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Lung cancer screening with MRI: Evaluation of MRI for lung cancer screening by comparison of LDCT- and MRI-derived Lung-RADS categories in the first two screening rounds

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Abstract

Purpose To evaluate MRI for lung cancer screening comparing LDCT- and MRI-derived Lung-RADS categories in the first two screening rounds.

Materials and methods 224 participants in a lung cancer screening study were examined with MRI and low-dose CT (LDCT). Acquired MRI sequences were T2, balanced, T1 and DWI. MRI was prospectively analysed regarding nodules. Minimum nodule size was 4 mm. Nodules were assigned a Lung-RADS score based on appearance and size at baseline and after 3, 6 and 12 months. MRI findings were correlated with LDCT.

Results The early recall rate dropped from 13.8% at baseline to 1.9% in the second screening round with biopsy rates of 3.6% in the first round and 0.5% in the second round. Histology revealed lung cancer in 8/9 participants undergoing biopsy/surgery. All eight cancers were accurately depicted by MRI. The following categories were assigned on MRI (results of LDCT in parentheses): 4B/4X in 10 (10) cases, 4A in 16 (15) cases, 3 in 13 (12) cases, 2 in 77 (92) cases and 1 in 140 (126) cases. Lung-RADS scoring correlated significantly between MRI and CT. The score was overestimated by MRI in one case for category 4A, in two cases for category 3 and in five cases for category 2. MRI-based Lung-RADS score was underestimated for category 1 in 20 cases.

Conclusion Lung-RADS might be applied for lung cancer screening with MRI, since findings correlated with LDCT. Relevant findings with a Lung-RADS score of 3 and higher were never missed or underestimated by MRI

Key Points

- *MRI performed comparably to low-dose CT in a lung cancer-screening programme.*
- *Lung-RADS might be applied for lung cancer screening with MRI.*
- *Lung-RADS findings score of 3 and higher were never missed by MRI.*

Keywords Magnetic resonance imaging · Multidetector computed tomography · Lung · Lung neoplasms · Early detection of cancer

Abbreviations

DWI	Diffusion-weighted imaging
LDCT	Low-dose computed tomography
Lung-RADS	Lung Screening Reporting and Data System
MVXD	MultiVane XD (Philips Healthcare, Best, The Netherlands)
NSCLC	Non-small cell lung cancer
SCLC	Small cell lung cancer
THRIVE T1	High Resolution Isotropic Volume Excitation (Philips Healthcare)

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Introduction

In 2011, the National Lung Screening Trial Research Team showed that annual screening with low-dose computed tomography (LDCT) can reduce lung cancer mortality by 20%

[1]. Four years later, the American College of Roentgenology (ACR) introduced the CT-based Lung Imaging Reporting and Data System (Lung-RADS) as a standardised classification for nodule assessment and subsequent management [2]. According to McKee et al, application of Lung-RADS increases the positive-predictive value without increasing false-negative results [3].

Magnetic resonance imaging (MRI) allows for radiation-free lung imaging, but it is still inferior to CT with regard to the assessment of small nodules. This is mainly due to susceptibility artefacts at air-tissue interfaces, low proton density of the lung parenchyma, or artefacts from respiratory and cardiovascular motion [4–6]. Nevertheless, growing knowledge and technical developments have made MRI a possible alternative to CT for lung cancer screening [7–9].

We evaluated MRI for lung cancer screening by comparison of LDCT- and MRI-derived Lung-RADS categories in the first two screening rounds.

Materials and methods

This prospective study was approved by the local institutional review board and by the German federal agency for radiation protection. Written informed consent was obtained from all participants.

A total of 233 consecutive participants took part in our lung cancer screening programme, but nine participants only obtained low-dose CT (LDCT) because of contraindications to MRI, eight of them because of claustrophobia and one because of a cochlear implant. A total of 224 participants (mean age 58.6 ± 5.7 years) were examined with MRI and LDCT for this study. Following the German lung cancer screening trial (LUSI), inclusion criteria were age 50–70 years as well as long-term nicotine abuse (at least 15 cigarettes per day for at least 25 years or at least 10 cigarettes per day for at least 30 years); participants were active smokers or had quit smoking for not more than 10 years previously [10].

