The Solitary Pulmonary Nodule

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Key Words

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Abstract

Due to the high etiological diversity and the potential for malignancy, pulmonary nodules represent a clinical challenge, becoming increasingly frequent as the number of CT examinations rises. The topic gains even more importance as clear evidence for the effectiveness of CT screening was provided by the National Lung Screening Trial (NLST). Yet, the results were tempered by the high false-positive rate and the requirement of performing further diagnostic procedures. The management of those detected solitary pulmonary nodules is currently based on the individuals' risk of developing lung cancer, the pulmonary nodule characteristics and the capability of diagnostic and therapeutic approaches.

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Introduction

A solitary pulmonary nodule (SPN) is defined as a round or oval opacity smaller than 3 cm in diameter that is completely surrounded by pulmonary parenchyma (fig. 1) with no other pulmonary abnormalities present. In contrast, pulmonary lesions with a diameter larger than 3 cm are classified as pulmonary masses and differ from SPN due to their higher likelihood of being malignant [1–3]. Owing to the high etiological diversity and the potential for malignancy, SPN represent a clinical challenge,

which becomes increasingly frequent as the number of CT examinations rises. The workup of these nodules is rather expensive and emotionally burdensome, especially when the patient has risk factors for bronchial carcinoma. SPN are noted in up to 0.2% of chest radiographs [4, 5], whereas 27.3% of patients undergoing the National Lung Screening Trial (NLST) had at least one SPN with a diameter >4 mm on their CT examination [6]. Differential diagnosis is extensive, but the majority of the identified nodules are comprised of granulomas, lung cancers and hamartomas [7, 8]. Against the background of potential malignancy and the poor prognosis of advanced lung cancer, rapid identification and resection of malignant SPN is crucial, leading to a 5-year survival rate of 60–80% in stage I [9, 10] non-small-cell lung carcinoma (NSCLC). Nonetheless, even in a population at high-risk for lung cancer, the vast majority of small SPN are benign. In the lung screening study of the National Cancer Institute, the lung cancer diagnosis rates were <5, 21.3 and 34.5% for nodules <10, 11–19 and >20 mm in diameter, respectively [11]. The management of an SPN should aim to identify malignancy as fast as possible in order to provide the option of potentially curative surgical treatment whilst avoiding invasive diagnostic procedures in the case of benign lesions. Numerous articles have been published addressing the optimal strategy of evaluating individuals with lung nodules, including the most recently published ACCP guideline for the diagnosis and management of lung cancer [12]. Those strategies are generally based on the individual's risk of developing lung cancer, the pulmonary nodule characteristics and the capability of the current diagnostic and therapeutic approaches.

Fig. 1. CT scan of a pulmonary nodule measuring 9 mm in diameter.

Lung Cancer Screening

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death worldwide [13, 14]. A significant reduction in mortality from lung cancer has been achieved as a result of smoking reduction and smoking cessation [14–16]. Additional improvements in outcome can be achieved by recent advances in lung cancer treatment, e.g. by targeted therapies in patients with epidermal growth factor receptor mutations [17], surgical approaches and the use of stereotactic radiotherapy [18, 19].

Nonetheless, lung cancer is still associated with an extremely poor prognosis, accompanied by a current 5-year survival rate of 16% [20]. Due to the late development of symptoms, most patients diagnosed with lung cancer already have advanced disease (40% stage IV, 30% stage III) at the time of diagnosis, resulting in the above-mentioned poor prognosis. Although earlier randomized controlled trials for lung cancer screening involving chest radiographs and sputum cytology were not able to show a reduction in lung cancer deaths [21–25], the appearance of low-dose CT (LDCT) with the ability of detecting small lung nodules has led to the initiation of several LDCT lung cancer screening studies [26–33]. The largest among those studies has been the NLST. The study examined 53,454 persons with high risk for lung cancer and showed promising results with a relative reduction in mortality from lung cancer of 20% compared to screening by chest radi-

ography [6]. Three hundred and twenty participants were needed to screen to prevent 1 lung cancer death. Three of 8 ongoing European trials comparing LDCT screening with no screening did not show a mortality benefit of LDCT screening; even so, none was sufficiently powered to identify a significant mortality benefit [31, 34, 35].

