Review Article

From diagnosis to therapy in lung cancer: management of CT detected pulmonary nodules, a summary of the 2015 Chinese-German Lung Cancer Expert Panel

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Abstract: The first Chinese-German Lung Cancer Expert Panel was held in November 2015 one day after the 7th Chinese-German Lung Cancer Forum, Shanghai. The intention of the meeting was to discuss strategies for the diagnosis and treatment of lung cancer within the context of lung cancer screening. Improved risk classification criteria and novel imaging approaches for screening populations are highly required as more than half of lung cancer cases are false positive during the initial screening round if the National Lung Screening Trial (NLST) demographic criteria [≥30 pack years (PY) of cigarettes, age ≥55 years] are applied. Moreover, if the NLST criteria are applied to the Chinese population a high number of lung cancer patients are not diagnosed due to non-smoking related risk factors in China. The primary goal in the evaluation of pulmonary nodules (PN) is to determine whether they are malignant or benign. Volumetric based screening concepts such as investigated in the Dutch-Belgian randomized lung cancer screening trial (NELSON) seem to achieve higher specificity. Chest CT is the best imaging technique to identify the origin and location of the nodule since 20% of suspected PN found on chest X-ray turn out to be non-pulmonary lesions. Moreover, novel state-of-the-art CT systems can reduce the radiation dose for lung cancer screening acquisitions down to a level of 0.1 mSv with improved image quality to novel reconstruction techniques and thus reduce concerns related to chest CT as the primary screening technology. The aim of the first part of

this manuscript was to summarize the current status of novel diagnostic techniques used for lung cancer screening and minimally invasive treatment techniques for progressive PNs that were discussed during the first Chinese-German Lung Cancer. This part should serve as an educational part for the readership of the techniques that were discussed during the Expert Panel. The second part summarizes the consensus recommendations that were interdisciplinary discussed by the Expert Panel.

Keywords: Lung cancer; modern imaging; molecular markers; screening, minimally-invasive therapy; response assessment; pulmonary nodules (PN)

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Introduction

Outside of screening environments, the majority of lung cancer patients are still detected with advanced disease. The 5-year overall survival (OS) rate of this group of lung cancer patients is still poor despite various improvements in lung cancer therapy in the recent years. As a potential to substantially impact on the overall prognosis of lung cancer patients, recent data from lung cancer screening trials using low dose computed tomography (LDCT) clearly demonstrated a significant reduction of lung cancer related mortality mainly due to detection of lung cancer at earlier stages. Consequently, lung cancer screening with LDCT is now recommended in at risk populations in the United States. However, even though proven to be effective to reduce lung cancer mortality, LDCT as originally applied in NLST is hampered by a high rate of false positive findings, overdiagnosis and high costs. Moreover, improved risk classification criteria for non US or European screening populations are needed since approximately more than half of lung cancer cases are missed if NLST criteria [≥30 pack years (PY), age ≥55 years] are applied to the Chinese population mainly due to non-smoking related risk factors.

Screening

Since effective lung cancer screening requires repetitive CT scans usually on an annual basis radiation dose reduction is critical for screening applications to avoid the induction of screening related malignancies new state-of-the-art CT systems equipped with the latest dose reduction technologies including optimized iterative reconstruction algorithms as well as spectral shaping with dedicated filters allow high quality chest CT acquisitions with radiation dose levels around 0.1 mSv. Beside dose reduction, more effective screening is mainly dependent of the measurement techniques of pulmonary nodules (PN) as well as follow-up strategies. Within this context, volumetry based screening concepts such as investigated in the NELSON trial seem to achieve higher specificity compared to data as recently published in NLST.

Treatment of progressive PNs

For fifteen to twenty percent of stage T2 or T3N0M0 (<5 cm) non-small cell lung cancers (NSCLC) with or without pleural involvement, surgery remains the reference standard treatment. In case surgery is not possible, such as patients with poor pulmonary function, poor performance status, significant medical comorbidities, or patients' refusal of ordinary surgery, minimally-invasive therapy techniques like radiofrequency ablation (RFA), microwave ablation (MWA) of recently introduced irreversible electroporation (IRE) are more frequently considered in progressive PNs using screening as well as in patients with of oligo-metastatic disease, where the patient had progressive disease in some of the nodules, while the rest has successfully been treated by a systemic treatment.

