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Advancements in lung cancer: a comprehensive perspective on diagnosis, staging, therapy and follow-up from the SAKK Working Group on Imaging in Diagnosis and Therapy Monitoring

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Summary

In 2015, around 4400 individuals received a diagnosis of lung cancer, and Switzerland recorded approximately 3200 deaths related to lung cancer. Advances in detection, such as lung cancer screening and improved treatments, have led to increased identification of early-stage lung cancer and higher chances of long-term survival. This progress has introduced new considerations in imaging, emphasising non-invasive diagnosis and characterisation techniques like radiomics. Treatment aspects, such as preoperative assessment and the implementation of immune response evaluation criteria in solid tumours (iRECIST), have also seen advancements. For those undergoing curative treatment for lung cancer, guidelines propose follow-up with computed tomography (CT) scans within a specific timeframe. However, discrepancies exist in published guidelines, and there is a lack of universally accepted recommendations for follow-up procedures.

This white paper aims to provide a certain standard regarding the use of imaging on the diagnosis, staging, treatment and follow-up of patients with lung cancer.

Introduction

Lung cancer is one of the most common cancers and the leading cause of cancer death worldwide in both men and women [1]. In Switzerland, on average, around 2700 men and 1800 women are diagnosed with lung cancer and approximately 2000 men and 1200 women die from lung cancer every year. This cancer was the most common in men, accounting for 21.3% of all cancer deaths [2], 2021.

Based on the National Lung Screening Trial (NLST) [3] and Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) trial data [4], efforts are being made throughout Europe, including Switzerland, to introduce national screening programmes to improve long-term survival by detecting early-stage lung cancer.

The increasing awareness and ongoing stage shift have implications for imaging-related non-invasive diagnosis and staging, requiring highly specific and sensitive imaging methods that allow a better patient-centred strategy towards curative surgery. Characterisation of tumour genomic abnormalities and clinical applications of anticancer agents that can effectively target these abnormalities have transformed treatment approaches and have brought precision therapy into the mainstream of lung cancer care [5]. This has implications on how to use imaging for tumour follow-up assessment beyond the general use of response evaluation criteria in solid tumours (RECIST), which might not be the tool of choice in the future [6].

Currently, different guidelines regarding postoperative follow-up are available [7, 8], but new tissue-sparing surgeries as well as non-surgical procedures (stereotactic body radiotherapy, radiofrequency ablation) require adaptation of the follow-up scheme and new imaging strategies [9].

This white paper aims to give an overview of the current advances in imaging in terms of diagnosis, staging, treatment and follow-up of patients, along with appropriate recommendations.

Imaging modalities

Conventional X-ray

Chest radiographs are still frequently used to screen for pulmonary anomalies. However, substantial limitations of this method are the limited accuracy for small lung lesions,

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reduced accuracy for part-solid and ground-glass lesions, the dependency of lesion location, the reduced spatial resolution and the difficulty of assessing the mediastinal structures; foremost potential lymph node involvement [10, 11]. An overview of the pros and cons of the various modalities is given in table 1.

Computed tomography

Computed tomography overcomes the limitations of conventional X-ray and since the dissemination of the results of the National Lung Screening Trial in 2011, low-dose chest CT has been promoted as the mainstay of lung cancer screening [12]. Compared with chest radiography, the CT screening group showed a reduced mortality from lung cancer by 20% [12]. In contrast to the promising results from the National Lung Screening Trial, the first European screening studies did not demonstrate an improved survival in a screening cohort. For instance, a pooled analysis of the Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays (DANTE) trial and the Multicentric Italian Lung Detection (MILD) trial did not show decreased mortality in the screening cohorts [13, 14]. Although the results were not statistically significant, both trials as well as the Danish Lung Cancer Screening Trial (DLCST) detected more cancers in the CT screening population. The heterogeneous results from these studies can be attributed to the study design which was underpowered to evaluate reduced mortality. With the results from the NELSON trial however, a significant reduction in lung cancer mortality was found. Based on these results, a general recommendation for CT screening in high-risk populations is under discussion.

In general, suspicious lesions on CT imaging are characterised by irregular, spiculated borders and heterogeneous morphology. Lung cancers tend to occur in the upper lobes and the apical segments of the lower lobes. For a comprehensive risk stratification, additional factors such as age, smoking history and a family history of lung cancer should be considered as well. Based on the overall risk assessment, further recommendations on the management of lesions can be provided, such as follow-up intervals, additional positron emission tomography (PET)-CT and/or invasive work-up (CT-guided biopsy, endobronchial ultrasound).

The clinical staging of lung cancer (currently in its 8th edition [120]) rests on either CT or CT in conjunction with PET. The local tumour extent is mainly determined by multiplanar CT measurements. In cases with bronchial obstruction, PET-CT can help to distinguish the lesion boundaries from atelectasis. Lymph node assessment in CT is mainly based on size criteria. Although lymph nodes vary in size depending on their location, a general threshold is deemed to be 1 cm in short-axis diameter. Additional criteria comprise texture (i.e. enhancement patterns) and shape. PET-CT is more sensitive for the nodal assessment and the depiction of distant metastasis. If metastatic spread to the brain is suspected, additional MR imaging is required to determine the M stage (figure 1).