Based on the strong evidence of the NLST, all current US guidelines recommend lung cancer screening using LDCT. Those recommendations apply mostly to individuals meeting the NLST inclusion criteria with small alterations in 2 cases [36, 37]. Yet, uncertainty about potential harm and the generalizability of the NLST results exist. Concerns have been raised about potential harm from lung cancer screening, mainly in terms of potential complications from unnecessary procedures done to investigate what are found to be benign, inconsequential nodules.

In the NLST, 4 in 1,000 fewer died from lung cancer. However, in the LDCT arm 25 in 1,000 had a false alarm leading to an invasive procedure, such as bronchoscopy, biopsy or surgery, and 3 in 1,000 had a major complication from such invasive procedures. Predetermined algorithms for nodule assessment can minimize the number of further imaging studies or invasive biopsies to what is truly necessary. In the NELSON and UK Lung Screen (UKLS) trials, prespecified algorithms are used to manage indeterminate nodules, rather than considering all nodules of a specific size as positive, as done in the NLST [38]. Results from these trials will contribute important additional information that could help to better design future screening programs.

The positive aspect of LDCT screening in the post-NLST area is obvious and seems to have been even underestimated in terms of the potential extent of mortality reduction. The NLST was designed to test the null hypothesis of no difference in effectiveness between the two types of screening (LDCT vs. chest radiography). Thus, the extent of mortality reduction was potentially diluted by the cessation of screening linked with a prolonged follow-up period [39].

Further improvement of future LDCT screening outcomes might be achieved through modification of the inclusion criteria by means of applying risk stratification models. Even though smoking history and age account for the broad majority of lung cancer risk, other risk factors such as socioeconomic status, family history, occupational exposure, pulmonary fibrosis and COPD also contribute to a higher lung cancer risk profile [40]. Compared to the NLST inclusion criteria, which are solely based on age and smoking history, a recently updated

lung cancer risk prediction model (PLCO_{M2012}) showed an improvement in sensitivity (83.0 vs. 71.1%, $p < 0.001$) and positive predictive value (PPV; 4.0 vs. 3.4%, $p = 0.01$), without loss of specificity. According to the analysis, 41.3% fewer lung cancers would have been missed by application of this model, leading to the conclusion that PLCO_{M2012} is more efficient in identifying persons suitable for lung cancer screening than the NLST criteria [41]. The implementation of an accurate model including additional risk factors in order to select appropriate persons for lung cancer screening is likely to be cost-effective and will reduce harm to people with the lowest risk of lung cancer [38, 41].

Yet, some unresolved issues and harms are accompanied by LDCT screening. The NLST as well as the ongoing European LDCT screening trials were carried out in particularly experienced centers for lung cancer, leading to results with limited generalizability. Even though current guidelines recommend that lung cancer screening should only take place in qualified centers, the question arises as to what extent the present data are representative of future upcoming screening on a broader scale. Especially in terms of adverse events, the evidence for considerably better outcomes of lung cancer surgery in dedicated centers such as those conducting LDCT trials relativizes the statement concerning the low risk of major complications following a positive screening test in some cases [42]. In the NLST, 1.2% of patients who finally had benign lesions had undergone an invasive procedure and 0.7% had had a thoracoscopy, mediastinoscopy or thoracotomy. In the NELSON trial, these numbers were 1.2 and 0.6%, respectively. Mortality from such resections was 1% in the NLST, which even compares favorably to that reported from high-volume thoracic centers [43]. In low-volume hospitals, mortality of major pulmonary resections ranges from 3 to 5% [43, 44]. Consequently, it should be encouraged that uniform standards and high-quality controls are implemented prior to screening on a broader scale. In their preliminary decision to cover lung cancer screening, Medicare addressed this point by defining strict eligibility criteria for screening [45].