Response assessment

Tumor response assessment in lung cancer patients undergoing targeted therapies, stereotactic body radiation therapy (SBRT) or non-surgical minimally invasive approaches require new strategies beyond RECIST and WHO criteria that are solely based on changes in tumor size. Yet a growing number of literature' suggests that the currently used objective criteria for progression may not always indicate clinical treatment failure and does not adequately determine disease biology, with the implication of potentially limiting their value in clinical trial analysis.

Therefore, these criteria represent pivotal determinants to the efficacy assessment for novel targeted therapies.

The motivation to organize this *German Chinese Lung Cancer Expert Panel* was the perception about an existing 'region gap' between German and China regarding different patient populations especially with respect to gender, smoking habit, and different environment influences. The *Expert Panel* entitled '*From diagnosis to therapy in lung cancer: Management of CT detective methods and pulmonary nodules*' was held on November 13–14, 2015, in Shanghai, China one day after the '*7th CGLCF 2015*'. The *Expert Panel* was divided into two main sessions. In the first educational part, invited imaging experts summarized the current scientific evidence on novel imaging techniques and the potential advantages and disadvantages for using these techniques in upcoming clinical trials and general clinical practice. In the second part, all invited multi-disciplinary experts discussed the value and the applicability of novel imaging and treatment techniques for various clinical scenarios. Accordingly, this article comprises two parts: a short review of the relevant subject areas followed by the recommendations of the Expert Panel.

Educational part

Lung cancer screening

Role of LDCT screening approaches

Driven by the well-known inverse relationship between stage and survival in lung cancer patients a variety of lung cancer screening and early detection approaches have been explored until today.

Opening new opportunities, the US National Lung Screening Trial (NLST) demonstrated for the first time a 20% reduction in lung cancer related mortality by screening for lung cancer using LDCT compared to chest X-ray. Screening population comprised of selected high risk individuals aged 50 and older and heavy ever smokers with more than 30 PY. The proven efficacy of the CT based screening approach prompted the US preventive services task force to recommend an annual lung screening program for high risk individuals effective from January 2015.

Despite the obvious success there may also be potential adverse outcomes in terms of high false positive rate, overdiagnosis (detection of cancer that would never have become symptomatic), bias and cost-effectiveness concerns. Following the recommendation of the Fleischner Society, all noncalcified nodules measuring at least 4 mm in any diameter were considered positive in NLST resulting ultimately in more 95% false positive cases. This triggered a controversial discussion about the potential harms of lung cancer screening and resulted in several suggestions to improve specificity such as increasing the threshold of positivity to 6 mm in diameter. Beside changes in unidimensional diameter other approaches such volumetry based lung cancer screening concepts are currently under clinical research, particular in Europe.

First reports from the NELSON lung cancer screening trial using volumetric nodule measurements yielded high specificity and sensitivity, with only a small number of interval cancers. The results of this study could be used to improve screening algorithms, and reduce the number of missed cancers. Small nodules (those with a volume <100 mm^3 or diameter <5 mm) are not predictive for lung cancer. Immediate diagnostic evaluation is necessary for large nodules (≥300 mm^3 or ≥10 mm). Volume doubling time assessment is advocated only for intermediate-sized nodules (with a volume ranging between 100–300 mm^3 or diameter of 5–10 mm). Nodule management protocols based on these thresholds performed better than the simulated ACCP nodule protocol (1). Overall, the diagnostic strategy in NELSON trial led to considerably less false-positive referrals compared to other lung cancer screening trials, with very high negative predictive values found in the first and second screening rounds. Mortality results are still pending, but the knowledge already gained in the NELSON trial and its side-studies provide valuable information in the field of screening for lung cancer (1,2).

Based on currently applied rigid inclusion criteria for lung cancer screening in the United States, it is estimated that up to 50% of all lung cancer cases will be missed (3). This clearly indicates an urgent need for improved selection criteria to possibility extend screening to additional segments at risk of the entire population.

Beside the need for a higher specificity of screening approaches an improved CT hardware with reduced radiation dose is of outmost importance. Dose reduction matters, particular if repeated CTs are performed like in lung cancer screening (4). Several lines of evidence indicate that radiation doses for CT imaging lead to increased cancer risk, even at higher age. For example the BEIR VII (Biological Effects of Ionizing Radiation) assumes a linear no threshold correlation between radiation dose and cancer risk in medical imaging. This issue has been rigorously addressed by several radiation dose reduction advances in CT scanner technology (5). Haubenreiser *et al.*

prospectively investigated image quality and radiation dose of 100 kVp spectral shaping chest CT using a dedicated tin filter on a 3rd generation dual-source CT (DSCT) in comparison to standard 100 kVp chest CT (6). The results of this study demonstrate that 100 kVp spectral shaping chest CT allows 90% dose reduction when compared to 100 kVp chest CT without spectral shaping.