MRI was performed at 1.5 T (Ingenia, Philips Healthcare, Best, The Netherlands) using a phased array body coil, head first and arms down. Acquired MRI sequences were transverse T2-weighted short tau inversion recovery (STIR) MultiVane XD (MVXD, Philips Healthcare), transverse and coronal T2-weighted MVXD, transverse balanced steady-state free precession (bSSFP), coronal 3D T1-weighted high-resolution isotropic volume excitation images (THRIVE, Philips Healthcare), and transverse diffusion-weighted images (DWI). For the scan protocol and technical data, see Table 1. Maximum MRI in-room time was 20 min.

LDCT was performed on a 128-slice spiral CT scanner (iCT, Philips Healthcare) in inspiratory breath-hold with a reconstructed slice thickness of 2 mm. MRI and LDCT were performed with a maximum of 1 week between the two examinations.

The LDCT scans were evaluated in the clinical routine by various readers, without knowledge of MRI findings and validated by a board-certified radiologist in all cases. MR images were prospectively viewed by two board-certified radiologists (Michael Meier-Schroers and Daniel Thomas) with experience of 6 years and 16 years, respectively. Both readers were unaware of the CT findings to eliminate a detection bias. MRI data sets were anonymised and randomly presented to the readers. All acquired MRI sequences were evaluated in synopsis.

In the first reading session, pulmonary nodules were prospectively assessed and categorised based on their appearance and size, following the recommendations of the Lung Imaging Reporting And Data System (Lung-RADS) [2]: solid nodules 4–5 mm, 6–7 mm, 8–14 mm or ≥ 15 mm, and sub-solid nodules < 20 mm or ≥ 20 mm. The

Table 1 Imaging parameters of the scan protocol

Parameter	tra T2 STIR MVXD	tra T2 MVXD	cor T2 MVXD	tra bSSFP	cor THRIVE	tra DWI
TR (ms) / TE (ms) / FA (°)	2,200–2,500 / 60 / 90	950–1,100 / 60 / 90	750–900 / 60 / 90	2.8 / 1.4 / 60	5.1 / 2.5 / 10	3,700–4,500 / 66 / 90
FOV (mm)	400	400	450	400	450	400
Matrix (mm)	432 x 432	432 x 432	432 x 432	432 x 432	432 x 432	352 x 352
Slice thickness (mm)	6	6	7	6	5	7
Parallel imaging	SENSE	SENSE	SENSE	SENSE	SENSE	SENSE
Partial Fourier	No	No	No	No	Yes	Yes
Gating	Respiratory	Respiratory	Respiratory	No	No	Respiratory
Breath-hold	No	No	No	Yes	Yes	No
Acquisition time (min)	03:18	03:18	03:54	4 x 0:13	00:16	00:56

tra transverse, *cor* coronal, *MVXD* MultiVane XD, *STIR* short tau inversion recovery, *bSSFP* balanced steady-state free precession, *THRIVE* T1 high resolution isotropic volume excitation, *DWI* diffusion-weighted imaging, *TR* time of repetition, *TE* echo time, *FA* flip angle, *FOV* field of view, *SENSE* sensitivity-encoded

minimum size of assessed nodules was 4 mm. Nodule size was defined as the average of the longest and shortest axial diameters rounded to the nearest whole number. Measurement was performed on the sequence that best displayed the nodule. Readers were asked to assign a Lung-RADS score ranging from 1 (no nodules or definitely benign nodules) to 4 (suspicious for lung cancer) for each MRI examination (Table 2). Nodules were assessed on baseline and follow-up examinations after 3, 6 and/or 12 months.

In the second reading session, MRI findings and MRI-based Lung-RADS scores were correlated with LDCT, which served as the reference imaging modality. This was done for baseline and follow-up examinations.

Both MRI and LDCT data sets were viewed on a professional medical monitor using IMPAX EE (AGFA Healthcare, Bonn, Germany).