Still, it is questionable whether the NLST results can be generalized with regard to different health care systems all over Europe. When Heuvers et al. [46] applied the NLST criteria to an ongoing prospective cohort study in the Netherlands, only around 30% of lung cancer cases that occurred in their cohort met the NLST inclusion criteria. In other words, 70% of cases would not have been included in this screening trial if based on the NLST inclusion criteria. Thus, a relative reduction of 20% in the

NLST would correlate with a 6% reduction of mortality in the Rotterdam study population.

Further aspects of LDCT screening that require careful examination before implementation include radiation exposure, overdiagnosis, potential harm through incidental findings and the possibly negative impact of screening on smoking behavior or quality of life.

The magnitude of potential harm is not entirely conceivable at the moment. Although there are indications that smoking behavior and quality of life are not negatively influenced by LDCT screening [47–49], clinical experience frequently reports that a potentially malignant diagnosis can have a significant impact on the individual's mind [50].

Twenty-four percent of people undergoing NLST screening had 'positive' and therefore potentially malignant results in their baseline CT examination. A total of 96.4% proved to be false-positive results at a later point of time, highlighting the extent of this issue. While the rate of invasive interventions and severe adverse events in this group was judged to be low [6], at least several follow-up CT scans, accompanied by additional radiation exposure, were necessary to rule out malignancy. Utilization of pre-determined algorithms for nodule assessment and application of volumetric CT, as used in the NELSON and UKLS trials may eventually reduce the number of false positives undergoing invasive diagnostic procedures and also assist with the management decisions concerning indeterminate nodules [38]. 3-D volumetric measurements are probably superior to 2-D diameter measurements in terms of accuracy and reproducibility because the whole nodule is analyzed, leading to an improvement of the PPV [16, 51]. The issue at hand is the low availability of this modern imaging approach to pulmonary nodules.

Overtreatment is of specific concern in lung cancer screening. The data from a recent analysis of the NLST dataset suggest that, at most, 18% of persons in the LDCT arm with screen-detected lung cancer and 22% of those in the LDCT arm with screen-detected NSCLC may be cases of overdiagnosis. In other words, if these individuals had not entered the NLST, they would not have received a lung cancer diagnosis or treatment, at least for the next 5 years [52]. This is most striking in patients with a diagnosis of minimally invasive adenocarcinomas, suggesting an indolent behavior and good long-term outcome. These data raise the question as to the necessity and type of therapy required if a diagnosis of minimally invasive adenocarcinoma is established, and challenge the diagnostic community to develop a classification scheme that could accurately phenotype all lung tumors [52]. In a recent

survey, 51% of all participants were unprepared to start a screening that results in more than 1 overtreated person per 1 life saved from death due to cancer [53]. The number of cases of overdiagnosis found among the 320 participants who would need to be screened in the NLST to prevent 1 death from lung cancer was 1.38 [52].

Another point concerns radiation exposure. The effective dose of LDCT averages about 1.5 mSv per examination, whereas diagnostic CT (~8 mSv) or positron emission tomography (PET)-CT (~14 mSv), which are applied in order to further investigate those nodules, account for most of the radiation exposure in screening studies. In the NLST, participants received approximately 8 mSv over 3 years of screening. Estimates of harm from such radiation are based on dose extrapolations from atomic bombings and nuclear industry workers. Based on the NLST data, these models predict about 1 cancer death caused by radiation from imaging per 2,500 participants screened. These estimations led to the conclusion that the mortality benefit of LDCT screening obviously outweighs the radiation risk [54]. Nonetheless, a recent analysis of the NLST data found that lung screening participants may experience a cumulative radiation exposure of up to 280 mSv over a 20-year period and 420 mSv over 30 years of ongoing LDCT screening. This would account for a nontrivial radiation dose, exceeding those of nuclear workers and atomic bomb survivors [55]. The authors came to the conclusion that the radiation exposure of current lung cancer screening protocols could independently increase the risk of lung cancer beyond cigarette smoking if conducted over 20- to 30-year periods [55].

