Incidental pulmonary nodules – current guidelines and management

Inzidentelle Lungenrundherde – aktuelle Leitlinien und Management

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ABSTRACT

Background Due to the greater use of high-resolution cross-sectional imaging, the number of incidental pulmonary nodules detected each year is increasing. Although the vast majority of incidental pulmonary nodules are benign, many early lung carcinomas could be diagnosed with consistent follow-up. However, for a variety of reasons, the existing recommendations are often not implemented correctly. Therefore, potential for improvement with respect to competence, communication, structure, and process is described.

Methods This article presents the recommendations for incidental pulmonary nodules from the current S3 guideline for lung cancer (July 2023). The internationally established recommendations (BTS guidelines and Fleischner criteria) are compared and further studies on optimized management were included after a systematic literature search in PubMed.

Results and Conclusion In particular, AI-based software solutions are promising, as they can be used in a support capacity on several levels at once and can lead to simpler and more automated management. However, to be applicable in routine clinical practice, software must fit well into the radiology workflow and be integrated. In addition, "Lung Nodule Management" programs or clinics that follow a high-quality procedure for patients with incidental lung nodules or nodules detected by screening have been established in the USA. Similar structures might also be implemented in Germany in a future screening program in which patients with incidental pulmonary nodules could be included.

Key Points

- Incidental pulmonary nodules are common but are often not adequately managed
- The updated S3 guideline for lung cancer now includes recommendations for incidental pulmonary nodules
- Competence, communication, structure, and process levels offer significant potential for improvement

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ZUSAMMENFASSUNG

Hintergrund Aufgrund der immer häufiger durchgeführten hochaufgelösten Schnittbildgebung steigt die Anzahl der jährlich detektierten inzidentellen Lungenrundherde. Obwohl die allermeisten inzidentellen Lungenrundherde gutartig sind, ließen sich durch eine konsequente Nachverfolgung viele frühe Lungenkarzinome diagnostizieren. Aus vielfältigen Gründen werden die existierenden Handlungsempfehlungen jedoch häufig nicht korrekt umgesetzt. Daher werden Verbesserungspotenziale auf den Ebenen der Kompetenz, Kommunikation, Struktur und des Prozesses beschrieben.

Methode In diesem Artikel werden die Handlungsempfehlungen für inzidentelle Lungenrundherde aus der aktuellen S3-Leitlinie des Lungenkarzinoms (Juli 2023) vorgestellt. Die international etablierten Handlungsempfehlungen (BTS-Guidelines und Fleischner-Kriterien) werden verglichen und weitere Studien zum optimierten Management wurden nach systematischer Literaturrecherche auf PubMed eingeschlossen.

Ergebnisse und Schussfolgerung Insbesondere KI-basierte Softwarelösungen sind vielversprechend, da sie gleich auf mehreren Ebenen unterstützend eingesetzt werden und zu einem einfacheren und automatisierten Management führen können. Um allerdings auch in der klinischen Routine an-

wendbar zu sein, muss sich Software gut in den radiologischen Arbeitsablauf einfügen und miteinander integriert werden. Darüber hinaus haben sich in den USA sogenannte „Lung Nodule Management"-Programme bzw. -Kliniken etabliert, die einen standardisierten Ablauf auf hohem Qualitätsniveau für Patienten mit inzidentell oder in der Früherkennung detektierten Lungenrundherden bieten. Gegebenenfalls könnten auch in Deutschland in einem zukünftigen Früherkennungsprogramm Strukturen geschaffen werden, in die auch Patienten mit inzidentellen Lungenrundherden eingebunden werden könnten.

