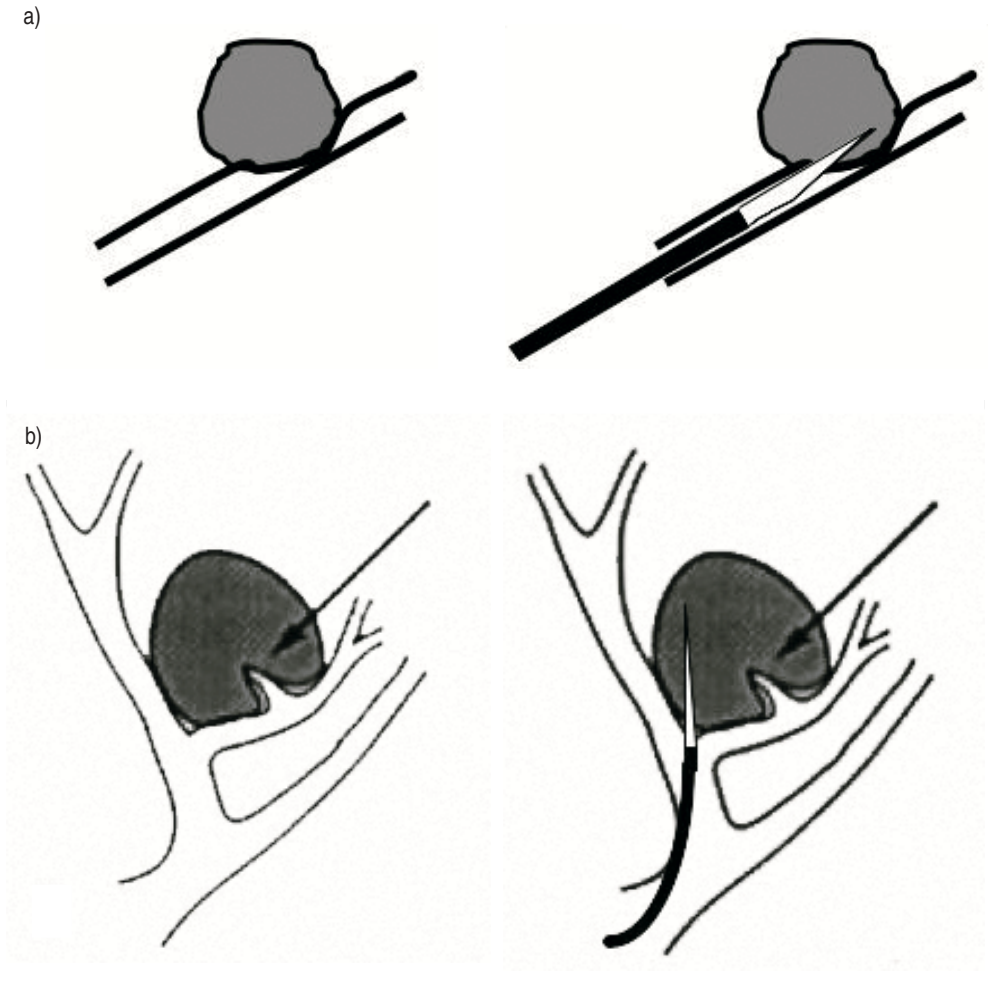

Fig. 3. – Possible relationships between the nodule and the airways, in which the needle is the only sampling instrument able to penetrate the lesion. a) The nodule is compressing the bronchus but it does not involve the mucosal surface. b) The nodule is located adjacent to a bronchiolar spur.

based on four different patterns: 1) bronchus cut-off; 2) bronchus penetrating the tumour or bronchus contained in the tumour; 3) bronchus compressed by peri/submucosal tumour spread; and 4) bronchus narrowed by peri/submucosal tumour spread. The best sensitivity of TBNA (86%) was obtained with the "bronchus compressed pattern" (intact mucosa), which is not included in the bronchus sign definition originally described by NAIDICH *et al.* [59]. Further studies are necessary to verify whether the predictive value of the bronchus sign can also be extended to the use of TBNA.