Cost-effectiveness depicts a fundamental requirement of screening implementation. At the moment, estimates regarding LDCT screening vary widely. Depending on the underlying assumptions and models used, lung screening has been judged in a broad margin, ranging from highly cost-effective to not cost-effective [56, 57], unless combined with smoking cessation interventions [58]. A recent analysis of Black et al. [59] estimated the costs per QALY gained to be USD 81,000. They concluded that the calculation was greatly altered by even modest changes in the underlying assumptions and would therefore depend on how screening is implemented outside the trial.

Broad consent exists, however, concerning the implementation of smoking cessation programs into lung cancer screening, which most likely depicts a 'teachable moment' to improve smoking cessation in this heavily smoking population [60–62].

The NLST has provided clear evidence for the effectiveness of CT screening, yet many questions concerning

the best possible execution of LDCT screening (e.g. management of lung nodules detected, inclusion criteria, screening duration and length of screening intervals) and reservations towards the above-discussed harms of LDCT screening remain. Based on those concerns, the European academic community is currently restrained with respect to giving recommendations comparable to those that exist in the US. The results of the European NELSON trial and the pooling of the EURACT trials will become available in 2015–2016. Those data will not only provide further mortality data on CT screening but also provide further information about cost-effectiveness, risk stratification and radiological protocols, which will likely reduce the number of false-positive results [16].

Management of SPN

The best possible management strategy of an SPN is based on clinical experience and on the profound knowledge of different diagnostic approaches, rather than on scientific evidence from controlled trials. To be evaluated by a randomized study, too many factors, such as the individual's risk for developing lung cancer and the respective health status or the radiological characteristics of the lung nodule, affect the optimal management strategy. As a result of upcoming LDCT screening, the optimal way of lung nodule management poses a significant clinical concern. Additionally, an increasing number of lung nodules are detected due to the more frequent implementation of image formatting [63–65] or computer-aided detection software as a 'second reader' [66–68].

When an SPN has been detected, assessment of the nodule's risk for being malignant guides further evaluation. This assessment is based on the radiological characteristics and the patients' individual risk of having lung cancer.

Radiological Evaluation

The most important predictor for malignancy is nodule size. According to the analysis of NLST baseline results, the PPV for 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, 21–30 and >30 mm, respectively [69].

When assessing the likelihood of malignancy, further image features should be considered. These include calcification as a strong predictor for benign disease (unless presenting in an eccentric pattern) [2, 3], as well as detec-

tion of intranodular fat [70]. Characteristics suggesting malignancy include spiculated and ragged margins [2, 71], vascular convergence [72], air bronchograms and pseudocavitation [71]. True cavitation, particularly when accompanied with a thick and irregular wall, depicts a strong predictor of malignancy. Although benign lesions can also show cavitation, the corresponding wall usually is thinner and smoother (approximately 95% of lesions with cavity walls thinner than 4 mm are benign) [73, 74]. In an analysis of the NELSON trial data, the combination of round shape, smooth margins and low attenuation was 100% predictive of benignity [75]. Nonetheless, earlier studies have shown that even nodules with smooth margins can be cancerous, with up to one third of malignant lesions having smooth margins [2, 76].

CT scan morphology helps to estimate the probability of malignancy, but rarely results in conclusive findings one can rely on without the need for further investigation. The difficulty in predicting which nodule might be malignant is emphasized by the low PPV in screening studies. With a cancer prevalence of 1–2%, the PPV of a nodule actually being malignant, but judged by the radiologist to be ‘suspicious’, large in size or with a VDT (volume doubling time) <400 days, was only around 35% in 2 studies [30, 77]. However, the implementation of VDT measurement seems to result in an improvement of the negative predictive value [30].