Lymph node assessment in CT is mainly based on size criteria. Although short axis thresholds vary depending on the location, a general threshold is deemed to be 1 cm in short-axis diameter. Additional criteria comprise texture (i.e. enhancement patterns) and shape [15, 16]. By comparison, PET-CT is more sensitive for the nodal assessment and the depiction of distant metastasis. In suspected tumour spread to the brain, additional MR imaging is required. An overview of the pros and cons of the various modalities is given in table 1. There are no established protocols for follow-up surveillance imaging after curative therapy, but it is advisable to consider annual imaging for at least the initial 5 years.

PET/CT

Several meta-analyses demonstrate high sensitivity (ca. 90%) and overall good specificity (ca. 78%) of fluorodeoxyglucose F 18 (^{18}F-FDG) (PET/CT for the assessment of unclear lung lesions [17–19]. The diagnostic accuracy of the PET/CT is strongly positively associated with the intensity of ^{18}F-FDG uptake in lesions [20]. The sen-

Table 1:
Summary of strengths and weaknesses of each imaging modality.

Imaging modality	Strengths	Weaknesses
Conventional X-ray	Rapidity	Low accuracy for small lesions
	Availability	Low accuracy for non-solid and partially solid lesions
	Low-cost	Difficulty of assessing lymph nodes
	Low radiation dose	
Computed tomography	Early detection of lung lesions	Low specificity for normal-sized lymph nodes
	Reproducibility	
	Availability	
Positron emission tomography-Computed tomography	Characterisation of lung nodules	Lack of sensitivity for brain metastases
	Detection of positive lymph nodes (and guide for invasive assessment)	
	Detection of distant metastases	
Magnetic resonance imaging	Quantitative imaging	Breathing artefacts
		Expensive
		Time-consuming
		High-end technology
Ultrasound	Assessment of parietal pleural and chest wall invasion	Low visibility of deep structures
Interventional radiology	Image-guided biopsies	Post-procedural complications
	Percutaneous thermal ablation	

sitivity is also higher for larger lesions (e.g. ca. 96% for lesions larger than 10 mm) [21] and vice versa. Small malignant lesions at the boundaries of the spatial resolution of PET scanners (2–6 mm, depending on the performance of the scanners) are often rated false-negatively [22]. The same applies to malignant lesions with low ^{18}F-FDG uptake such as bronchoalveolar cell carcinoma or carcinoid tumours. The lower rates of specificity are caused by accumulation of ^{18}F-FDG in reactive and inflammatory tissues. Whole-body ^{18}F-FDG PET/CT is a powerful method for the detection of lymph nodal or distant metastases of non-small cell lung cancer (NSCLC) and, in this regard, is superior than CT alone (figure 2).

Different meta-analyses show a sensitivity of 74–85% and a specificity of 85–92% for differentiation between a N0–1 status and a N2–3 status [18, 23–26]. The sensitivity and specificity of the ^{18}F-FDG PET/CT for metastases of non-small cell lung cancer in CT-morphologically non-suspicious lymph nodes are 70% and 94%, respectively [25]. In a randomised prospective clinical trial, futile surgical treatments could be reduced by 50% when ^{18}F-FDG PET/CT was performed prior to the surgical intervention [27]. Another clinical trial demonstrated that the number of invasive tests, especially of mediastinoscopies and thoracotomies, is significantly reduced by prior ^{18}F-FDG PET/CT [27, 28]. For the detection of distant metastases of non-small cell lung cancer in ^{18}F-FDG PET/CT, a meta-analysis revealed a sensitivity of 93% and a specificity of 96% [29]. The majority of distant metastases are found in osseous structures and the adrenal glands [20]. Since brain tissue shows a physiologically high ^{18}F-FDG uptake, the sensitivity for the detection of brain metastases with ^{18}F-FDG PET/CT is significantly reduced [30]. ^{18}F-FDG PET/CT is frequently able to identify additional sites of small cell lung cancer (SCLC) thereby changing the tumour stage from “limited disease” to “extensive disease” [31, 32].

For primary staging of small cell lung cancer, ^{18}F-FDG PET/CT demonstrated superior performance (sensitivity of 93%) when compared with conventional imaging modalities (CT and bone scan, sensitivity: 79%) [31]. Specificity was 100% for both PET/CT and conventional methods [31]. In several studies, ^{18}F-FDG PET/CT changed the initially planned therapy in 8–17% of patients [31, 33, 34]. The performance of ^{18}F-FDG PET/CT regarding the N status of small cell lung cancer is supposed to be similar to that of non-small cell lung cancer. In a meta-analysis, ^{18}F-FDG PET/CT showed a sensitivity of 99% and a specificity of 89% regarding the detection of recurrent local cancer after initial surgery [19]. Further studies confirmed these results [35, 36]. Besides the detection of recurrent local tumour, ^{18}F-FDG PET/CT also provides an excellent tool for the simultaneous detection of distant metastases as described above. Response evaluation is recommended after 2–3 cycles of chemotherapy or immunotherapy, using the same initial radiographic investigation that demonstrated tumour lesions (level of evidence IV, grade of recommendation B). The same procedure and timing (every 6–9 weeks) should be applied for the response evaluation in patients treated with targeted therapies and/or immunotherapy. Follow-up with PET is not routinely recommended, due to its high sensitivity and relatively low specificity.