Management followed the Lungs-RADS recommendation and was based on results of LDCT [2] (Table 2). Subjects with a Lung-RADS category ≥ 3 at baseline were scheduled for immediate recall or follow-up after 3 or 6 months (defined as early recall due to a positive screening result). Cases with Lung-RADS category 4A and 4B/4X were further discussed in an interdisciplinary conference with thoracic surgeons, pulmonologists and oncologists.

Statistical analysis was performed with SPSS 24 (IBM, Armonk, NY, USA). The Pearson coefficient was applied for correlations of nodule size as measured by MRI and LDCT, and the Spearman coefficient was applied for correlations of Lung-RADS scores between MRI and LDCT.

Table 2 Lung-RADS assessment categories (modified according to American College of Radiology [2])

Category		Findings	Management
1	Negative	No nodules Calcified or fat-containing nodules	Continue annual screening in 12 months
2	Benign appearance or behavior	*Solid:* < 6 mm Subsolid: < 20 mm at baseline *OR* ≥ 20 mm and unchanged or slowly growing	
3	Probably benign	*Solid:* ≥ 6 to < 8 mm at baseline *OR* new 4 to < 6 mm *Subsolid:* ≥ 20 mm at baseline or new	Follow-up in 6 months
4A	Suspicious	*Solid:* ≥ 8 to < 15 mm at baseline *OR* growing < 8 mm *OR* new 6 to < 8 mm	Follow-up in 3 months
4B		*Solid:* ≥ 15 mm *OR* new or growing ≥ 8 mm	CT with or without contrast, PET/CT and/or tissue sampling depending on probability of malignancy and co-morbidities
4X		Category 3 or 4 nodules with additional features or imaging findings that increase the suspicion of malignancy	

Results

The early recall rate of the first screening round was 13.0% based on LDCT (29 of 224 participants). Since the MRI findings did not have an actual impact on patient management, the virtual early recall rate of the first round was 13.8% for MRI (31 of 224 participants). In one case, a 6-mm nodule on MRI was actually a streaky opacity on LDCT and therefore erroneously diagnosed as a nodule (Lung-RADS category 1 on LDCT). In the other case, a 6-mm nodule was accurately depicted by MRI, but the presence of fat inside the nodule as a sign of benignancy (Lung-RADS category 1 on LDCT) could not be determined by MRI. Histology (biopsy or surgery) was obtained in eight of 224 cases; hence, the biopsy rate of LDCT was 3.6% at baseline. The virtual biopsy rate of MRI was equal to LDCT. Histology revealed lung cancer in all of these eight cases with seven non-small cell lung cancers (NSCLCs) and one small cell lung cancer (SCLC).

The early recall rate of LDCT and the virtual early recall rate of MRI dropped to 1.9% in the second screening round (four of 208 participants) with a biopsy rate and a virtual biopsy rate, respectively, of 0.5% (one of 208 participants). Histology of this one newly developed suspicious tumour of the second screening round revealed tuberculous granuloma.

The drop-out rate after the first screening round was 3.6% (eight of 224 participants); seven participants lost interest in the study, and one was diagnosed with melanoma. After the second screening round, one subject dropped out because of a diagnosis of breast cancer, so the dropout rate was 0.5% (one of 208).

Altogether, there were 141 different nodules with a minimum size of 4 mm on baseline and follow-up examinations according to LDCT. MRI accurately detected 62 of 89 solid nodules with a size of < 6 mm, 40 of 41 solid nodules with a size of ≥ 6 mm and eight of 11 sub-solid nodules with a size of < 20 mm. Nodule size on MRI (mean 6.56 mm, median 5 mm) significantly correlated with LDCT (mean 6.11 mm, median 5 mm) ($p < 0.001$).