Another factor that could affect the sensitivity of transbronchial approach to SPNs is the operator's experience. For TBNA of the hilar and mediastinal lymph nodes there are several studies which show that the skill and experience of the bronchoscopist greatly influence the results [61–63]; however, no studies on the role of the operator's experience have been conducted for the approach to peripheral lesions and evidence is lacking.

The transbronchial approach to SPNs is a safe technique and complications are rare. In a study of 1,027 patients [35], 570 of whom underwent transbronchial biopsy using

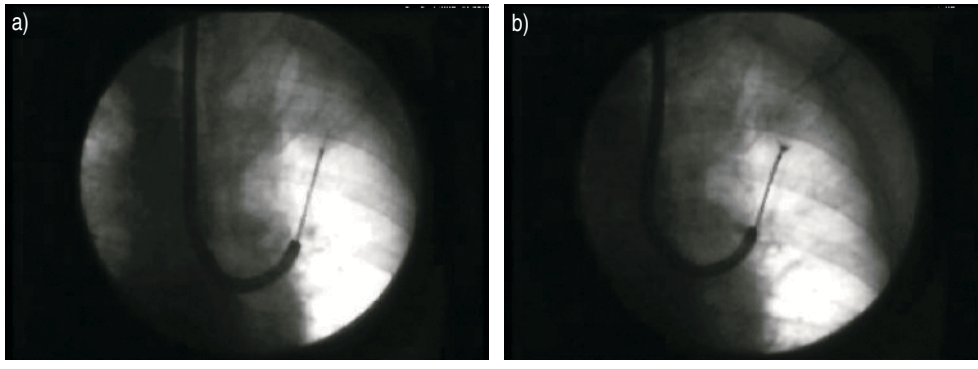

Fig. 4. – a) Transbronchial needle aspiration and b) transbronchial biopsy of a solitary pulmonary nodule of the left upper lobe.

the needle and/or biopsy forceps, the most frequent complication was haemoptysis (3.7%), which was moderate (<100 mL) in 15 (2.7%) patients and severe (>100 mL) in six (1%) patients. Pneumothorax was observed in two (0.2%) patients with the need for chest drainage in one (0.1%) patient. Other complications were perilesional intrapulmonary haemorrhage (n=3, 0.5%) and severe bronchospasm (n=1, 0.1%).

New technology for the transbronchial approach to SPN

In recent years, new technology has been proposed for a bronchoscopic approach to SPNs. These new developments mainly include ultra-thin bronchoscopes, which are able to penetrate more distally into the bronchial tree, and new guidance systems such as virtual bronchoscopy, endobronchial ultrasound (EBUS) and electromagnetic navigation.

Ultra-thin bronchoscopes have an external diameter ranging 2–3.6 mm and are provided with a working channel (1.2–1.7 mm) that allows small biopsy forceps to be introduced [64–70]. These bronchoscopes have been utilised under fluoroscopic guidance [64, 67, 69] or under virtual bronchoscopy, generated by helical CT images as a means to identify the bronchial route leading to the lesion, and under CT fluoroscopy [65, 66, 68, 69].

In a study with an ultra-thin bronchoscope in a large series of 102 patients with peripheral pulmonary lesions ranging in size from 11 to 76 mm (mean 34.3 mm), OKI *et al.* [70] obtained diagnostic material in 74% of the cases with malignancy and in 60% of the patients with benign disease. Better sensitivity on small SPNs has been reported by SHINAGAWA *et al.* [69] who obtained 66% of diagnostic results in 83 patients with small SPNs <2 cm. However, SHINAGAWA *et al.* [69] utilised a complex guidance system, including the generation of a virtual bronchoscopy, to guide the bronchoscope into the target bronchus and then used the real-time multislice CT scan to evaluate the position of the forceps biopsy. It is not possible to evaluate whether the results of this study are a result of the ultra-thin bronchoscope or of the guidance system that was employed.