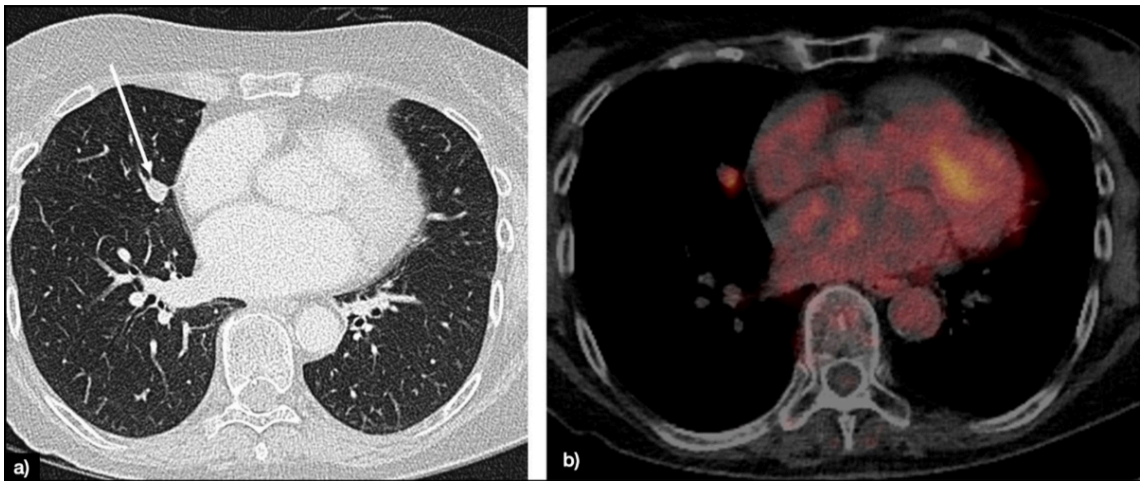
An overview of the pros and cons of the various modalities is given in table 1.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) [37] offers improved soft tissue contrast as well as the ability to image without the use of ionising radiation and is routinely used in cancer imaging at multiple disease sites (e.g. prostate cancer, liver tumours, etc.). Unfortunately, several challenges have so far impeded any widespread adoption of MRI in detection or staging of lung cancer, most importantly breathing artefacts due to comparably long scan times and an inferior signal-to-noise ratio due to the low proton density of air. However, technical improvements over the last few years (for example, shorter examination times resulting in single breath-hold examinations) have increased interest in the use of MRI in lung cancer; furthermore, some promising pilot studies have been published, suggesting that MRI may be of value in detecting lung nodules ≥6 mm [38], and may be used in follow-up studies after prior CT imaging [39].

MRI also offers the ability to quantify (patho-)physiological parameters of the tumour, thus potentially gaining in-

Figure 1: Lung solid nodule of 12 mm in the middle lobe (white arrow), classified as Lung-RADS 4A (suspicious) **(A)**. The patient underwent PET-CT, showing fluorodeoxyglucose (FDG) avidity only of the nodule (**B**).



creased insight into the tumour microenvironment. For example, Razek et al. [40] showed that the apparent diffusion coefficient (ADC) of diffusion-weighted imaging in lung cancer was correlated with the tumour's pathological grade and the presence of metastatic lymph nodes, while Chang et al. demonstrated a potential value of dynamic contrast-enhanced MRI in the assessment of treatment response in a small group of 11 patients [41]. While these results are certainly promising, the use of MRI in lung cancer detection and staging is currently mostly limited to clinical trials. However, given the increasing availability of MR as part of PET/MR and the greater technical performance of clinical MR scanners, MRI may be of value in routine clinical practice in the future. An overview of the pros and cons of the various modalities is given in table 1.

Ultrasound

Ultrasound plays a minor role in the diagnosis, staging and follow-up of lung tumours. Nevertheless, transthoracic ultrasound could be used as an additional tool in specific settings such as assessing parietal pleural and chest wall invasion [42]. An overview of the pros and cons of the various modalities is given in table 1.