Kernaussagen

- Inzidentelle Lungenrundherde sind häufig, aber werden oft nicht leitliniengerecht aufgearbeitet
- Die aktualisierte S3-Leitlinie des Lungenkarzinoms umfasst nun auch Handlungsempfehlungen für inzidentelle Lungenrundherde
- Kompetenz-, Kommunikations-, Struktur- und Prozessebene bieten zahlreiche Verbesserungspotenziale für das Rundherdmanagement der IPNs

Introduction

An incidental pulmonary nodule (IPN) is a single, well-defined process in the lungs that is found incidentally and does not exceed 3 cm in diameter [1–3]. The increased use of high-resolution cross-sectional imaging in recent decades has significantly increased the detection rate of IPNs [4]. In the Netherlands, too, the identification of IPNs in chest CTs has steadily increased over the past decade and was associated with more stage I lung cancer diagnoses [5].

The vast majority of IPNs in clinical CT examinations are benign, but a very small proportion turn out to be lung cancer. In Germany, approximately 57 000 people develop lung cancer each year. Lung cancer is one of the most prognostically unfavorable tumors, which is reflected in a low relative 5-year survival rate of around 21 percent in women and 15 percent in men, as reported in Germany in 2019 [6]. Survival rates in lung cancer vary significantly depending on the stage of the disease. Since patients with lung cancer often do not report any complaints in the early stages, the disease is often discovered late and unexpectedly. Native low-dose computed tomography (LDCT) detects lung cancer at earlier stages than chest radiography, and leads to a reduction in lung cancer-related mortality in both structured screening programs for the high-risk population [7–11] and consistent follow-up of IPNs [12].

However, while only high-risk groups meet the inclusion criteria for lung cancer screening, a broader population would benefit from consistent follow-up of IPNs [4]. This is very important because a large number of patients with lung cancer do not meet the usual inclusion criteria of an early detection program for the high-risk population [13, 14]. For example, more than 10 % of lung cancer cases occur in patients who have never smoked [15]. Furthermore, the participation rate of the high-risk group in an early detection program is often low [16–18]. For example, in Mississippi in the USA, 38 % of cancer diagnoses were made in a structured IPN program for consistent guideline-compliant follow-up of IPNs, compared to 8 % in the screening program for the high-risk population and 54 % with symptoms in the clinic (clinic group). Approximately 51 % of patients with lung cancer diagnosed through the IPN program did not meet the inclusion criteria of the screening program for the high-risk population. Furthermore, a better 5-year survival compared to the clinic group could be demonstrated [19]. Therefore, consistent IPN follow-up would make an additional contribution to the population in addition to the success of screening [19].

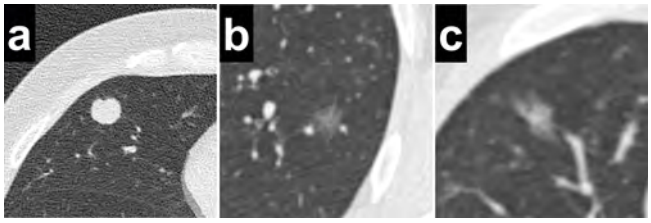
Although there are already many national and international recommendations for action [1–3], in reality, they are often not known, communicated or implemented [4, 20–22]. In addition to recommendations for action, several technical approaches are now available to optimize detection, risk assessment, and follow-up.

This article provides a review of the current national and international recommendations for action, the typical pitfalls, and possible solutions for more effective follow-up.

Main part

What are incidental pulmonary nodules and how common are they?

Pulmonary nodules are deemed incidental if they are discovered by chance during other examinations. These may include examinations of neighboring organs and structures in which the lungs have been partially screened too, e. g., CT of the shoulder or MRI of the spine. Exceptions are examinations with oncological or infectious indications, as this increases the likelihood of nodules. They are usually largely roundish dense nodules up to and including 30 mm in diameter that are at least partially surrounded by lung tissue. For larger dense nodules, the term space-occupying lesion is used. Depending on their radiation transparency, these nodules are referred to as solid or subsolid. Subsolid nodules are again divided into ground-glass opacity nodules and partially solid nodules, in which the underlying lung structure can be fully or partially delineated (▶ **Fig. 1**). Furthermore, there must be no atelectasis, a plump hilum or pleural effusion, or other evidence of advanced intrathoracic tumors [1–3, 23].