A baseline Lung-RADS score of 4B/4X was accurately given by MRI in six of six cases (four cases with nodules ≥ 15 mm and two cases with spiculated nodules measuring 8–14 mm; one is shown in Fig. 1). All six cases were NSCLCs. MRI accurately assigned a Lung-RADS score of 4A in 12 of 12 cases and a Lung-RADS score of 3 in 10 of 10 cases. The

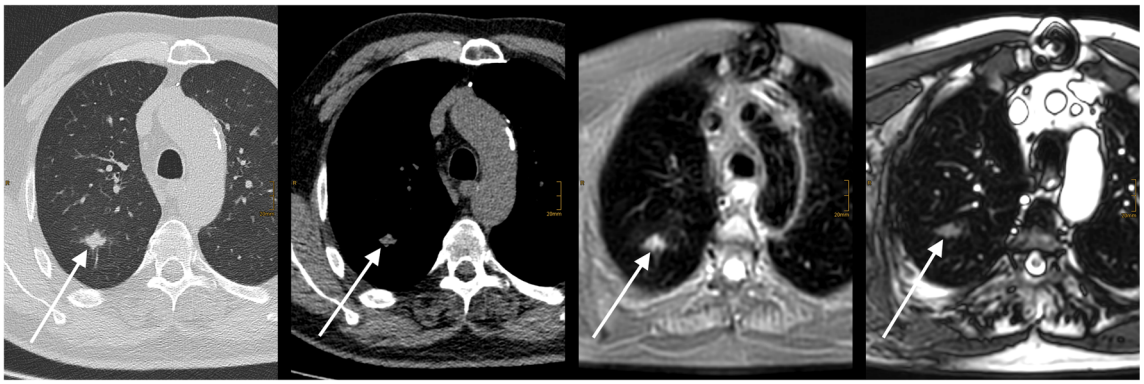

Fig. 1 Solid 13-mm nodule in the right upper lobe. This nodule was clearly visible on all MRI sequences and classified as Lung-RADS 4X because of spicules (from left to right: CT lung window, CT soft tissue window, MRI T2 STIR, MRI balanced steady-state free precession)

Lung-RADS category was overestimated by MRI at baseline in three cases for LungRADS 4A and 3. In one of these subjects, the 4A score was too high, since a nodule measured 9 mm on MRI, but only 7 mm on LDCT (actually Lung-RADS 3). Two other cases with an MRI-based score of 3 at baseline were actually LungRADS 1, as mentioned above.

Fifty-two of 52 participants presenting with solid nodules 4–5 mm or sub-solid nodules < 20 mm were accurately categorised as Lung-RADS 2 by baseline MRI. One of the sub-solid nodules is shown in Fig. 2. In four cases, MRI diagnosed nodules with a size of 4–5 mm that were not seen as nodules on LDCT; hence, the score was overestimated by MRI (false-positive results, actually Lung-RADS 1). In two of these cases, pulmonary vessels were erroneously diagnosed as nodules. In the other two cases, alleged nodules on MRI were streaky opacities on LDCT (probably inflammatory or scar tissue).

Baseline MRI did not show any nodules in 135 cases and apparently calcified nodules with a size of ≥ 6 mm in two cases (Lung-RADS 1). In comparison, LDCT revealed solid nodules with a size of 4–5 mm in 18 subjects and sub-solid nodules with a size of < 20 mm in two subjects neither of which were visible on MRI (false negative on MRI, actually Lung-RADS 2). Thus, the Lung-RADS score was underestimated by MRI in 20 cases at baseline. In addition, five calcified nodules with a size of 4–5 mm were not detectable on MRI; these were category 1 nodules in any case.

In 20 of 23 cases with a baseline Lung-RADS score of 4A or 3, findings were stable after 3 or 6 months; hence, the score was downgraded to 2. In all cases, nodule size was accurately indicated as stable by MRI.

One category 4A nodule grew from 8 mm at baseline to 10 mm 3 months later (upgrade to Lung-RADS 4B, Fig. 3). This was accurately depicted by MRI and subsequent surgery revealed NSCLC. In another case, MRI accurately indicated that a nodule grew from 7 mm to 8 mm after 6 months, and was then categorised as Lung-RADS 4B. This nodule was stable after another 3 months and 12 months, confirming its benignancy. A different participant with a 7-mm nodule underwent 3-month follow-up only with LDCT despite the recommendation of the interdisciplinary conference for a 6-month follow-up. This nodule was broadly stable after 3 months, but grew distinctly from 7 mm to 25 mm after another 9-month interval. Clinical staging then showed brain and liver metastases, and biopsy revealed SCLC.