Summary

- Lung cancer screening with LDCT is effective to significantly reduce lung cancer mortality but is still hampered by a high rate of false positive findings, overdiagnosis and not neglecting costs;
- Improved risk classification criteria for screening populations are needed as more than half of lung cancer cases are missed if NLST criteria (≥30 PY, age ≥55 years) are applied;
- Radiation dose reduction is crucial for screening applications. New generation CT systems work with radiation doses down to 0.1 mSv for LDCT of the chest and are helpful tools in screening;
- Volumetric based screening concepts such as investigated in the NELSON trial seem to achieve higher specificity.

Role of biomarkers

Early detection of lung cancer can be achieved by analysis of biomarkers from tissue samples within the respiratory tract such as sputum, saliva, nasal/bronchial airway epithelial cells and exhaled breath condensate or through peripheral biofluids such as blood, serum and urine (7). Autofluorescence bronchoscopy has been employed in research setting to identify pre-invasive lesions not identified on CT scan. Although most of these modalities are not yet commercially available in clinic setting, they will be available in the near future and clinicians who care for patients with lung cancer should be aware. As non-invasive screening test causing no discomfort to participants the use of volatile organic compounds as biomarker for lung cancer has been subject to intensive research within the last years. As reported by Fu *et al.*, the concentrations of 2-butanone, 2-hydroxyacetaldehyde, 3-hydroxy-2-butanone, and 4-hydroxyhexenal (4-HHE) in the exhaled breath of lung cancer patients (n=97) were significantly higher than in the exhaled breath of healthy smoker and nonsmoker controls (n=88) and patients with benign PNs (n=32). The concentration of 2-butanone in exhaled breath of patients (n=51) with stages II though IV NSCLC was significantly higher than in exhaled breath of patients with stage I (n=34). The carbonyl and volatile organic compounds profile in exhaled breath determined using this new silicon microreactor technology provides for the noninvasive detection of lung cancer (8,9).

Exhaled breath analysis in lung cancer patients reaches in small to midsized discovery trials sensitivities and specificities up to ≥90%. However large scale trials in a true screening environment are still missing.

Gas chromatography with mass spectroscopy is currently the most widely used technique but new sensor technology will allow the development of point of care testing. Once more broadly available and standardized, the combination of exhaled breath testing with imaging in terms of an integrated screening approach seems a promising expansion strategy of screening to reach a broader population. Albeit lung cancer is the current research & development focus further malignancies but also inflammatory diseases such as COPD or Asthma are candidates (10).

Summary

Novel biomarkers could aid in early detection and refine risk classification of individuals within screening programs. Volatile organic compounds have significant potential for early cancer detection. However, large scale clinical trials in a true screening setting are still missing.

Minimally-invasive therapy in lung cancer

The method of percutaneous ablation essentially incorporates two methods: thermal and non-thermal therapy. RFA has been established as an effective and often used thermal therapy for treatment of primary lung cancer. MWA as an alternative to RFA, has some principal advantages for lung ablation, such as less severe heat sink effect and a faster and higher heating.

Beland *et al.* reported in 2010 that 57% of the patients under RFA have a median disease-free survival of 23 months (11). This was confirmed by Lanuti *et al.* analyzing long-term results of RFA for inoperable early-stage lung cancers (12). Mean maximum diameter of the 38 treated tumors was 2.0±1.0 cm (range, 0.8–4.4 cm). Median OS was 30 months and 2- and 4-year survival rates were 78% and 47%, respectively.

Bi *et al.* compared the effectiveness of RFA with SBRT in inoperable stage I NSCLC (13). The local control rate (LCR) for SBRT is significantly higher than that for RFA; 3-year LCR was 55% *vs.* 88%, though OS is not different between the two groups.