▶ **Fig. 1** Morphological classification of the nodules depending on their radiation transparency into (**a**) solid, (**b**) ground-glass and (**c**) semi-solid.

The increasing detection of IPNs in recent years has been associated with more frequent imaging and improved techniques [4]. For example, between 2006 and 2012 in the USA, the annual number of chest CTs increased from 1.3 % to 1.9 % in all adults, while the frequency of identification of nodules increased from 24 % to 31 % in all examinations performed [4]. Moreover, a higher level of awareness after the initial publication of the Fleischner criteria in 2005 may have further contributed to this [24]. Studies from France and China have shown a more frequent occurrence with increasing age, in men and in smokers or those exposed to smoke, or in people with lung disease [25, 26]. Nevertheless, IPNs are often also discovered in individuals who do not meet the usual inclusion criteria of lung cancer screening. Nodules were detected in 8.5 % of polytrauma examinations, of which over 80 % required follow-up according to the Fleischner criteria [27]. Even in a young cohort aged between 18 and 24, an incidence of clinically relevant nodules of 0.6 per 1,000 person years could still be determined [28].

Risk stratification of pulmonary nodules

The risk of malignancy of a nodule and the general condition of the patient generally serve as the basis for further management. On the one hand, morphological criteria or characteristics of the nodule are used for the malignancy risk; on the other hand, independent risk factors can also be taken into account to statistically estimate the risk.

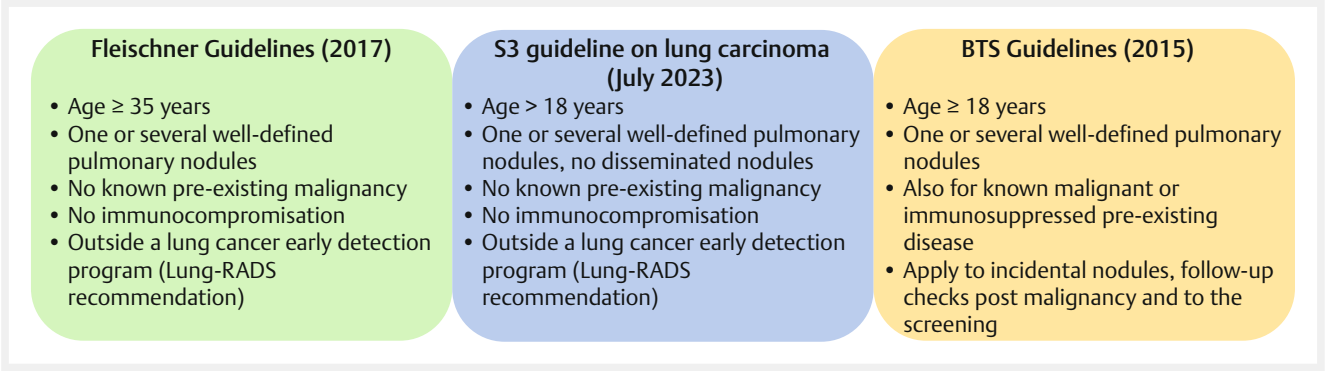
With regard to the nodule criteria, size is the dominant factor for malignancy [29]. Growth behavior can also provide crucial information regarding the etiology of a nodule. For example, solid nodules with volume doubling times of approximately 50–400 days and subsolid nodules between 3–5 years are suspected of being malignant. Faster growth is more indicative of an inflammatory event [30, 31]. Persistent subsolid nodules usually correspond to precursors of adenocarcinoma with very slow growth. New or growing solid parts of a partially solid nodule are highly likely to be malignant. Spiculation or pleural involvement are also typical morphological malignancy criteria [29]. Nodules on caverns or cysts represent a typical malignant manifestation – usually of adenocarcinoma [32–37]. Furthermore, localization in the upper lobe, 1–4 nodules [29], or concomitant pulmonary fibrosis and emphysema are associated with an increased risk of malignancy [38]. However, it is important to distinguish nodules that are undoubtedly benign such as calcified granulomas, apical calluses, or fatty hamartomas.[29]. Even larger (> 6 mm) perifissural, subpleural, or juxtapleural nodules usually represent benign lymph nodes as long as they are smooth, oval, or triangular, and should not be checked [2]. However, as soon as morphological abnormalities such as spiculation, retraction of the pleura, or a history of lung cancer are present, follow-up after 6–12 months is recommended by the Fleischner Society [2].