Due to eight carcinomas and eight dropouts, 208 of the initial 224 study participants took part in the second screening round. 204 of these 208 participants presented with stable

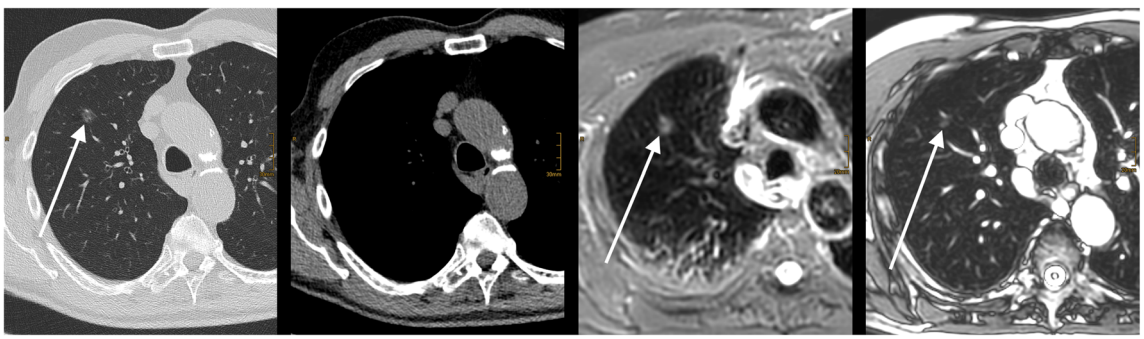

Fig. 2 Sub-solid 13-mm nodule in the right upper lobe classified as LungRADS 2. This nodule was only slightly hyperintense on T2-weighted sequences and hardly detectable on balanced steady-state free-precession images (from left to right: CT lung window, CT soft tissue window, MRI T2 STIR, MRI balanced steady-state free precession)

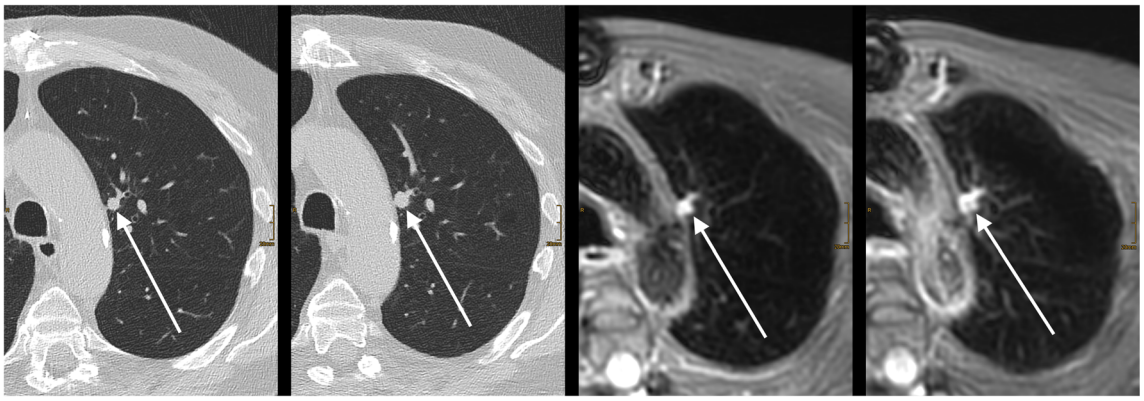

Fig. 3 Solid nodule in the left upper lobe, which grew from 8 mm at baseline (Lung-RADS 4A) to 10 mm at 3-month follow-up (Lung-RADS 4B) (from left to right: CT at baseline, CT after 3 months, MRI T2 STIR at baseline, MRI T2 STIR after 3 months)

findings (Lung-RADS 1 or 2); all 204 cases were accurately classified as stable by MRI. In two cases, nodules grew from 6 mm at baseline to 7 mm after 12 months (Lung-RADS 4A), most likely due to slight atelectasis adjacent to the nodules, since both nodules were stable again after another 3 months (Lung-RADS 2). Another subject showed a new nodule with a size of 5 mm in the second round (Lung-RADS 3), and a different new nodule with a size of 12 mm after another 6 months (Lung-RADS 4A); both lesions were regressive again and most likely had inflammatory changes. A fourth participant with two new nodules (14 mm and 9 mm, Fig. 4) was assigned a Lung-RADS score of 4X in the second round; according to the histology of the subsequent surgery, both nodules were tuberculous granulomas. MRI accurately detected nodule growth and the presence of new nodules, respectively, in all four of these participants. The patient flow of this study is shown in Fig. 5.