Intervention

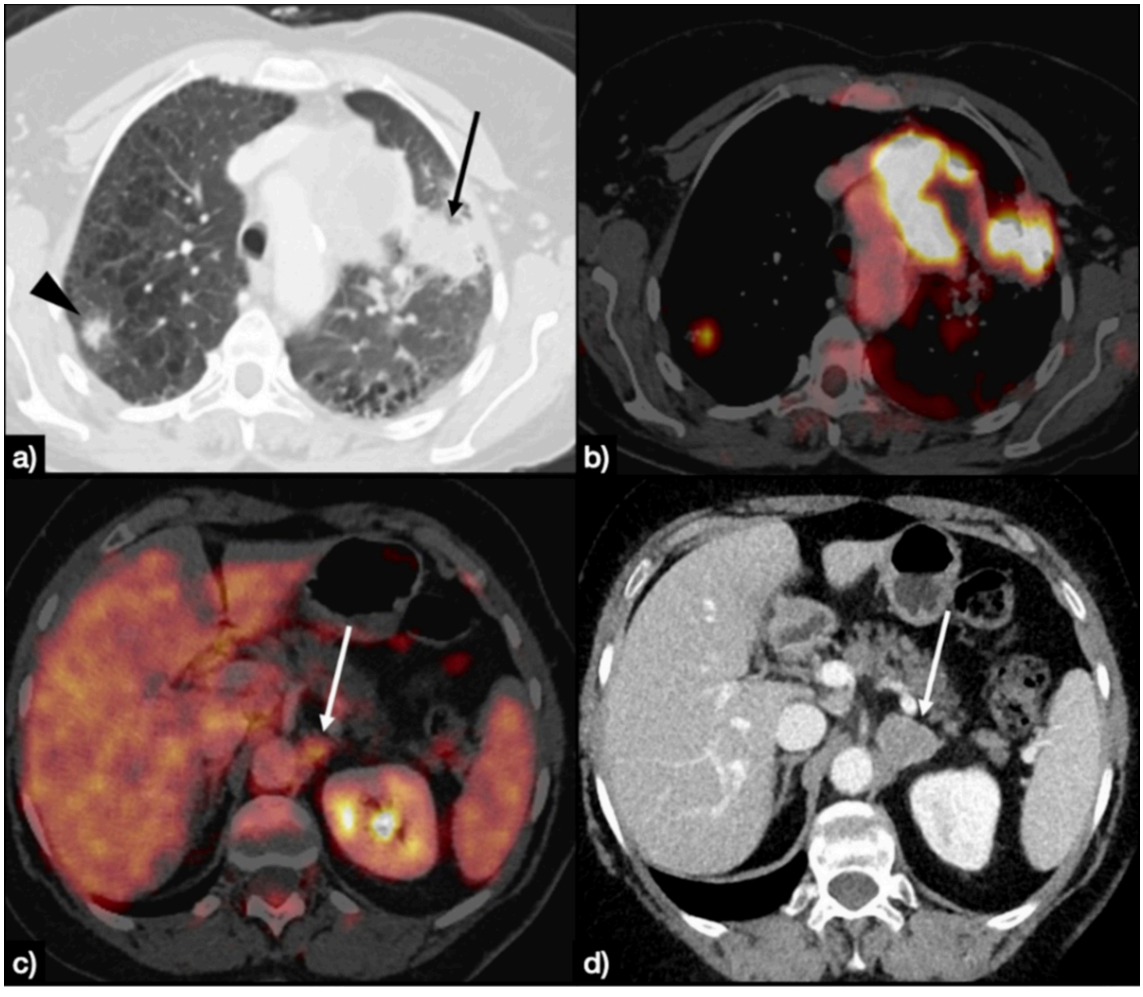
Image-guided biopsy

The Fleischner Society 2017 Guidelines recommend tissue sampling in solid, noncalcified lung nodules larger than 8 mm either by minimally invasive surgery, transbronchial endoscopic access or transthoracic needle biopsy [15]. CT-guided lung biopsy, performed under local anaesthesia, is an established method with an excellent diagnostic accuracy ranging from 80% to 90% [43]. Major complications are rare; however, the risk of pneumothorax ranges from 10% to 40% with chest tube insertion in 5% to 15% of cases [44]. Tumour seeding through the needle tract represents a very rare complication with a prevalence reported in the literature between 0.012% and 0.061% [45].

Percutaneous thermal ablation

The current European Society of Medical Oncology guidelines consider surgery as the standard of care for early-stage (Stage IA) non-small cell lung cancer [46, 47]. In non-operable patients, accounting for about 20% to 30% of patients at time of diagnosis [48, 49], stereotactic body radiotherapy is recommended with thermal ablation being a reasonable alternative with curative intent [50]. Recent

Figure 2: Large solid mass of the left upper lung (black arrow), with concomitant contralateral nodule (black arrowhead) (**A**), fluorodeoxyglucose (FDG)-avid on PET-CT (**B**). PET-CT also raised suspicion of a lesion in the left adrenal (white arrow in panel **C**), that was confirmed as an adrenal lesion at the subsequent CT scan, as an enlargement of the gland (white arrow in panel **D**).



studies showed comparable outcomes in stage IA non-small cell lung cancer for thermal ablation compared to stereotactic body radiotherapy [51–55]. With thermal ablative techniques, 1-year local tumour control and overall survival rates of 77–85% and 78–91% can be achieved [56, 57]. The most common complication after thermal ablation is pneumothorax with a chest tube insertion rate of about 20% [56]. Serious adverse events such as systemic air embolism are reported in less than 1% of cases [56, 57]. Moreover, thermal ablation has multiple advantages [58, 59]:

– Tissue sampling can be performed during the same procedure;
– Thermal ablation can be repeated as often as necessary without any dose limitations;
– Thermal ablation has no negative effect on lung function even after treatment of multiple lesions;
– Thermal ablation is more cost-effective than stereotactic body radiotherapy.