By taking into account further epidemiological information such as age, gender, ethnicity, family history of lung cancer, or information regarding exposure to noxious agents such as smoking, the individual risk of malignancy can be calculated using statistical models, including in particular, the Mayo Clinic model, the Brock model (CT) or the Herder model (CT+PET) [29, 39]. However, it should be noted that the models were developed based on cohorts with high pre-test probabilities, meaning that corresponding deviations may occur in patients with IPNs and a lower overall risk [29, 39, 40]. Nevertheless, the recommendations for action of the Fleischner Society, the British Thoracic Society (BTS), and the current S3 guideline on lung cancer recommend the use of IPN risk calculators [1–3].

Although it has been shown that nodules > 5 mm can be detected quite reliably with MRI [41–43] and that a sensitivity and specificity comparable to PET-CT can be achieved using MR diffusion and MR perfusion imaging [44–46], the BTS guidelines do not recommend an MRI malignancy assessment if a PET-CT is available (BTS).

S3 guideline on lung cancer

In the revision of the S3 guideline on lung cancer published in December 2022 (version 2.1), the chapter on IPNs was modified and supplemented. Similarly, the current S3 guideline (version 2.2 dated July 2023) refers to the already established international recommendations for action of the Fleischner Society and the British Thoracic Society [1–3]. Regarding applicability, it should be noted that the BTS criteria cover all nodules occurring in patients aged 18 years and over, which have not been pathologically found to be lung cancer or metastasis. They therefore also apply to lung carcinoma screening. For screening examinations, the Fleischner criteria and the S3 guideline refer to the use of the Lung-RADS classification of the American College of Radiology [47]. Furthermore, the Fleischner criteria should only be used in people aged 35 or over, without known or suspected tumors or immunosuppression. The S3 guideline uses a combination of these inclusion criteria with a minimum age of 18 years, without known pre-existing malignancy or immunocompromisation. Furthermore, although it applies to multiple nodules, it does not apply to disseminated nodules, without this being discussed in more detail (▶ **Fig. 2**). Very small nodules (solid or subsolid) < 5 mm (< 80 mm^3), benign nodules (e. g., calcified or fatty), or nodules in patients whose general condition does not allow diagnostic confirmation or treatment should not be clarified according to the S3 guideline (▶ **Fig. 3**). Furthermore, any prior imaging should be used to assess the growth behavior. For nodules (solid or subsolid) ≥ 5 mm and ≤ 8 mm (≥ 80 mm^3 and ≤ 250 mm^3), follow-up checks should be performed. Follow-up intervals are 3, 6–12, and 18–24 months. Follow-up after 3 months serves primarily to exclude inflammatory changes in subsolid nodules. In the case of persistent subsolid nodules, check-ups should be performed over a duration of 3–5 years due to the usually slower growth behavior. The BTS guidelines recommend follow-ups after 1, 2, and 4 years; for partially solid nodules, the Fleischner Society even recommends annual follow-ups (▶ **Fig. 4**). Furthermore, if subsolid nodules are found, the size of any solid part that may form should be used to estimate the probability of malignancy, depending on the patient's age, smoking status, peripheral eosinophilia, history of lung carcinoma, and the radiomorphology of the nodules. Longer intervals generally allow for a more accurate estimation of the growth behavior by calculating the volume doubling time (VDT). Patients with nodule growth of < 25 % per year (< 2 mm increase in diameter) or a VDT of > 600 days or with a limiting general condition can be exempted from follow-up. In the case of



▶ **Fig. 2** A comparison of the inclusion criteria for the management of incidental pulmonary nodules of the S3 guideline for lung carcinoma, the Fleischner criteria, and BTS guidelines.