Pretest Probability

Evaluating pretest probability enables further selection and interpretation of subsequent diagnostic workup properly. Several quantitative models have been created in order to accurately estimate pretest probabilities. The most extensively validated model is based on the analysis of six independent predictors of malignancy and was developed by investigating 419 patients with noncalcified nodules that measured 4–30 mm in diameter on chest radiography [78, 79]. Those independent predictors include older age, current or past smoking history, nodule diameter, history of extrathoracic cancer >5 years before nodule detection, spiculation and upper lobe location. Three studies that were investigating the accuracy of those models came to the conclusion that clinical judgment and models appear to have similar accuracy for lung nodule characterization [5, 80, 81]. However, agreement between judgment and the models was modest, suggesting that qualitative and quantitative approaches might provide complementary information.

After assessing the likelihood of malignancy based on radiographic and clinical characteristics, one can decide

on the course of further workup. However, before ordering imaging tests or biopsy procedures, an accurate estimation of the individuals’ condition and respective perception is inevitable. Obviously a 90-year-old patient with several comorbidities requires a different approach than a 50-year-old patient in good health. Yet, the sheer mass of recommendations and the scarce time schedule of everyday clinical practice potentially makes us lose grip on patient-centered, individual medicine.

Based on the recommendations of the recently updated ACCP guidelines, further management depends on nodule size with a cutoff value of 8 mm [12].

Lung Nodules ≤8 mm in Diameter

Resulting from the extremely low prevalence of malignancy among small lung nodules, being <1 and 2.3–6% for nodules with a diameter of <5 and 5–9 mm, respectively [11, 82], nodules of this size are normally followed up by LDCT. Risks of both a surgical approach and lung biopsy would outweigh benefit, whereas PET-CT yields unreliable results in small lung nodules [83, 84].

Due to the different probability for malignancy and the different growth rate, lung nodules are further classified into solid, subsolid and pure ground-glass nodules. While most malignant nodules are solid, partly solid nodules are most likely to be cancerous, with 40–50% being malignant though having a diameter of <1.5 cm [82, 85]. Hence, patients with these nodules should be referred sooner for bioptic or surgical procedures (fig. 1).

In an analysis of growth rates of small lung cancers detected during a 3-year mass-screening program, VDT for ground-glass, subsolid or solid nodules were 813, 457 and 149 days, respectively [86]. This fact, as well as uncertainty about sensitivity of needle biopsy and PET scan, high prevalence of premalignant disease, challenges with determining growth on serial CT scans and concerns regarding an increasing incidence of adenocarcinomas in younger and nonsmoking individuals [82], led to new recommendations of the Fleischner Society, solely addressing subsolid nodules [87].

Those recommendations are summarized in table 1. They weight multiple factors such as nodule size, variable growth rate, clinical risk factors and limited accuracy of available techniques for determining growth. The recommendations only apply to the evaluation of asymptomatic patients with no history of extrathoracic malignancy.

One main concern should be the use of the lowest possible radiation dose in order to minimize cumulative radiation exposure in light of the likelihood of multiple follow-up CT scans.

Table 1. Recommendations for the management of pulmonary nodules referring to the statements from the Fleischner Society

Management of solid nodules smaller than 8 mm		
<i>Nodule size</i>	<i>Low-risk patient</i>	<i>High-risk patient</i>
≤4 mm	No follow-up needed	Follow-up at 12 months; if unchanged, no further follow-up
>4–6 mm	Follow-up CT 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 and 24 months if no change
>8 mm	Follow-up CT at around 3, 9, and 24 months, dynamic contrast-enhanced CT, PET and/or biopsy	Same as for low-risk patient
Management of subsolid nodules – solitary pure ground-glass nodule		
<i>Nodule size</i>		
≤5 mm	No follow-up needed (obtain contiguous 1-mm-thick sections to confirm that nodule is truly a pure ground-glass nodule)	
>5 mm	Initial follow-up CT at 3 months; if persistent annual CT for ≥3 years (FDG PET is of limited value, potentially misleading and therefore not recommended)	
Management of subsolid nodules – solitary part-solid nodule		
<i>Solid component size</i>		
<5 mm	Initial follow-up CT at 3 months; if persistent, annual CT for ≥3 years	
>5 mm	Initial follow-up CT at 3 months; if persistent, biopsy or surgical resection (consider PET/CT for part-solid nodules with a solid component >8 mm)	