A phase II study performed by Higuchi *et al.* confirmed the effectiveness of RFA for unresectable primary and secondary thoracic malignancies. [18F]Fluorodeoxyglucose

(FDG)-PET analysis, 3–6 months after ablation, is a useful tool to assess LCR (14). Percutaneous ablation of small cell lung cancer (SCLC) and NSCLC has been demonstrated to be both, feasible and safe in nonsurgical candidates. RFA, the most commonly used technique for ablation, has a reported rate of complete ablation of ~90%, with best results obtained in tumors <2 to 3 cm in diameter. The best reported 1-, 3-, and 5-year OS rates after RFA of NSCLC are 97.7%, 72.9%, and 55.7%, respectively. Since RFA in NSCLC is a method used often for the unfit, in most studies cancer-specific survival is greater than OS due to severe comorbidities in patients. Aside from tumor size and stage, these comorbidities are predictors for survival (15).

To summarize recent publications on RFA of NSCLC: the indication includes mostly 1–2 lesions of <2 cm in diameter; slow growing disease; there is no detection of recurrence possible with standard CT before 6 months follow-up (16) and by PET after 3 months (17); frequently false positive lymph nodes (LN) after RFA (reaction to treatment, disappear after 6 months, also possible for needle tract).

MWA versus RFA

Today, MWA is a standard and routine ablation method for inoperable tumors. The reason is that the extent of MWA zones was not significantly different among completely different tissues, such as liver, adipose tissues, and muscles (18). MWA with ≥5 minutes' time duration can induce coagulation zones with clinical relevant shape. However, future clinical studies are still required to determine the role of MWA in different tissues. MWA create larger ablations than RFA if controlled for power in *ex vivo* tissue. For RFA complete ablation was in 78–96% in tumors <2 cm, but however, in tumors >2 cm there was seen a shorter PFS and a high recurrence rate. Using MWA has the advantage that if the tumor <5 cm, complete ablation resulted in 95% of patients (18-21).

Planché *et al.* (*Cardiovascular and Interventional Radiology* 2013) found that larger tumor size and the use of an internally cooled electrode were independent risk factors for local progression after RFA of lung tumors. In a recent paper it was shown that MWA has less heat sink effect: in models a single MWA antenna can create ablation zones large enough to cover lung tumor of <4 cm diameter with no heat sink effect for vessels up to 6 mm (22). In clinical practice the advantage of the method MWA lies in faster reaching therapeutic temperatures, applicable higher temperatures, and faster ablation.

But MWA also has some possible complications as pneumothorax, hematoma, bronchopleural fistula, missed ablation of the needle track, injury of different structures, bronchi, pericardium vessels (skin burn) among others.

A paper published in *Translational Lung Cancer Research* showed similar effect of lobectomy or sub lobar resection in comparison to SBRT, RFA, and MWA (23). Thus, if patients cannot benefit from surgery, then RFA and MWA can be an alternative treatment choice. Still these new treatments have not enough support in evidence by clinical trials; hence, their optimal role has not yet been determined. Treatment recommendations should be given at an individualized level, based primarily on the size and location of the tumor, the patient's age, comorbidities, and performance status, and the strength of the available evidence.

IRE

IRE as described by Neumann in 1982 is based on short, pulsed electric fields and can increase permeability of cell membrane. The theory of "pore formation" can be described as electroporation (24). Applications of electroporation were used first for water sterilization for industrial use to eliminate microorganisms. It is now being used as IRE for tumor therapy (25,26). The advantages of IRE for tumor ablation comprises the following facts: non-thermal, short, pulsed electric fields; nanometer-sized pores in phospholipid layer; disturbance of homoeostasis; induction of apoptosis; tissue selectivity, no thermal damage (which means extracellular matrix/fibrous structures remain intact as bile ducts, vascular structures, renal pelvis); sharp ablation margins; no heat sink effects; "short ablation times" (minutes); and peri-interventional delineation [CT, ultrasound, magnetic resonance imaging (MRI)]. Disadvantages of IRE are small ablation areas; use of multiple needles; muscle contractions caused by direct excitation of motor end plate, which will often apply general anesthesia for relaxation; and cardiac arrhythmias can happen also. There are no long term results and no randomized studies yet available. IRE had shown some beneficial survival data in the treatment of pancreatic tumors (27).

Technical obstacles using IRE in lung cancer are the facts that electrodes may be have closed contact to surrounding solid tissue and in comparison with the target tissue showing relative homogenous conductivity. The main reason why IRE is challenging in lung is that air filled pulmonary alveoli are a strong isolator. So a phase II trial on lung malignancies did not show a survival benefit using IRE. But it should notice that patient selection may encumber better result for IRE treatment (28).