faster growth with a VDT of < 400 days (≥ 2 mm increase in diameter) or formation or increase in the solid part of a partially solid nodule, definitive pathological clarification should be sought. Solid nodules > 8 mm to ≤ 30 mm can also be monitored if the risk of malignancy (Brock model) is < 10 %. For nodules with an initial risk of malignancy > 10 %, diagnostic confirmation using PET-CT should be offered in accordance with the S3 guideline, provided that the nodule is above the detection threshold of PET-CT. The risk can then be re-evaluated using the Herder model, which takes into account the FDG avidity of a nodule. If the risk of malignancy is still > 10 %, definitive histological clarification is recommended. However, check-ups may continue to be performed in cases of a high puncture risk or patient preference. If there is a very high risk of malignancy > 70 %, resection with rapid incision can be considered even without prior pathological confirmation. In case of inoperability, nonsurgical ablative or radiotherapeutic treatment can also be performed. An online calculator for the Brock model, the Herder model, and for the VDT is available free of charge at https://www.brit-thoracic.org.uk/quality-improvement/guidelines/pulmonary-nodules/pn-risk-calculator/.

Further diagnostic and therapeutic courses of action for suspicious nodules should in principle be decided in a multidisciplinary manner, with the involvement of pneumology, thoracic surgery, and radiology, and according to the patient's wishes.

The size of a nodule should ideally be determined semi- or fully-automatically using volumetry, as this has been shown to be reproducible and more sensitive compared to size progression [48–51]. However, different software can lead to significant differences in volumetry, so the same algorithm should always be used for follow-ups [52, 53]. If this technical tool is not available, diameters are still specified in the abovementioned guidelines. It should be noted that the recommendations for action in the S3 guideline and the Fleischner criteria use the arithmetic mean of the longitudinal and transverse diameter of the nodule in the same transverse, coronary, or sagittal CT reconstruction. The BTS guidelines use the maximum diameter of the three spatial planes.