Solid Lung Nodules >8 mm in Diameter

In contrast to small lung nodules, with nodules >8 mm, evaluation of cancer probability by functional imaging tests (e.g. PET scan) or bioptic procedures, yields more valid results. Due to the higher probability of malignancy and higher diversity of reasonable diagnostic possibilities, several workup strategies have to be taken into account. A definitive diagnosis and concurrent treatment of malignant nodules is accomplished by surgery. Nevertheless, for patients with benign nodules, this procedure should be avoided. Nonsurgical biopsy can establish a specific benign or malignant diagnosis. However, even a bioptic approach is invasive, potentially accompanied by adverse events, and depending on nodule size often nondiagnostic. CT scan surveillance avoids potential side effects in patients with benign nodules, but delays diagnosis and treatment in cases of malignancy.

A management algorithm, based on the recommendations of the recently updated ACCP guidelines, is presented in figure 2. After a possible investigation by functional imaging, further management approaches are decided according to the probability of cancer and include either surveillance with serial CT scans, nonsurgical biopsy, or primary surgery. A decision analysis investigating the best possible approach to the initial management of SPN showed that the decision is a ‘close call’ [88]. In

the analysis, a primary surgical approach yielded a slightly longer average life expectancy when the probability of cancer was very high. Needle aspiration biopsy or bronchoscopy had a narrow advantage when the probability of cancer was intermediate. In contrast, serial chest films followed by surgery in case of nodule growth produced slightly longer average life expectancy when the probability of malignancy was very low. As different strategies yield similar results, patients should be encouraged to actively participate in decision making with individual preferences guiding the further workup strategy.

In the following, more details on diagnostic procedures are outlined.

Functional Imaging

A meta-analysis of 44 studies about PET, single-photon emission CT (SPECT), dynamic CT and dynamic magnetic resonance tomography came to the conclusion that these noninvasive investigations are accurate in distinguishing malignant from benign SPN [89]. Sensitivity ranged from 93% for dynamic CT to 95% for both PET and SPECT scans, whereas specificity ranged from 76% for dynamic CT to 82% for PET/SPECT scans. The ability to provide additional information about lung cancer staging gives PET scanning an advantage over alternative functional imaging techniques. Though yielding good re-

Fig. 2. Management algorithm for individuals with solid nodules measuring 8–30 mm in diameter. SBRT = Stereotactic body radiotherapy.

sults for sensitivity, a negative PET scan result does not reliably exclude malignancy when investigating patients with a high pretest probability. Hence, those patients with a negative PET scan result should be either followed up by serial CT scans or referred for needle biopsy in order to confirm benignity. Since fluorodeoxyglucose uptake in the primary tumor has been shown to inversely correlate with survival [90, 91], patients with a negative PET scan finding show a favorable prognosis although definitive surgical treatment is delayed by a period of observation as long as 238 days [92, 93]. False-positive PET findings often represent infections or inflammatory conditions, including tuberculosis, mycoses, rheumatoid nodules and sarcoidosis. Accordingly, the current ACCP guidelines make the following recommendation. In the individual with a solid, indeterminate nodule that measures >8 mm in diameter and low to moderate pretest probab-

ility of malignancy (5–65%), functional imaging, preferably with PET, should be performed to characterize the nodule (grade 2C). However, functional imaging should not be performed in the individual with a solid, indeterminate nodule and a high pretest probability of malignancy [12].

Nonsurgical Biopsy

For SPN with a diameter >8 mm, invasive diagnosis or surgery is recommended, except when the probability of cancer is very low [12, 94, 95]. Nonsurgical biopsy by transthoracic needle biopsy (TTNB) or bronchoscopy is the procedure of choice in individuals with a high surgical risk and when imaging results and pretest probability are discordant and probability of malignancy is low to moderate [12]. However, even for patients with several comorbidities and a high risk for surgical complications and for

Fig. 3. Pulmonary nodule sampled by fluoroscopic guided bronchoscopy.