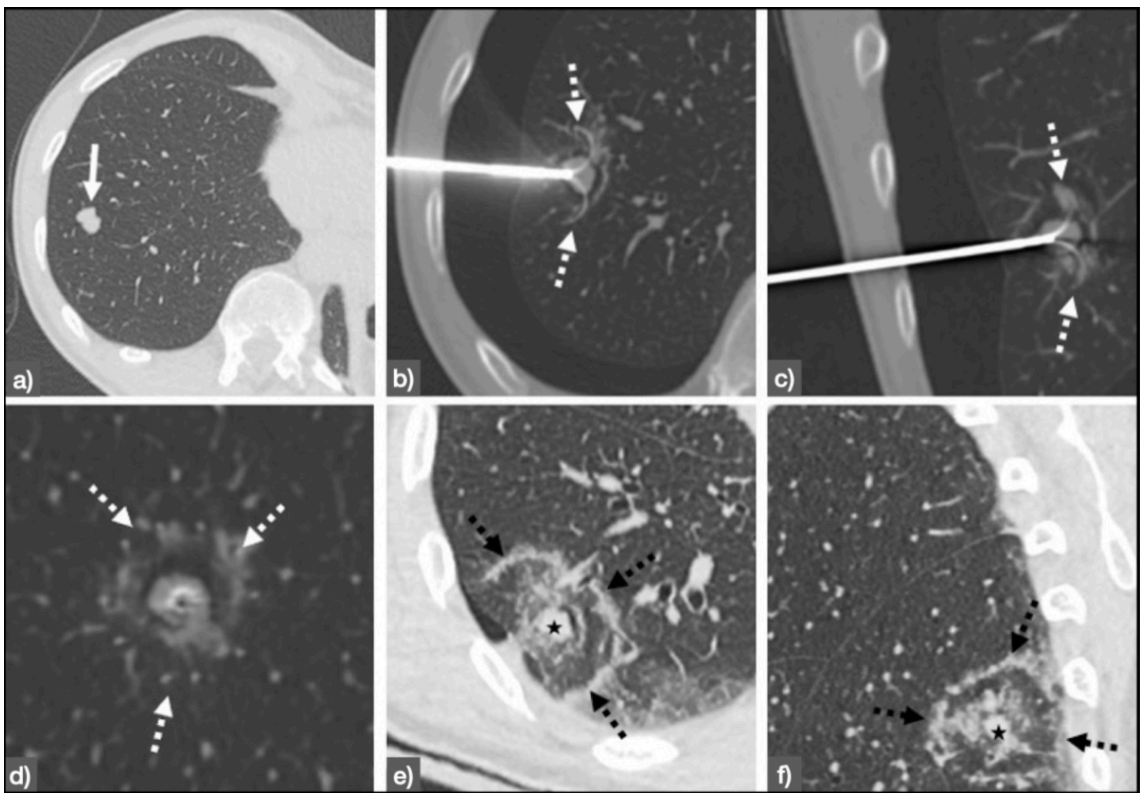
In thermal ablation, tissue destruction is achieved either through application of heat or cold. The most studied technique so far is radiofrequency ablation (figure 3). Other thermal ablative techniques include microwave ablation and cryoablation, both with comparable results to radiofrequency ablation [56, 60]. Cryoablation in particular has shown promising results in recent years with the multicentre, prospective SOLSTICE trial and long-term results by the prospective ECLIPSE trial with local tumour control rates of 85–90% [61, 62]. One of the main advantages of cryoablation is the painless ablation technique, which makes general anaesthesia obsolete [63]. In addition, pleural tumours can be treated without postoperative pain. Further comparative studies have to be performed to compare the effectiveness of the two techniques.

Reporting

What should be included

In the context of screening, the radiological report should include details about imaging parameters like the radiation dose. It should also provide a concise overview of the screening results along with specific management suggestions, as well as any additional findings [64]. Standardised templates are preferred to ensure uniform reporting and guideline adherence [65]. Further, the use of a common terminology is recommended for data collection, quality control and increased efficiency [66, 67]. Each nodule should be described with its location (lobe, segment), size (determined on lung window images and reported as the average diameter), attenuation (soft tissue, type of calcification, fat), morphology (solid, non-solid and part-solid), margins (smooth, lobulated, spiculated) and compared to preliminary examinations (growth, change of composition) [68]. For unification reasons, nodules need to be classified by an established classification system such as Lung-RADS 1.1 [69].

Figure 3: Radiofrequency ablation of histologically proven early-stage (Stage IA) non-small cell lung cancer [46] in a 65-year-old patient. Panel **A** shows the planning CT depicting the tumour (white arrow) before intervention. Panels **B** (axial), **C** (sagittal) and **D** (coronal) show the deployable radiofrequency ablation (RFA) needle (LeVeen 3.5 cm, Boston Scientific, Natick, MA, USA) in place covering the entire lesion (white dotted arrows). Panels **E** (axial) and **F** (coronal) show the control scan immediately after the procedure, in which the ablation margin (black dotted arrows) is clearly visible with sufficient distance to the treated tumour (black star). After one year, no signs of local recurrence were detected.



How to include concomitant findings

For lung cancer screening, the American College of Radiology (ACR) proposed in the CT Screening Reporting and Data System [70] the category "S", where the radiologist can mention non-lung cancer findings that he or she believes are clinically relevant [69]. We propose that a similar tag be used in imaging reports of lung cancer patients to outline findings that are not directly related to the patients' malignancy but of potential relevance for the patients' further work-up. The ACR Incidental Findings Committee has published a set of recommendations for managing incidentally detected lung findings on thoracic CT [71] to assist the radiologist in this important task.

TNM

The tumour, node, metastasis (TNM) classification system for lung cancer was introduced in its 8th edition by the Union for International Cancer Control (UICC) in 2016 and came into effect in January 2017 with authorisation by the American Joint Committee on Cancer (AJCC) in January 2018. The changes made to the 7th edition were based on recommendations from the International Association for the Study of Lung Cancer [72] Staging Project, including the analysis of an international database of 94,708 patients from 46 sites and 19 countries. The UICC recommends the inclusion of the TNM classification in the data reporting. The classification applies to carcinomas of the lung including non-small cell lung cancer, small cell lung cancer and bronchopulmonary carcinoid tumours, but does not apply to sarcomas and other rare tumours of the lung. The classification consists of a clinical and a histopathological part. The *clinical classification* (cTNM) is essential for selecting and evaluating the therapy. It is based on evidence acquired before treatment, from physical examination, imaging (CT and PET-CT), endoscopy, biopsy, surgical exploration and other relevant examinations. The *pathological classification* (pTNM) represents a postsurgical classification, used to guide adjuvant therapy and provide additional data to estimate the patient's prognosis. Compared to the cTNM, it is supplemented or modified by data from surgery and pathological examination.