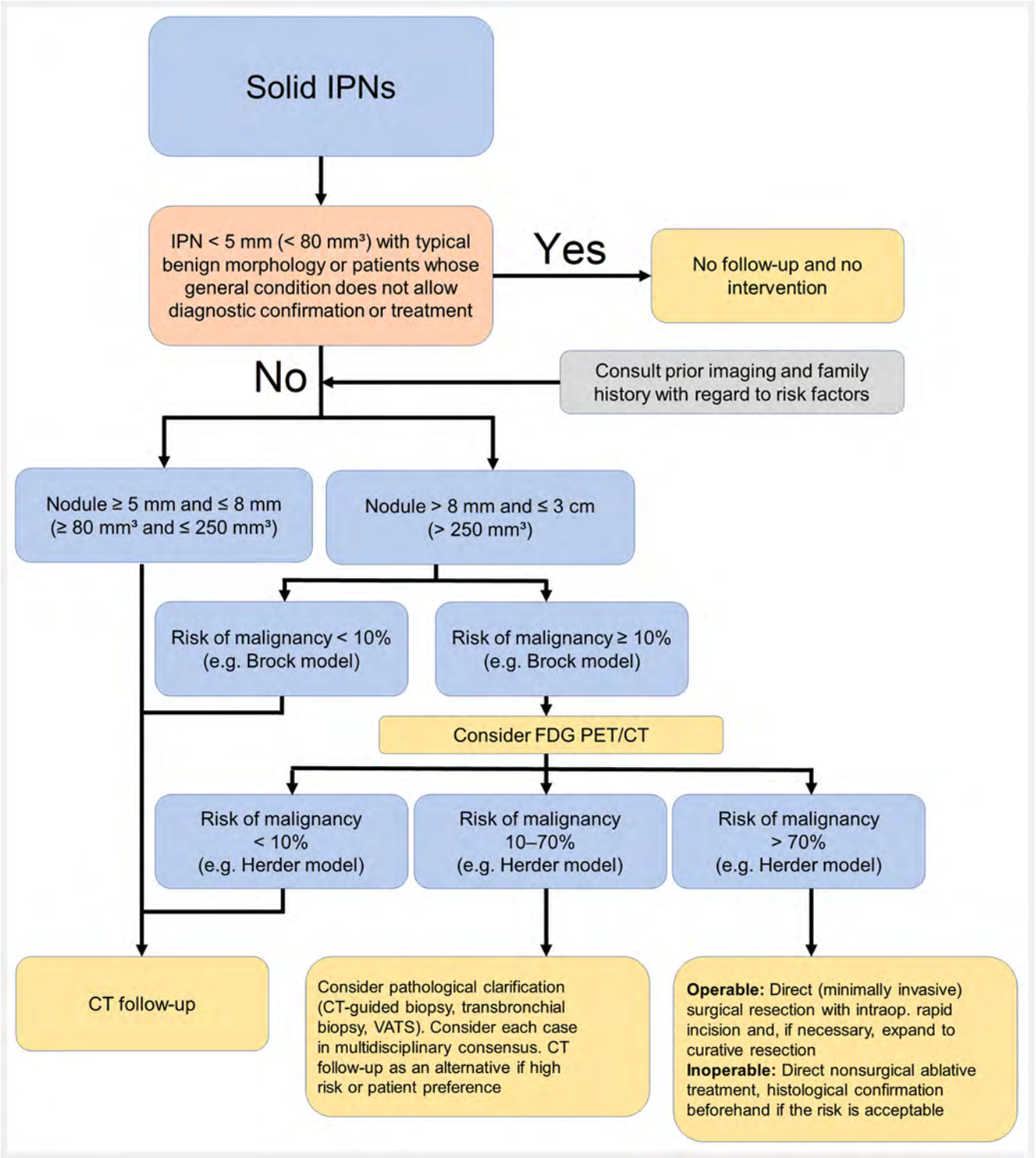
The S3 guideline does not address the question of how to handle IPNs in cases of pulmonary parenchyma that is not completely detected. In the case of a medium-sized (6–8 mm) lump, the Fleischner Society recommends monitoring the entire chest after an appropriate interval (3–12 months depending on the clinical risk). If a nodule is large or looks very suspicious, a complete chest CT examination is recommended [2].

CT examinations used for the detection of nodules or their follow-up should always be examined with a native low-dose protocol that complies with the specifications of the Federal Office for Radiation Protection for the early detection of lung cancer [54]: An isotropic spatial resolution of 1 mm or less must be achieved. Only in this way can the images be viewed equally from all sides, and only in this way is volumetry of lesions that are only a few millimeters in size possible with sufficient accuracy and reproducibility. For the LDCT scan, a maximum CT dose index (CTDI) of 1.3 mGy is permitted (based on the standard patient of 80 kg, 175 cm, BMI 26). This value can and should be significantly lower on modern devices. An important dose reduction measure in LDCT is the use of patient-specific prefilters (e. g., tin or silver), which can be appropriately selected via a filter change mechanism.

How are the guidelines implemented?