Functional imaging for response assessment to targeted therapies in lung cancer

Tumor response assessment in patients undergoing targeted therapies requires new strategies beyond RECIST and WHO criteria, which always used size to evaluate response. Although Herbst *et al.* found 65% stable disease (SD) and 20% partial remission (PR) in erlotinib plus bevacizumab treated group, anti-angiogenetic drug can cause central necrosis and cavitation, which suggested that size is a poor criterion for response (29). Yet a growing number of literature suggests that our current objective criteria for progression may not always indicate treatment failure and do not adequately capture disease biology, potentially limiting their value in clinical trial analysis (30). Thus, they proposed for upcoming trials a "personalized' tumor response assessment by applying cancer- and therapy-specific criteria to correct pitfalls of conventional criteria (31). Therefore, these criteria represent a critically important contribution to the assessment of efficacy by novel targeted therapies, allowing the radiology community to be part of personalized cancer care in the era of molecular medicine. Response patterns in different treatment scenarios are various, such as chemotherapy, anti-angiogenetic therapy and immunotherapy.

Thus, Zhao *et al.* found that compared with the uni- and bi-dimensional techniques, semi-automated tumor segmentation enables the identification of a larger number of patients with absolute changes in tumor volume of at least 20% and 30% (32). Volumetric measurements more accurately predict PR in patients with lung cancer. However, inter-observer reproducibility of semi-automatic tumor diameter measurement and volumetric analysis in patients with lung cancer exist, by using computer-assisted size assessment in primary lung tumor, inter-observer variability can be reduced to about half to one-third compared to standard manual measurements (33). Hence, Lee *et al.* evaluated new response criteria in patients treated with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) compared with RECIST, and proposed new criteria for a more accurate response assessment in patients with NSCLC undergoing EGFR-TKI therapy (34). In this study, a decrease of tumor attenuation in Hounsfield units was an accurate marker of therapy response even in tumors with a less than 30% decrease in maximum size. The decrease in tumor attenuation was caused by the high incidence of tumor cavitation after EGFR-TKI therapy as a surrogate of central tumor necrosis. This sign of therapy response was not observed in patients undergoing standard chemotherapy. By applying these criteria, patients classified as responders showed a higher median OS (18.4 months) than patients with poor response (8.5 months). In contrast, RECIST criteria were negative in 16 patients that achieved response according to the new criteria (35).

Early FDG PET-CT after the start of erlotinib treatment identified patients who benefited from this targeted therapy (36). Thirty-four patients with untreated stage IV NSCLC were evaluated in this phase II trial. Changes in FDG and FLT uptake after 1 (early) and 6 (late) weeks of erlotinib treatment were compared with non-progression measured by computed tomography after 6 weeks of treatment, progression-free survival (PFS), and OS. Results showed early FDG-PET predicts PFS, OS, and non-progression after 6 weeks of therapy with erlotinib in unselected, previously untreated patients with advanced NSCLC independent from *EGFR* mutational status (37). PET-CT detected early recurrence in 24% of patients after radical radiotherapy with or without chemotherapy. 3% of recurrences were detected in asymptomatic patients who underwent potential curative treatment (38).

Dynamic contrast-enhanced CT (DCE-CT): volume perfusion CT

Tumor angiogenesis leads to an increase of regional blood flow (BF) and blood volume (BV) and, thereby, contrast-enhancement of lung cancer tissue. Tumor perfusion and therapy-induced perfusion changes can be quantified by DCE-CT, i.e., it can assess tumor density at different times, based on consecutive CT scans that are acquired after the injection of contrast material. The technique provides quantitative data of tumor BF, BV, permeability, and the mean transit time (MTT) of iodinated contrast material through the tumor. NSCLC with higher perfusion is more sensitive to chemo-radiation therapy than that with lower perfusion (39). After chemo-radiation therapy, findings at perfusion CT can act as a significant predictor of early tumor response and OS among NSCLC patients. CT-perfusion can adequately evaluate therapy-induced alterations in NSCLC, and perfusion parameters correlate with therapy response assessment performed with RECIST criteria (40). Evaluating perfusion parameters, CT-perfusion can demonstrate therapy-induced changes in patients with different types of lung cancer and identify response to treatment with excellent agreement to RECIST measurements. Their results showed that some therapy-induced changes could be anticipated on the basis of CT-perfusion parameters of the lesions at baseline examinations. In particular, baseline values of BF, BV and time to progression (TTP) were different among PR,

PD and SD patients.