Major changes introduced by the TNM 8th edition were: tumour size cut points in every T category, based on 1 cm intervals up to 5 cm, thus creating new IA subgroups (IA1, IA2, IA3); the classification of main bronchus involvement as T2 (with subsequent removal of the 2 cm distance from the carina as a limit between pT2 and pT3 tumours); classification of partial and total atelectasis as T2; categorisation of diaphragm invasion as T4. Mediastinal pleural invasion was removed from the criteria of T3 definition due to infrequent use. No changes were made to the N categories, though the new TNM categories led to further subgrouping of the III stage category (IIIA, IIIB, IIIC), corresponding to different treatments and outcomes [73]. Likewise, a new M1b descriptor was introduced for patients with a single extrathoracic metastatic lesion in a single organ, because they have better survival and different treatment options, compared with those with multiple extrathoracic lesions (M1c) [74].

The UICC also defined prognostic factors, subcategorised into tumour-related, host-related and environment-related factors. For example, tumour-related factors for surgically resected non-small cell lung cancer patients are T category, N category or extracapsular nodal extension; patient-related factors for surgically resected non-small cell lung cancer patients are parameters such as weight loss and/or performance status; environment-related factors for non-small cell lung cancer patients are resection margins or adequacy of mediastinal dissection.

New promising prognostic factors such as tumour-related molecular/biological markers as well as quality-of-life assessments have been named and might be addressed in future TNM editions.

RECIST and iRECIST

RECIST (response evaluation criteria in solid tumours) are objective criteria used for evaluation of cancer therapy response in patients included in clinical trials. The latest and currently used version of RECIST (v1.1) was published in 2009. According to Eisenhauer et al. [75], lesions to be followed during treatment are defined at baseline (no more than 4 weeks before the beginning of the treatment) and separated as target lesions (up to 5 lesions with maximum diameter >10 mm and/or lymph nodes with short axis >15 mm) and non-target lesions (consisting of measurable lesions not meeting the target lesion criteria and non-measurable lesions such as effusions and bony lesions). The sum of the diameters of target lesions is compared to the nadir value to define complete response (disappearance of lesions), partial response (at least a 30% decrease), stable disease (changes insufficient to define partial response or progressive disease) or progressive disease (at least a 20% increase). The appearance of one or more new lesions is always considered progressive disease. Non-target lesions are evaluated qualitatively. Immunotherapy aims to enhance the immunological response of patients to the cancer cells. The effects of these therapies may lead to a response, to a pseudo-progression or, in a limited number of cases, to a so-called hyperprogressive disease, representing a rapid progression after starting the treatment [76]. Considering hyperprogressive disease and pseudoprogression, the RECIST working group developed the immune response evaluation criteria in solid tumours (iRECIST) [77], where the first assessment of progressive disease is considered unconfirmed until reassessment, usually after 6–8 weeks.

Volumetry

From lung cancer screening trials, we know that the best predictors of malignancy are nodule size and volume doubling time [78–80]. In a screening setting, the recommended cut-off for malignant tumours would be a volume doubling time of <600 days [81] – although the range of volume doubling time for malignant tumours is larger (50–800 days), especially due to the slow growth of less frequent adenocarcinomas [82]. For tumour restaging and follow-up CT exams, there is no need for volumetry since the RECIST criteria define the response to chemotherapy. However, volumetry may be helpful in the assessment of lung nodules in patients with primary cancers outside the lung, a screening setting or the appearance of a new lung nodule in a healed cancer patient. There is substantial interobserver variability among volume software and radiolo-

gists; therefore, it is mandatory to use the same software or radiologist with the same reconstruction filter of the CT images (hard/soft) to reduce measurement errors [83]. The nodule volume can be calculated manually by the Schwartz formula (volume doubling time = [t log2] / [log Vt/V0], where t is the time between scans, Vt is the second volume, and V0 is the first volume) or more simply by using an online calculator.

When to follow up and at what interval

Annual screening has already been proven to reduce lung cancer mortality in large trials [4, 12, 84], therefore annual screening should be preferred. Nevertheless, the MILD trial provides original evidence that prolonged screening beyond five years with every 2 years low-dose computerised tomography (LDCT) can achieve a lung cancer mortality reduction comparable to annual LDCT in subjects with a negative baseline examination [85, 86]. In the future, scores based on individual risk assessments will further stratify the screening follow-ups [87].

Future perspectives

Patient-centred precision medicine, circulating tumour DNA and artificial intelligence

Precision medicine is the integration of genetics, clinics, imaging and environmental patient features with the aim of finding the most suitable treatment for each individual patient, with maximum benefit and limited toxicity [5].