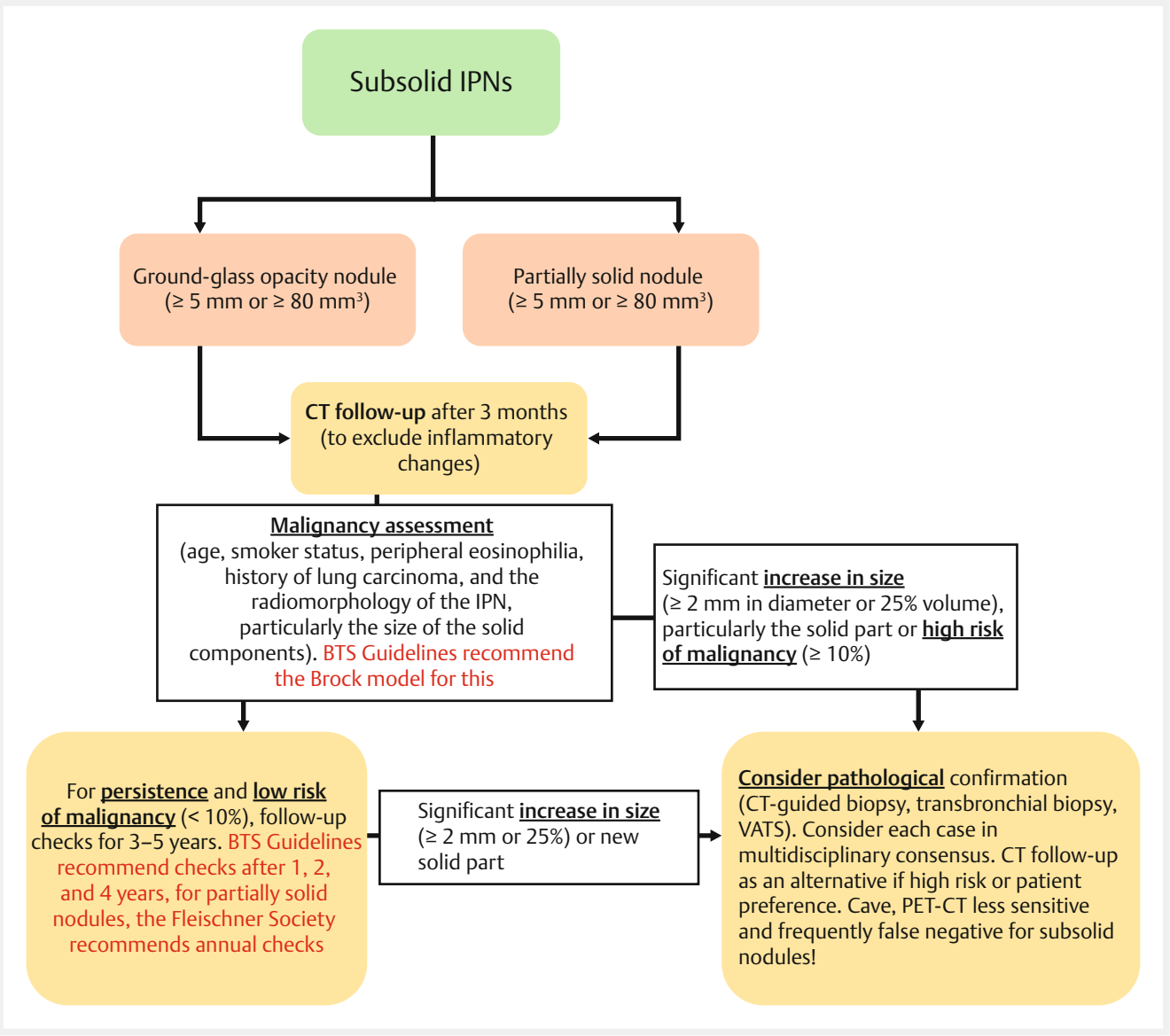
Although established national and international recommendations for action already exist, there are numerous indications that these are insufficiently implemented. In some cases, radiologists, pulmonologists, or other specialists are not aware of the recommendations for action [55, 56], or, despite knowing them, they are not correctly applied [57, 58]. This can lead not only to missed or delayed follow-ups. Premature follow-ups can also be problematic due to greater inaccuracy in estimating growth behavior and excessive accumulated radiation exposure. In addition, unnecessary invasive diagnostics or nuclear medicine examinations could be avoided. However, even simple measures, such as displaying the recommendations for action at the radiologists' workstations [59] or attaching a description of the respective malignancy risk [60, 61] to the CT report templates [21] and findings [62], could lead to improved adherence on the part of the radiologists or referring physicians.