Altogether, there was a significant correlation between MRI and LDCT regarding Lung-RADS scoring ($p < 0.001$). Table 3 summarises the Lung-RADS scores assigned by MRI and LDCT, respectively.

Discussion

The Lung Screening Reporting And Data System (Lung-RADS) was developed for low-dose computed tomography (LDCT) to assess pulmonary nodules in participants in a lung cancer-screening programme [2]. Our study results show that Lung-RADS might also be applied for magnetic resonance imaging (MRI). This finding supports the hypothesis that MRI could be an effective tool for lung cancer screening [7].

According to the Lung-RADS classification, only solid nodules ≥ 6 mm and growing nodules have an elevated risk of malignancy (Lung-RADS category 3 and 4) [2]. According to Biederer et al and Gierada et al, the recommended cut-off for a positive screening result will probably be set to 5–6 mm in the near future [7, 11]. This would fit well with the sensitivity of MRI for nodule detection as reported in this present study and in recent other studies [8, 9, 12, 13].

Nodules being categorised as Lung-RADS 3 or higher were never underestimated or missed by MRI in all 36 cases of our study population. Also, even slight changes in nodule growth could be detected by MRI. Because of overestimation

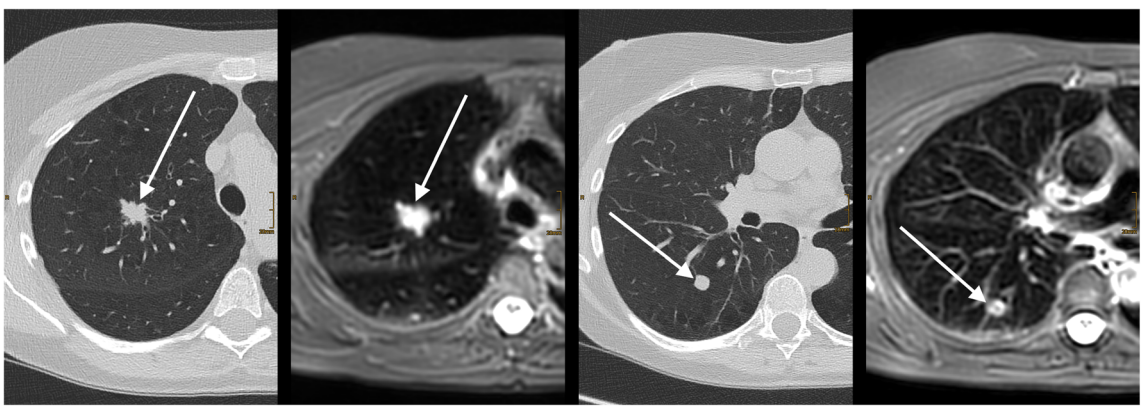

Fig. 4 Two nodules highly suspicious for cancer (14 mm in the right upper lobe and 9 mm in the right lower lobe) being diagnosed in the second screening round. Histology after surgery revealed tuberculous granulomas for both lesions (from left to right: CT upper lobe, MRI T2 STIR upper lobe, CT lower lobe, MRI T2 STIR lower lobe)