In lung cancer this concept may be currently exemplified by targeted therapy and immunotherapy. Targeted therapy is based on the use of drugs specifically directed against oncogenic driver mutations. The two currently most used drugs of this category are directed to the epidermal growth factor receptor mutations and anaplastic lymphoma kinase (ALK) rearrangements. Evidence already exists supporting the use of alternative therapeutic agents for specific target alterations (e.g. BRAF, ROS1, among others). At some point during these therapies, an acquired resistance may present, and imaging may play a pivotal role for its early identification [5, 88]. Furthermore, radiomics is a recently introduced field of research that may well represent the role of imaging in lung cancer precision medicine. Radiomics refers to the extraction of qualitative and quantitative information from digital images and to perform a correlation with clinical data with or without associated gene expression, in order to support evidence-based clinical decision-making [89]. Research studies show that CT radiomics features may be helpful in more patient-specific selection of therapy, based on the correlation of these characteristics with mutational status and prognostication [90–92].

In the context of precision medicine, liquid biopsy must also be mentioned as a crucial non-invasive technique for managing lung cancer. Liquid biopsy is a non-invasive technique critical for managing lung cancer. It analyses circulating tumour DNA (ctDNA) and circulating tumour cells (CTCs) in the blood to detect cancer-specific genetic mutations, such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase and KRAS. This method allows for early detection and continuous monitoring of the disease, providing insights into treatment effectiveness and resistance [93]. Liquid biopsies also help detect minimal residual disease, which could be beneficial in the future for selecting patients who may benefit from adjuvant treatment after surgery. Additionally, they help monitor cancer recurrence post-treatment. Although not a complete replacement for traditional biopsies, liquid biopsies are safer, less invasive and a valuable complement to enhance lung cancer management [94].

Artificial intelligence refers to specific algorithms driven by existing data that allow objects to be predicted or classified. With the exponential growth of the computational power of microchips over the last decades, linear and logistic regression algorithms have given way to complex algorithms based on machine learning, such as decision trees, support vector machines and Bayesian networks. Furthermore, deep learning, which uses several layers of machine learning algorithms, paved the way to even more advanced analysis, such as artificial neural networks [95], convolutional networks, recurrent neural networks, long-term/short-term memory and generative adversarial networks [96]. Supervised learning systems are considered the most accurate models for training algorithms, requiring researchers to label patient data with inputs and outputs, often used to predict survival, cancer risk, nodule detection and nodule characteristics. Unsupervised learning does not require data labelling and is used to identify associations between samples. There are also semi-supervised learning models and reinforcement learning models, the latter using a reward function to adjust the algorithm.

By supporting diagnosis and predicting clinical outcomes, artificial intelligence can play a central role in shaping individual patient management. The most direct contributions of artificial intelligence to precision medicine are drug selection, prediction of treatment response [97] and estimation of survival [98]. Artificial intelligence-based models can also anticipate treatment-related toxicity, as recently documented for radiation-induced pneumonitis [99, 100]. Nevertheless, many technical challenges hamper the widespread implementation of artificial intelligence-based models. The reproducibility and standardisation of artificial intelligence methodology are critical aspects that need to be refined [101], and these account for the publication of the Image Biomarker Standardization Initiative [102] and the introduction of the radiomic quality score [103].

Augmented reality partially falls within the scope of artificial intelligence systems, and is currently underway in generating holograms for more precise surgical planning as well as for teaching purposes. As mentioned above, low-dose CT enables early detection of lung cancer and increases the survival of lung cancer patients. Recently, the LUNA16 challenge was set up, where several algorithms were tested, with the best algorithm providing a sensitivity of more than 95% at fewer than 1.0 false-positive per scan over a database of 888 CT scans [104]. Artificial intelligence-based screening models represent promising tools for the role of a second reader, as they detected up to 70% of lung cancers not detected by the radiologist, but did not detect about 20% of the lung cancers initially identified by the radiologist [105]. Moreover, once a nodule is detected, artificial intelligence can be used to predict the histopathological characteristics [106] and to stratify the risk of ma-

lignancy [107]. In the International Symposium on Biomedical Imaging (ISBI) 2018 Lung Nodule Malignancy Prediction Challenge [108], the top five participants used deep learning models with area under the curve (AUC) between 0.87 and 0.91 without significant differences. Another recent artificial intelligence model achieved an accuracy of 93%, with a sensitivity of 82% and a precision of 84% [109]. In addition, artificial intelligence-based models can distinguish between small cell lung cancer and non-small cell lung cancer [110], differentiate non-small cell lung cancer subtypes [111], identify specific molecular features (i.e. Ki-67, anaplastic lymphoma kinase, PDL1 or EGFR expression) through radiomic analysis [112].

Pulmonologist's perspective

The role of the pulmonologist is critical in detecting patients at risk of lung cancer early, in diagnosing suspected lung cancer patients and in evaluating disease extent as well as treating lung cancer [113]. Diagnosis and definition of disease extent and staging are not only crucial in determining prognosis but also necessary to direct treatment strategies [114]. Pulmonary interventions offer less invasive diagnostic and staging possibilities for the assessment of lung cancer patients. Following radiological imaging, bronchoscopy allows for cytopathological and histopathological sampling, which can be used to determine the precise type of cancer and thus guide treatment strategies. Direct biopsy (e.g. forceps) can be used for visible endobronchial lesions, while radioscopic or endobronchial ultrasound-guided transbronchial forceps biopsy can help to establish diagnosis in peripheral pulmonary lesions. Various techniques are available for diagnostic purposes (e.g. needle techniques endobronchial ultrasound-needle aspiration, endoscopic ultrasound-needle aspiration and combined endobronchial ultrasound/endoscopic ultrasound-needle aspiration) [115]. For staging purposes, endobronchial and endoscopic oesophageal ultrasound-guided transbronchial needle aspiration has replaced surgical mediastinal nodal staging as the initial procedure [116]. Pleural effusion puncture can determine stage IV lung cancer. Treatment decisions are based on the underlying lung cancer type, staging and comorbidities. The pulmonologist evaluates lung functional performance to evaluate operability and determine risk before possible other treatment approaches (e.g. chemotherapy and radiation therapy). The treatment decision and treatment administration is usually decided in a multidisciplinary setting where the pulmonologist plays a pivotal role for patients with lung cancer.