Although hundreds of thousands of IPNs are discovered on CT scans each year, follow-up care appears to be inadequate in most of the newly discovered nodules, with follow-up rates ranging from 29 % to 39 % [22, 63, 64], which raises the question of why approximately 2 out of 3 patients with IPNs do not receive ade-



▶ **Fig. 3** Initial diagnostic algorithm for solid incidental pulmonary nodules (IPN). Fig. 3 is based on data from the current S3 guideline on prevention, diagnosis, treatment, and follow-up care of lung carcinoma (July 2023) [1].

quate radiological and clinical follow-up care [22]. These results are interesting in that most radiological reports (up to 68 %) recommended a follow-up examination of the pulmonary nodules [22], indicating that in many patients with potential early stage cancer, adequate examination of the lump is not performed. Several pitfalls have been described in the literature that may be responsible for inadequate treatment of IPNs, which shows that while radiologists initiate the process of treatment of IPNs by documenting them in the radiological report, they are not solely responsible for the fact that IPNs are often neglected. Diverse healthcare providers and patients are also important factors in the success of IPN management [65].



▶ **Fig. 4** Initial diagnostic algorithm for subsolid incidental pulmonary nodules (IPN) based on data from the current S3 guideline on prevention, diagnosis, treatment, and follow-up care of lung carcinoma (July 2023) [1]. Supplementary recommendations of the Fleischner Society and the BTS guidelines in red [2, 3].

Software for nodule detection and structured follow-up

Automated AI-based nodule detection has developed significantly over the past few years, so that there are now several commercial software solutions with FDA or CE labels. However, these techniques are not yet widely used. Ideally, the nodules are automatically detected, volumetrized, categorized, and their malignancy risk is estimated using the model-based Brock score, for example. In addition to the statistical risk models mentioned above, there are promising approaches in which nodule characterization is carried out using quantitative image analysis (radiomics) or deep learning algorithms [66]. The latter has already managed to achieve a high level of sensitivity and specificity similar to that of experienced radiologists [67–70]. AI-based software is also making inroads in the areas of speech recognition, structured report generation, and image reconstruction.

An important component of improving the description of the nodules is incorporating important nodule characteristics into the radiological findings template. This significantly increased the complete description of the nodules from 12 % to 47 % [61]. Optimal integration into the radiological work process is always very important for all the techniques mentioned. Only in this way can the available technical possibilities be applied in clinical routine.

In this regard, there are various communication and follow-up systems between radiologists, referring physicians, and patients, which can be used to check the timely implementation of follow-ups and, otherwise, to send automated reminders to referring physicians and patients [71–73]. By implementing the Radiology

Result Alert and Development of Automated Resolution (RADAR), the timely follow-ups could be significantly improved from 64.5 % to 84.3 % [72].

In recent years, specialized IPN clinics and Lung Nodule Management programs have been established in the USA. The special feature of these facilities is the Lung Navigator, a person who plans the coordinated procedure for each patient and provides the patient with important information as the contact person. Other specialized personnel support the patients and processes in the facilities [74]. This, in addition to an increase in compliance in combination with a structured screening program, also resulted in a stage shift of lung cancer [12].

Conclusion

In order to reduce lung cancer mortality, consistent guideline-compliant follow-up of IPNs should be performed in addition to a structured early detection program for the high-risk population. Both measures would have synergistic and additive effects, covering a broader population, and thus diagnosing more lung cancer in earlier stages. In order to ensure comprehensive follow-up of IPNs in accordance with the guidelines, the competence level of radiologists and referring practitioners, the communication level, the process level, and also the structural level should be improved. If necessary, in Germany too, patients with IPNs can be integrated into the structures and processes of a future structured screening program, so that the quality requirements of the current S3 guideline can be implemented in practice.

Conflict of Interest

Jens Vogel-Claussen declares for the last 3 years:
Research support: German Center for Lung Research (DZL, BMBF), NIH, Siemens Healthineers, GSK, AstraZeneca, Boehringer Ingelheim, Novartis
Fees for lectures/consulting: Siemens Healthineers, GSK, AstraZeneca, Boehringer Ingelheim, Novartis, Coreline Soft, Bayer, Roche

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