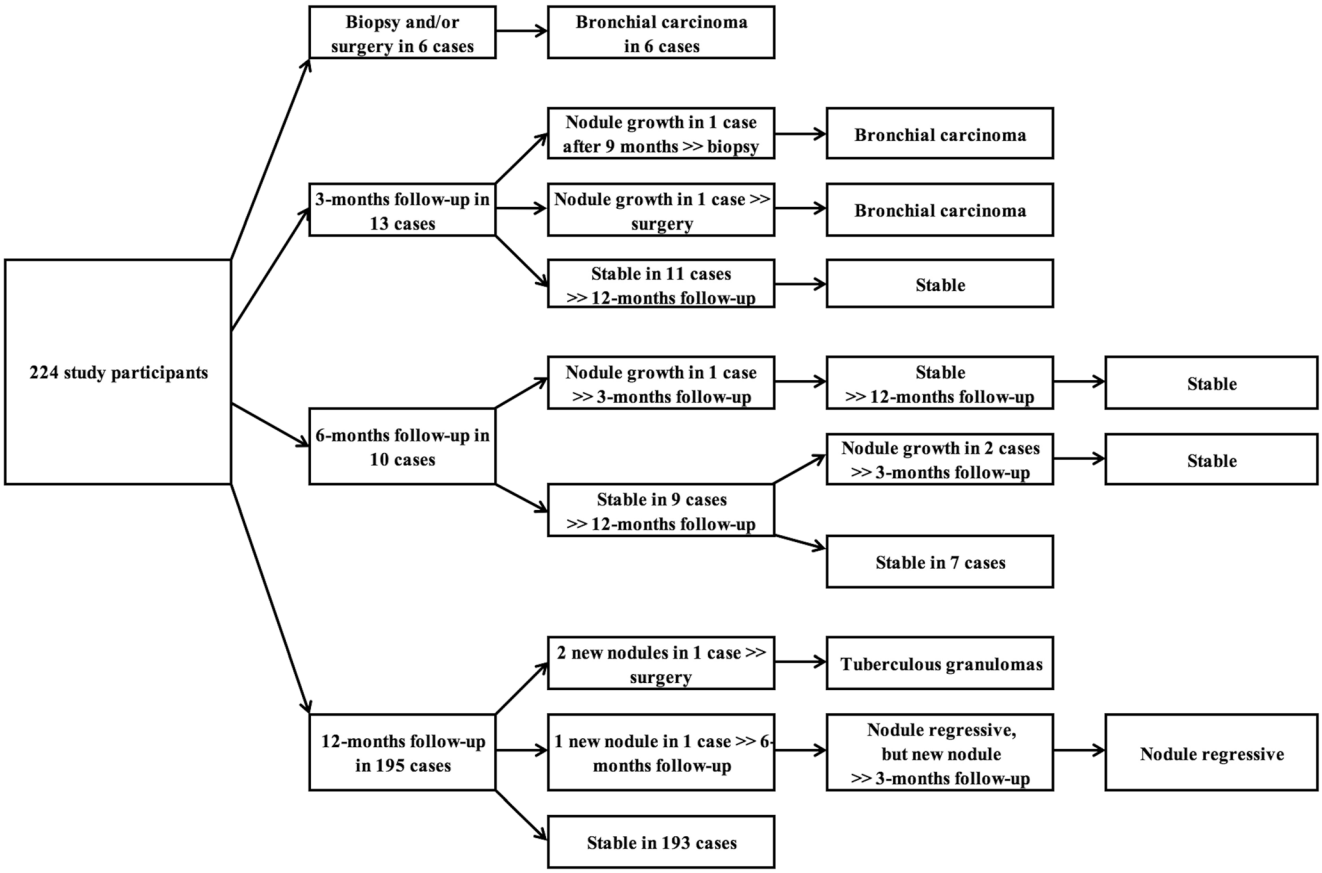

Fig. 5 Flow-chart showing the study population

of the Lung-RADS score by MRI, only three participants would have been scheduled for an unnecessary follow-up if only MRI had been performed. On the other hand, the LungRADS score was underestimated in only 20 cases with a Lung-RADS category of 2 in both screening rounds. These nodules could have probably been detected if we had implemented a high-resolution multiparametric scan protocol with contrast-enhanced sequences, since the assumed threshold for lung nodule detection with MRI at optimum conditions is believed to be 3–4 mm [7, 14]. Instead, we decided for a fast scan protocol that was easy to perform and optimised for screening with a maximum in-room time of 20 min. Moreover, Lung-RADS 2-nodules have a very low likelihood of becoming a clinically active cancer, and they are very common in long-term smokers [2, 15]; thus, missing these nodules is likely irrelevant.