The description of new guidance systems for approaching peripheral pulmonary lesions, such as EBUS and electromagnetic navigation, is not the aim of this section and these new technologies will be analysed in depth in other chapters of this *ERM*. However, table 4 reports the studies and results obtained using these technological innovations, including ultra-thin bronchoscopes and new guidance systems. Looking at the results of these studies, in comparison with those reported with the use of traditional fluoroscopy (table 3), it seems that the diagnostic yield is higher on average, especially

Table 4. – Diagnostic yield of transbronchial approach in peripheral pulmonary lesions using different new technologies

First author [Ref.]	Patients n	Technique	Lesion size	Diagnostic yield %
ROONEY [64]	17	Ultra-thin bronchoscope (3.6 mm)	All (1.5–7 cm)	29
		Small brush	<3 cm	10
		Fluoroscopic guidance		
SHINAGAWA [66]	25	Ultra-thin bronchoscope (2.8 mm)	13.2 mm (average)	65
		Biopsy forceps		
		Virtual bronchoscopy and CT guidance		
YAMAMOTO [67]	35	Ultra-thin bronchoscope (2.8 mm)	10–40 mm	60
		Biopsy forceps		
		Fluoroscopic guidance		
ASANO [68]	37	Ultra-thin bronchoscope (2.8 mm)	≤3 cm	81
		Biopsy forceps		
		Virtual bronchoscopy + fluoroscopy		
SHINAGAWA [69]	83	Ultra-thin bronchoscope (2.8 mm)	<2 cm	66
		Biopsy forceps		
		Virtual bronchoscopy and CT guidance		
OKI [70]	102	Ultra-thin bronchoscope (3.5 mm)	All (11–76 mm)	69
		Biopsy forceps	≥20 mm	73
		Fluoroscopic guidance	<20 mm	57
HERTH [71]	50	EBUS guidance	All (20–60 mm)	80
		Biopsy forceps	>3 cm	79
			<3 cm	80
KURIMOTO [72]	150	EBUS guidance	All	77
		Biopsy forceps/brushing	>3 cm	92
		Fluoroscopy to verify the EBUS sheath position	>2–≤3 cm	77
			>1.5–≤2 cm	69
			>1–≤1.5 cm	76
			≤1 cm	76
KIKUCHI [73]	24	EBUS guidance + fluoroscopy	All (0.8–2.7 cm)	58
		Biopsy forceps + brushing	<2 cm	53
PAONE [74]	97	EBUS guidance	>3 cm	83
		Biopsy forceps	<3 cm	75
			<2 cm	71
ASAHINA [75]	29	EBUS guidance + virtual bronchoscopy + fluoroscopy	All (1–3 cm)	63
		Biopsy forceps + brushing	2–3 cm	92
			<2 cm	44
HERTH [76]	54	EBUS guidance	All (1.4–3.3 cm)	70
		Biopsy forceps		
BECKER [77]	29	EN bronchoscopy	1.2–10.6 cm	69
SCHWARZ [78]	13	EN bronchoscopy	1.5–5 cm	69
GILDEA [79]	56	EN bronchoscopy	All (0.8–7.8 cm)	74
			>3 cm	82
			<3 cm	72
EBERHARDT [80]	89	EN bronchoscopy	All (1–5.8 cm)	67
			>3 cm	75
			≤3 cm	67
			≤2 cm	63
MAKRIS [81]	40	EN bronchoscopy	All (0.8–4.9 cm)	62
			>3 cm	77
			>2–≤3 cm	71
			>1–≤2 cm	44
EBERHARDT [82]	120	Randomised trial using:	All (1.3–5.8 cm)	
		EBUS guidance only	EBUS	69
		EN only	EN	59
		EBUS + EN	EBUS+EN	88

CT: computed tomography; EBUS: endobronchial ultrasound; EN: electromagnetic navigation.