Fig. 4. EBUS displays a pulmonary nodule.

patients who desire proof of malignancy prior to surgery, nonsurgical biopsy should be recommended. The optimal approach to SPN is to surgically resect all malignant nodules while sparing the benign ones. Yet, in many cases, one deals with inoperable patients, accounting for 73% of individuals diagnosed with an SPN in one study [96].

For identifying malignancy in a high-prevalence population, TTNB yields high sensitivity values around 90%, with a slightly lower sensitivity of 68–78% for smaller lesions (≤ 15 mm in diameter) [97, 98]. Sensitivity drops further with increasing distance between the nodule and pleura [99, 100]. A retrospective study of 114 patients found that the addition of TTNB reduced the frequency of missed surgical cure from 10 to 7% and reduced the frequency of unnecessary surgery for a benign lesion from 39 to 15% [101]. Approximately 15% of patients undergoing TTNB suffer from pneumothorax with 6.6% requiring chest tube insertion [102]. This depicts a major

problem since many of these patients have severe comorbidities like COPD associated with a small cardiopulmonary reserve.

Bronchoscopy, with a risk of $<3\%$ for pneumothorax, depicts a less invasive approach for diagnosing SPN. Yet, the conventional bronchoscopic approach, composed of transbronchial biopsies under fluoroscopic guidance (fig. 3), yields relatively low sensitivity scores for peripheral small nodules. Sensitivity averages around 34 and 63% for nodules with a diameter of <2 and >2 cm, respectively [103]. Besides size, diagnostic yield depends on the location of the lesion, fluoroscopic visibility, biopsy method (forceps biopsy 57%, brush 54%, wash 43%), number of biopsies taken and the presence of an air bronchogram, providing a road map to the bronchial lesion [104–106].

In order to achieve better results in diagnosing smaller SPN, several innovative navigation methods have recently been developed. Those include endobronchial ultrasound (EBUS), guide-sheath, ultrathin bronchoscopy, virtual bronchoscopy (VBN) and electromagnetic navigation (ENB). EBUS enables the investigator to visualize peripheral lesions through different ultrasound absorption characteristics of lung tissue and solid structures. The ultrasound transducer is advanced through the working channel of the bronchoscope and provides a 360° ultrasonic view of small airways and surrounding tissue (fig. 4). It has significantly enhanced the bronchoscopic diagnostic yield for small pulmonary nodules [107–109] and can be used in combination with other navigation modalities like fluoroscopy or ENB. Particularly for small nodules <25 mm, EBUS shows promising results with a pooled sensitivity of 71% across 7 studies enrolling 580 patients [12]. When used in combination with ENB, a

study could demonstrate a higher diagnostic yield for the combined procedure (88%) than for EBUS-transbronchial biopsy (EBUS-TBB; 69%) or ENB (59%) alone. ENB uses technology similar to a car GPS (global positioning system) and provides navigational assistance coupled with steering ability to localize and sample pulmonary nodules. A sensor, located at the tip of the steerable catheter, is accurately localized through an electromagnetic field. With the aid of reconstructed CT scan data, a pulmonary nodule can be tracked, visualized and sampled [110]. The diagnostic yield of ENB-guided TBB for nodules <2 cm ranged from 44 to 75% (median, 68.5%) [12]. A similar technology is VBN. It uses data derived from CT scans to simulate a virtual endobronchial pathway to the pulmonary nodule, thus facilitating bronchoscopic navigation. New bronchoscopic approaches to accessing lesions in the lung parenchyma are being investigated [111].

A recent meta-analysis identified 39 studies using novel bronchoscopic guiding technologies such as EBUS, ENB, VBN, guide sheath and ultrathin bronchoscopy showed a pooled diagnostic yield of 70% [112]. For nodules measuring ≤ 2 cm in diameter, the diagnostic yield was 61%, which is substantially higher than conventional bronchoscopy (34%). However, studies were limited by low scores for study quality, inconsistent results and the indirectness that characterizes most studies of diagnostic accuracy [12].