The virtual early recall rate of MRI in our screening study dropped from 13.8% at baseline to 1.9% in the second round, which is a good indication of the quality of our screening compared with the German LUSI study (22% and 3–4%) [16] and with the assumed optimum recall rate of a mammography screening [17]. The lower rates in our study compared to the LUSI study were mainly attributable to the lower threshold for early recall (6 mm vs. 5 mm).

Our study has some limitations. First, both the 2015 British Thoracic Society Guideline on management of

Table 3 Number of Lung-RADS scores assigned on MRI and LDCT (at baseline, and when the score changed in follow-up examinations after 3, 6 and 12 months)

Lung-RADS	Baseline MRI	Baseline LDCT	Follow-up MRI	Follow-up LDCT	Over- or underestimation by MRI
1	137	123	3	3	Underestimation in 20 cases
2	56	72	21	20	Overestimation in five cases, no underestimation
3	12	11	1	1	Overestimation in two cases, no underestimation
4A	13	12	3	3	Overestimation in one case, no underestimation
4B/4X	6	6	4	4	No over- or underestimation

pulmonary nodules [18] and the 2017 Fleischner Guidelines [15] recommend semi-automated volumetric nodule assessment for baseline and follow-up examinations with LDCT, since volumetric measurement has been shown to have superior sensitivity in the detection of nodule growth. Volumetric nodule assessment was not performed in our study, since not all of the nodules were visible on the two implemented coronal sequences, probably due to an elevated slice thickness (7 mm for the coronal T2-weighted sequence and 5 mm for the THRIVE sequence). Thus, future studies on the detection of nodule growth with MRI should implement higher spatial resolution or 3D imaging with isotropic voxels. However, an approach with high-resolution MRI always has to overcome the difficulties of a lower signal-to-noise ratio. Moreover, appropriate tools for volumetric assessment of small nodules with MRI are not commercially available at present.

A second limitation, even though the total number of study participants was reasonably high for a prospective MRI study on the detection of pulmonary nodules, was that it was rather low for a screening study.

Third, MR images were read by two radiologists experienced in body MRI and especially in lung MRI. Inexperienced readers would probably not achieve a comparably high diagnostic performance.

Fourth, because the minimum nodule size was 4 mm in our study, growing nodules < 4 mm were not assessed, even though they would have been categorised as Lung-RADS 4A. However, based on our experience, growing nodules smaller than 4 mm are very rare findings, and these nodules were not present according to LDCT in our study.

Fifth, we did not assess partly solid nodules, as they are difficult to discriminate from solid nodules and pure groundglass nodules on MR images. Consequently, partly solid nodules were subsumed as solid nodules, since the management of these nodules is very similar to the solid ones according to the Lung-RADS criteria [2].

In conclusion, Lung-RADS might be applied for lung cancer screening with MRI, since findings significantly correlated with LDCT. Relevant findings with a Lung-RADS score of 3 and higher were never missed or underestimated by MRI. Still, further studies of much larger data sets are needed to finally confirm or refute the results of this present study.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Daniel Thomas.

Conflict of interest One co-author of this manuscript, Jürgen Gieseke, is an employee of Philips Healthcare Germany. However, he did not have any influence on the study design, evaluation or interpretation of results. His main contribution was optimising the MR sequences and reviewing the manuscript.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all patients in this study.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap All study subjects are participants of our lung cancer screening program. The performance of MRI regarding the detection of lung nodules in the first screening round were published in 2017 (Meier-Schroers M, Homsi R, Skowasch D, Buermann J, Zipfel M, Schild HH, Thomas D. Lung cancer screening with MRI: results of the first screening round. J Cancer Res Clin Oncol. 2017 Sep 20. [Epub ahead of print]). The current study reports on the first two screening rounds including all follow-ups and on the applicability of the Lung-RADS classification.

Methodology
- prospective
- diagnostic study
- performed at one institution

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