for small lesions. The main advantage of new guidance techniques could be related to the possibility of approaching even small lesions that are not visible by fluoroscopy. However, even the new techniques can not overcome the major limitation of the transbronchial approach to SPN, which is the unavailability, in some cases, of a bronchus leading into the lesion. Regardless of which guidance system is used, if the nodule is located outside the bronchial tree it can not be reached transbronchially. The only comparative studies between new technologies and traditional transbronchial approach are those by HERTH *et al.* [71] and by PAONE *et al.* [74]. In the first study, HERTH *et al.* [71] took a transbronchial approach to peripheral lesions in 50 consecutive patients utilising both fluoroscopic and EBUS guidance at random. The diagnostic yield was not different (80% for EBUS and 76% for fluoroscopy), even if a better nonsignificant trend for EBUS than fluoroscopy was observed for lesions <3 cm. In the study by PAONE *et al.* [74], 293 patients with peripheral lesions were randomised to receive EBUS-guided biopsy or transbronchial biopsy without EBUS. Ultrasound guidance provided a significantly better yield for lesions <3 cm, but fluoroscopic guidance was not utilised in the non-EBUS group and the biopsies were performed through the segmental bronchus previously identified by CT scan. Since there are several factors that can influence the diagnostic yield of the transbronchial approach to SPNs and one of these factors is the skill and the experience of the operator, it would be advisable that randomised controlled studies be performed by the same team comparing fluoroscopy and the new systems before drawing definitive conclusions on the real improvement that may be introduced by expensive technology in this clinical field. ACCP guidelines on the diagnosis and management of lung cancer [17] recommend that bronchoscopy should be performed in cases of SPNs that measure at least 8–10 mm in an institute with expertise in newer guidance techniques. On the basis of the previously mentioned considerations, there is not yet enough evidence to support this recommendation and further studies are necessary.

Comparison and integration of transbronchial and percutaneous approach to SPN

SPN can also be approached for bioptic purposes by percutaneous needle aspiration (PCNA), using fluoroscopic or, more frequently, CT guidance. However, another chapter of this *ERM* is entirely dedicated to transthoracic fine-needle aspiration. In this section, I would like to emphasise the relationship that exists between the two types of approaches to SPN and the possibility of integrating both techniques in the management of SPNs. The diagnostic yield of PCNA for SPN is higher than that of the transbronchial approach, ranging 88–92%, and has a lower variability [35, 83, 84]. Conversely, PCNA does not provide any information about the staging of the disease and the risk of complication is higher, especially for pneumothorax which is reported in ~25% of the procedures [84]. Even if only 5% of pneumothoraces require chest drainage, this complication may determine some risk for patients with respiratory failure and could lead to an increase in hospitalisation costs and a delay in the treatment. Based on these considerations, we proposed an integrated team approach using TBNA and biopsy under fluoroscopic guidance as a first step in the cases of peripheral pulmonary lesions [35]. The presence of an on-site cytopathologist is a fundamental strong point of this protocol, since we have the chance to immediately know whether the sampled material by TBNA is diagnostic or not. If the transbronchial sample is diagnostic, the procedure is considered to be complete; otherwise, TBNA is repeated with the possibility of trying to find a better position for the needle. If the second TBNA is still not diagnostic, one

should proceed to the second step of the procedure, which is to carry out a percutaneous approach. With this integrated approach, we obtained a total sensitivity of 95.2% in 1,027 patients affected by peripheral lesions ranging in size between 0.8–8 cm [35]. In another study, sensitivity in relation to the size of the lesion was also evaluated, showing that the integrated approach was able to diagnose 86.7% of nodules ≤ 2 cm [51]. This type of integrated biopsy approach was later proposed by WELKER *et al.* [85] who performed a prospective study of 118 patients with a peripheral lesion <4 cm. Patients first underwent a transbronchial approach of the nodule and, in the case of a negative result, a PCNA under fluoroscopy or CT scan guidance was performed. If no diagnosis was obtained, patients were subjected to a follow-up CT scan and repeat biopsy, which were both performed up to four times. The diagnostic accuracy of this protocol was 100% and none of the patients with a delayed diagnosis, obtained at the second and fourth biopsy sessions, experienced a change in their disease stage from the original CT findings [85].