Dual-energy CT (DECT)

DECT is selective iodine quantification as a marker of tumor BV. Kim *et al.* evaluated tumor responses to anti-angiogenic therapy and compared with the baseline CT results using both RECIST (size changes only) and Choi's criteria (reflecting net tumor enhancement). They found DECT may serve as a useful tool for response evaluation after anti-angiogenic treatment in NSCLC patients by providing information on the net enhancement of target lesions without obtaining non-enhanced images (41). To investigate the correlation between maximum standardized uptake value (SUVmax) of FDG PET-CT and iodine-related attenuation (IRA) of DECT of primary tumors and FDG PET-CT positive thoracic LN in patients with lung cancer. A strong correlation was found in patients with study intervals ≤21 days (n=17; r=0.768; P=0.017). Analysis of histological subtypes of lung cancer showed a strong correlation between SUVmax and maximum IRA in the analysis of all patients with NSCLC (r=0.785; P=0.001) and in patients with NSCLC and study intervals ≤21 days (r=0.876; P=0.024). DECT could serve as a valuable functional imaging test for patients with NSCLC as the IRA of DECT correlates with SUVmax of FDG PET-CT (42).

Thus, DECT seems to be an attractive and cost-effective method to monitor response to treatment in patients undergoing anti-angiogenic therapies although one has to acknowledge that based on the currently available evidence, the technique is still not "ready for prime time" to replace RECIST of WHO criteria in prospective clinical trials.

Diffusion weighted MRI (DW-MRI)

DW-MRI is a tool for the accurate staging of mediastinal LN and the evaluation of tumor response during therapy. DW-MRI visualizes the microscopic movement of water molecules within tissues and has been proposed for the differentiation between benign and malignant LN's. In metastatic LN's, diffusion is limited due to the obstruction of LN by tumor cells. Therefore, metastatic LN's have significantly lower apparent diffusion coefficient (ADC) values than those of the benign LN's. Nomori *et al.* directly compared the accuracy of DWI-MRI and FDG PET-CT for determining nodule category in patients with NSCLC and compared the results of both modalities to those, of histopathological examination (43). Among 734 analyzed LN stations, histopathology revealed 36 metastatic and 698 non-metastatic LN's. There was no significant difference between DW-MRI and FDG PET-CT in the detection of metastatic LN stations. However, DW-MRI was more accurate than FDG PET-CT in the identification of non-metastatic LN stations because of the lower rate of false-positive results (43,44).

Expert Panel Consensus (EPC)

EPC: general comments

After the summary of diagnosis and management of CT detected size progressive PNs, it became clear that there is a need for interdisciplinary interaction on imaging and treatment due to the given region gap between China and Germany in clinically useful measures and required radiology research, as well as among clinicians about the ongoing developments and opportunities in imaging. All participants agreed that the communication between radiologists and clinicians has to be improved in terms of quantity and quality. Moreover, the communication between Germany and China on ongoing developments and their potential applications in clinical trials should be formalized and accelerated. There was also a general consensus about the requirement for more integrative access of Chinese and German lung cancer specialists for the planning of clinical trials. This should ensure that the most appropriate imaging methods are applied and will be further validated in upcoming clinical trials investigating targeted therapies.

Overall, it was considered essential that in the era of molecular oncology the radiology and oncology community should get more actively involved in clinical trials and patient care.

EPC: lung cancer screening

The US NLST demonstrated a 20% reduction in lung cancer mortality and a 6.7% decrease in all-cause mortality. The NLST is the only trial showing positive results in a high-risk population, such as in patients with old age and in heavy (ever) smokers. Lung cancer screening using a low-dose chest CT might be beneficial for the high-risk group. However, there may also be potential of adverse outcomes in terms of high false positive rates, over diagnoses, bias and cost-effectiveness. Based on currently applied rigid inclusion criteria for lung cancer screening up to 50% of all cases will be missed. There is a need for higher specificity of screening and an improved CT hardware with a reduced radiation dose. Also, there is an urgent need to improved selection criteria

and the possibility for an extension of screening population. Dose reduction matters, particular if repeated CTs are performed like in lung cancer screening. Typical radiation doses for CT imaging lead to increased cancer risk, even at a higher age. Obviously a correlation between radiation dose and cancer risk is seen Radiation dose reduction by advances in CT scanner technology is mandatory. Nensa *et al.* posted on ECR 2013 have shown that with different CT devices, such as Gated-helix or flash-helix, a dose reduction for CT coronary angiograms of about 90% can be realized.