Even though novel bronchoscopic guiding technologies do not provide a sensitivity as high as that of TTNB, the preferable side effect profile favors a bronchoscopic approach to pulmonary nodules. The choice between bronchoscopy and TTNB should be based on clinical and radiological features of individual patients. For example, radiological findings may predict a lower diagnostic yield of EBUS-TBB (e.g. SPN in apicoposterior bronchial segments [113], pleural-based lesions and subpleural lesions [114, 115]) or a higher risk for complications with TTNB (e.g. perihilar-located lesions, emphysema or lesion size [114, 116]).

In case of nondiagnostic results, it is important to realize that neither TTNB nor bronchoscopic biopsy rules out malignancy.

Therapy

The gold standard for diagnosis and definitive treatment of malignant nodules remains surgical resection, while benign nodules usually undergo conservative

treatment. After considering surgical risk and benefits of definitive diagnosis and treatment, lung nodules are preferentially approached by thoracoscopic wedge resection. If a nodule proves to be malignant, lobectomy and systematic sampling of mediastinal lymph nodes are the standard of care for complete oncological resection and staging [94]. Thoracoscopic lobectomy is accompanied by 30-day mortality below 2% [117]. Sublobar resection is only recommended for individuals with a poor cardiac performance or limited pulmonary reserve since the risk for locoregional recurrence is increased [118, 119].

In case of functional inoperability, therapeutic alternatives include external beam radiation therapy (EBRT) and percutaneous image-guided radiofrequency ablation (RFA). Newer techniques of EBRT like intensity-modulated radiation therapy or stereotactic body radiation therapy allow a more accurate therapy while lowering the radiation exposure to nearby healthy tissues. Local tumor control by EBRT can be achieved in about 70–100% with a 2-year survival rate of 22–72% being reported in stage I/II NSCLC [94, 120].

RFA is a minimally invasive technique with the ability to produce large volumes of coagulation necrosis in a controlled fashion. A prospective multicenter study could show a complete response of target tumors lasting at least 1 year in 88% of cases and 1-year overall survival of 70% [121]. However, like TTNB, the percutaneous approach was accompanied by an increased rate of complications like pneumothorax and airway bleeding.

Bronchoscopic treatment approaches are under development. In order to enhance the accuracy of EBRT, so-called ‘fiducials’ can be placed under ENB or EBUS guidance [122–124]. Furthermore, endoluminal brachytherapy is being investigated [125].

Another treatment approach represents bronchoscopic RFA. After proving the safety, feasibility and effectiveness of bronchoscopy-guided RFA in an animal study [126], Tanabe et al. [127] conducted a study enrolling 10 patients with NSCLC stage IA. The histological analysis after definitive surgical resection revealed vital tumor cells around the necrotic tissue, indicating a yet insufficient ablation effect. However, the authors of the study assume to achieve a larger and thus sufficient coagulation effect through increase of power output, making it a potential therapeutic approach for medically inoperable patients with stage I NSCLC in the future.

Conclusion

SPN are detected more frequently with the aid of improved imaging techniques. This depicts a major clinical and socioeconomic challenge. Since the NLST has provided compelling evidence of the efficacy of low-dose CT screening by showing a reduction of lung cancer mortality, screening is being recommended by an increasing number of national guidelines. Results of several European LDCT trials are awaited in the near future and will hopefully shed light on some of the open questions regarding this topic. The CT scan morphology of pulmonary nodules often enables us to estimate the probability of malignancy, but rarely results in reliable and conclu-

sive findings. Further management of detected pulmonary nodules is primarily based on nodule size, pretest probability of malignancy and the aforementioned radiological morphology. Besides sequential follow-up investigations by LDCT and definite diagnosis through surgery, nonsurgical biopsy is often the chosen way of diagnosing pulmonary nodules. Until recently, TTNB has been the method of choice when assessing small pulmonary nodules nonsurgically. However, the development of more sophisticated ways of bronchoscopic sampling makes this method an important alternative. The rapid progress in these bronchoscopic techniques will aid in the quick determination of malignancy of these nodules.

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