The use of the transbronchial approach for SPNs as an initial procedure may reduce the use of PCNA in the majority of cases, allowing the reduction of related complications [86]. PCNA aspiration should be performed if bronchoscopic approach fails, and the transbronchial and percutaneous approaches should not be considered as alternatives but as complementary techniques in the management of SPNs.

Conclusions

In conclusion, the transbronchial approach to SPN is a safe technique that is able to provide a cytohistological definition of the nodule in a percentage of cases that could approach 80%. Different forms of sampling and guidance techniques can be used in this diagnostic procedure. While the use of washing or BAL alone is not recommended because of very poor results, there is enough evidence to support the routine employment of TBNA which provides a better diagnostic yield. There is also evidence that the use of more than one sampling instrument may improve the results. While fluoroscopy is still the guidance system that is most commonly used, new technologies that are able to localise the nodule, such as EBUS and electromagnetic navigation, have been recently proposed. Although it seems that these new systems may increase the diagnostic yield, especially for smaller nodules <2 cm, no prospective comparative studies have been performed to fully support this observation. However, a guidance system should be available in any health centre performing bronchoscopy for the diagnosis of SPN. Due to fewer complications and to the possible staging information that bronchoscopy can provide, the transbronchial approach should be taken into consideration before the PCNA in the SPN diagnostic flow-chart, especially for patients with severe impairment of the respiratory function, for whom a risk of pneumothorax may be increased, and for candidates for surgery, for whom accurate staging is required. Transbronchial and percutaneous approaches to SPNs must be considered as complementary techniques and the set-up of teams who are able to utilise both approaches in the same context, with the cytopathologist present in the diagnostic room for the immediate cytological assessment, should be encouraged to optimise the bioptic management of SPNs.

Summary

Diagnostic management of solitary pulmonary nodule (SPN) is a common problem for which universally accepted guidelines have not yet been defined. The definition of SPN should be reconsidered since small nodules (<0.8–1 cm in diameter) and non-solid nodules with a ground-glass appearance may need to be managed differently. For nodules >0.8 cm in diameter, in the case of high probability for malignancy and in good surgical candidates, the possibility of immediate surgery could be considered. Nevertheless, in most patients a bioptic assessment is necessary.

An SPN, for bioptic purposes, may be approached both transbronchially and percutaneously. The bronchoscopic approach should always be performed by using a guidance system to verify the sampling site. Fluoroscopy is the traditional guidance system that is widely employed. Published results obtained with fluoroscopic guidance vary greatly (up to 83%) and this variability may be related to several factors, such as the size of the lesion, the sampling instrument used, the number of sampling instruments and the operator's experience.

Among the sampling instruments, the transbronchial needle provides the best sensitivity. There is also evidence that the use of more than one sampling instrument provides better results. Washing and bronchoalveolar lavage have low diagnostic yield and should not be used alone. New technology (endobronchial ultrasound and electromagnetic navigation) have been recently proposed as guidance systems. It seems that these new systems may increase the diagnostic yield, especially for smaller nodules <2 cm in diameter (up to 92%), but no comparative studies to fully support this observation have been performed.

Sensitivity of the transbronchial approach to SPN is lower than that obtained with the percutaneous approach (88–92%), but bronchoscopy has a lower incidence of complications and has the advantage of providing important information for staging (airways and lymph node involvement). The transbronchial approach to SPN should be the first step and percutaneous needle aspiration should be considered when bronchoscopy has failed. The set-up of teams able to utilise both approaches should be encouraged to optimise the bioptic management of SPNs.

Keywords: Bronchoscopy, lung cancer, peripheral pulmonary lesions, solitary pulmonary nodule, transbronchial lung biopsy, transbronchial needle aspiration.

Statement of interest
None declared.

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