EPC

PET-CT, dynamic contrast enhanced CT as well as DECT might be useful tools to better characterize detected solitary PN's. Further research is necessary to define thresholds and standardize procedures. Novel biomarkers could aid in early detection and refine risk classification of individuals within screening programs. Volatile organic compounds have significant potential for early cancer detection. However, large scale clinical trials in a real screening setting are still warranted. The panel also suggests considering the difference between China and Germany, in terms of different smoking habits, occupational exposures, infections, driver gene mutation rates, and gender. High risk of non-smoker lung cancer: the panel discussed that there is no current evidence that would support an ideal risk population. However, there is consensus that the screening population in China is different due to the air and indoor pollution, and different EGFR mutation rates. Thus, the panel encourages studies which will investigate concurrent specific population for China. The following questions should be addressed: 'Can we promote screening combined with smoking cession? What is the status of Germany or China?' The panel is aware of the fact that there is an increasing number of female smokers seen nowadays in lung cancer. The panel also suggests being careful about smoking cessation program, as more and more non-smokers were detected to be lung cancer patients.

EPC: PNs

CT is an important tool in the evaluation of solitary and multiple PN. There is a wide variety of PN's, which represents a diagnostic challenge. The primary goal in the evaluation of these nodules is to determine whether they are malignant or benign. Chest CT is the best imaging technique to identify the origin and location of the nodule as 20% of 'nodules' found on chest X-ray turn out to be non-pulmonary when imaged with another technique.

EPC

CT scans of 1 mm images are important to show the PNs. Most small solid nodules found incidentally in lung cancer screening are intrapulmonary LN's. Further development of new technologies and improvement of currently available methods of less and noninvasive methods of diagnosis are the key components of the never-ending process of refinement of our ability to accurately determine the etiology of LN's.

Future research is required to study the role of biological and biochemical markers in the diagnosis of small LN's, as well as to determine potential new therapeutic strategies for malignant LN's, such as therapies targeting signal pathways, angiogenesis, immunotherapy, and cryotherapy.

EPC: DCE-CT

Tumor angiogenesis leads to an increase of regional BF and BV and, thereby, contrast enhancement of lung cancer tissue. Tumor perfusion and therapy-induced perfusion changes can be quantified by DCE-CT. DCE-CT can assess tumor density at different times, based on consecutive CT scans that are acquired after the injection of contrast material. The technique provides quantitative data of tumor BF, BV, permeability, and MTT of iodinated contrast material through the tumor. NSCLC with higher perfusion is more sensitive to chemo-radiation therapy than that with lower perfusion. After chemo-radiation therapy, findings at perfusion CT are a significant predictor of early tumor response and OS among patients with NSCLC. CT-perfusion can adequately evaluate therapy induced alterations in NSCLC, and perfusion parameters correlate with therapy response assessment performed with RECIST criteria.

Recommendations

Evaluating perfusion parameters, CT-perfusion can demonstrate therapy-induced changes in patients with different types of lung cancer and identify response to treatment with excellent agreement to RECIST measurements.

EPC: DECT

DECT is selective for iodine quantification as a marker of tumor BV. Yoo Na Kim *et al.* evaluated tumor responses to anti-angiogenic therapy and compared with the baseline CT results using both RECIST (size changes only) and Choi's criteria (reflecting net tumor enhancement). They found

DECT may serve as a useful tool for response evaluation after anti-angiogenic treatment in NSCLC patients by providing information on the net enhancement of target lesions without obtaining non-enhanced images. To investigate the correlation between SUVmax of FDG PET-CT and IRA of DECT of primary tumors and FDG PET-CT positive thoracic LN's in patients with lung cancer. A strong correlation was found in patients with study intervals ≤21 days (n=17; r=0.768; P=0.017). Analysis of histological subtypes of lung cancer showed a strong correlation between SUVmax and maximum IRA in the analysis of all patients with NSCLC (r=0.785; P=0.001) and in patients with NSCLC and study intervals ≤21 days (r=0.876; P=0.024). DECT could serve as a valuable functional imaging test for patients with NSCLC as the IRA of DECT correlates with SUVmax of FDG PET-CT.

EPC

DCE-CT seems to be an attractive and cost-effective method to monitor response to treatment in patients undergoing anti-angiogenic therapies although one has to acknowledge, that based on the currently available evidence, the technique is still not "ready for prime time" to replace RECIST of WHO criteria in prospective clinical trials.