Thoracic surgeon's perspective

Promising and significant developments have recently occurred in the treatment of lung carcinoma, in part due to modern oncology. This is also reflected in the current histopathological subtyping of lung carcinoma, which now distinguishes numerous tumour entities leading to different treatment approaches. In addition to the histopathological and molecular characteristics of the tumour, the prognosis is also determined by the patient's sex, general condition and concomitant diseases. The three modalities for treating lung cancer remain surgery, radiation and systemic therapy, which are increasingly recommended in a patient-orientated and multimodality approach due to the aforementioned development. A curative therapy claim exists for non-small cell lung cancer [117] in early and, in some cases, advanced stages. However, for the majority of stage IIIB/C and IV patients, therapy is not curative. In recent years, drug development has led to a significant improvement in the prognosis of many patients thanks to immune checkpoint and kinase inhibitors in combination with predictive biomarkers. Important advances have also been made in the surgical treatment of lung cancer thanks to technical advances in minimally invasive surgery. Efforts to resect tumours in a way that spares lung tissue are also likely to advance patient-centred tumour therapy. Other developments in therapy include local endoscopic and percutaneous interventional therapy and new options in palliative care. The current staging of non-small cell lung cancer is based on the TNM classification and the UICC8 criteria [118–120]. Due to the diversity of treatment strategies, the very heterogeneous stage IIIA with ipsilateral mediastinal lymph node involvement is additionally classified according to Robinson [121]. As a rule, cytological or histological confirmation should be performed if N2 or N3 metastasis is suspected. For this purpose, further clarification by endobronchial or endo-oesophageal ultrasound (EBUS/EUS) is primarily indicated. If this does not lead to a diagnosis, surgical biopsy by video-assisted mediastinoscopy / video-assisted mediastinoscopic lymphadenectomy (VAM/VAMLA) or video-assisted thoracoscopy (VATS) is another diagnostic option [118, 122, 123]. Therapeutic advances have necessitated the development of new pathological classifications of lung cancer [124]. One reason for this is the importance of molecular testing in addition to histopathological diagnosis, which must also be feasible from small tissue samples. If there are no primary contraindications for surgery, neither from the tumour situation nor from comorbidities, the expected postoperative lung function and the perioperative cardiovascular risk are crucial for planning the anatomical lung resection. Clarifying algorithms for determining cardiopulmonary reserve have been established, for example, by the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS) [125]. The recommendations for local therapy with curative intent apply to the entire group of non-small cell lung cancers. For systemic therapy without curative intent, recommendations are differentiated by histological, immunological and genetic markers. With the advent of systemic molecular targeted therapy, checkpoint inhibitors and multimodality multidisciplinary therapy, even patients with metastatic disease and especially patients with oligometastatic tumour stage can achieve survival greater than 5 years. The main method of cure is surgery. A prerequisite for this treatment option is the performance of an anatomical lung resection. The current standard of minimal expansion is lobectomy [126]. If resectability for a minimally invasive surgical approach is given (cT1–3, cN0–1), lobectomy should be performed minimally invasive, uniportally or multiportally video-assisted (uniportal or multiportal VATS lobectomy). This is now the standard procedure for stage I tumours and is associated with less postoperative morbidity and physical impairment [127]. For tumours ≤2 cm in diameter, anatomical segment resection is an alternative to lobectomy. Currently, data are available from the Japanese JCOG0802 trial, in which n = 1106 stage IA patients were randomly assigned

to lobectomy or anatomical segment resection [128]. The 5-year survival rate without recurrence was not different between the two groups, 87.9% and 88.0%, respectively. However, the 5-year survival rate showed a significant advantage in favour of segment resection (94.3% versus 91.1%). This advantage was primarily due to lower mortality from second malignancies and a higher rate of curative therapy for second malignancies in the segmental group. In both groups combined, 4.9% of patients died from their primary lung cancer and 7.8% from another cause of death, primarily second malignancy, during the observation period (median 7.3 years) [128]. For central tumour location, the larger resection extents of pneumonectomy or the more technically challenging but parenchyma-sparing sleeve resections are available. The mortality after pneumonectomy is two to three times higher than after lobectomy, due in part to the greater loss of lung parenchyma and the associated burden on the right heart. The goal of complete removal of the hilar and mediastinal lymph nodes during tumour surgery is to improve prognosis by accurately determining tumour stage (N status) as a basis for stage-appropriate postoperative therapy. There is no evidence of increased postoperative morbidity or mortality associated with radical mediastinal lymphadenectomy. Even in PET-negative mediastinum, systematic intraoperative lymph node dissection reveals tumour-involved lymph nodes in 10–16%, depending on tumour location and size [129].

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest**.** MFC reports grants from CSL Behring and consulting fees from Boehringer Ingelheim, MSD, Pfizer, GSK, Syndax and AstraZeneca, all paid to her institution. The other authors did not disclose any potential conflicts of interest related to the content of this manuscript.

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