EPC: DW-MRI

DW-MRI is a tool for accurate staging of mediastinal LNs and the evaluation of tumor response during therapy. DW-MRI visualizes the microscopic movement of water molecules within tissues and has been proposed for the differentiation between benign and malignant LN's. In metastatic LN's, diffusion is limited due to the obstruction of LN's by tumor cells. Therefore, metastatic LN's have significantly lower ADC values than that of the benign LN's. Nomori *et al.* directly compared the accuracy of DWI-MRI and FDG PET-CT for determining nodule category in patients with NSCLC and compared the results of both modalities to those, of histopathological examination. Among 734 analyzed LN stations, histopathology revealed 36 metastatic and 698 non-metastatic LN's. There was no significant difference between DW-MRI and FDG PET-CT in the detection of metastatic LN stations.

EPC

DW-MRI was more accurate than FDG PET-CT in the identification of non-metastatic LN stations because of the lower rate of false-positive results.

Can we improve of lung cancer screening by an integrated (biomarker plus imaging) approach?

Rational lines at refine selection of high risk patients for LDCT screening to increase pre-test probability, and better preselection would ultimately allow the expansion of screening programs beyond groups matching NLST criteria. Test requirements should be as follows: Sufficient high statistical power; ready availability; ease of use; non-invasive with high acceptance rate; cost-effectiveness. Exhaled breath analysis in lung cancer patients reaches in small to midsized discovery trials sensitivities and specificities up to ≥90%. Large scale trials in a real screening environment are still missing. Gas chromatography with mass spectroscopy is currently the most widely used technique. New sensor technology will allow the development of point of care testing. Combination of exhaled breath testing with imaging in terms of an integrated screening approach is promising. Albeit lung cancer is the current research and development focus further malignancies but also inflammatory diseases such as COPD or Asthma are candidates.

EPC

It is recommended that data of a large patient number should be collected. With reduction in lung cancer related mortality of 20% LDCT lung cancer screening (NLST) proved its effectiveness but is compromised by a high rate of false positives, over diagnoses and costs. Improved risk classification criteria for screening populations are needed as more than half of lung cancer cases are missed if NLST criteria (≥30 PY, age ≥55 years) are applied. There is a need for higher specificity of screening and improved CT hardware with reduced doses. Therefore, advanced methods for effectively perform lung cancer screening are clinically needed.

EPC: RFA

RFA has been increasingly reported in the literature as an effective therapy for treatment of primary lung cancer. RFA is becoming an accepted treatment for primary NSCLC in patients who are not candidates for sub-segmental resection or lobectomy. The role of RFA and other percutaneous ablative therapies has still to be established, either as a stand-alone therapy or in combination with other modalities such as radiation therapy. RFA is safe and feasible for the treatment of unresectable stage I lung cancer. Limitations of this technology for solid tumor ablation in the lung

are tumor size and proximity to blood vessels. The major advantages of RFA therapy for the treatment of medically unresectable stage I NSCLC are low morbidity, single application, reduced hospital stay, and well-defined zones of tissue destruction. In contrast, conventional radiotherapy and stereotactic radiotherapy require multiple treatments and are often associated with pneumonitis, bronchial stenosis, esophagitis, and complications of fiducial markers.

EPC

It was agreed in the discussion that whenever possible, RFA should be implemented in those NSCLC patients where surgery and SBRT cannot be tolerated in case of 1–2 lesions, size <2 cm, and slow growing disease. There is no detection of recurrence possible with standard CT before 6 months follow-up, by PET after 3 months, to identify frequently false positive relapse after RFA. However, caution is warranted due to the relatively limited number of RFA studies.

EPC: RFA versus MWA

A thermal ablation technique in which microwave energy is used provides all of the benefits of RFA and some substantial advantages. Preliminary work in this field shows that MWA may be effective for treating solid neoplasms in the lung. Possible benefits of MVA include consistently higher intra-tumor temperatures, an improved convection profile, the capability of using multiple applicators, larger tumor ablation volumes, and no need for grounding pads. However, there is no known literature for lung tumor RFA using these devices. Microwave technology allows multiple applicator techniques to be used during a single ablation treatment, each powered by an individual microwave generator.

EPC

RFA can be used to treat small, localized tumor, which keep distance to structures at risk, and have a promising results in 2 years OS with lesions <2 cm. MWA technique is less effected by heat sink, and can be used at larger tumors than with RFA, but is not yet common in applied studies.

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Footnote

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