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Developing a lung nodule management protocol specifically for cardiac CT: Methodology in the DISCHARGE trial

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ABSTRACT

Purpose: In this methodology paper we describe the development of a lung nodule management algorithm specifically for patients undergoing cardiac CT.
Methods: We modified the Lung-RADS algorithm specifically to manage lung nodules incidentally detected on cardiac CT (Lung-RADS for cardiac CT). We will evaluate the modified algorithm as part of the DISCHARGE trial (www.dischargetrial.eu) in which patients with suspected coronary artery disease are randomly assigned to cardiac CT or invasive coronary angiography across Europe at 16 sites involving 3546 patients. Patients will be followed for up to four years.
Results: The major adjustments to Lung-RADS specifically for cardiac CT relate to 1) incomplete coverage of the lungs by cardiac CT compared with chest CT, and when to order a completion chest CT versus a follow up chest CT, 2) cardiac CT findings will not trigger annual lung-cancer screening, and 3) a lower threshold of at least 10 mm for classifying new ground glass nodules as probably benign (category 3).
Conclusions: The DISCHARGE trial will assess a lung nodule management algorithm designed specifically for cardiac CT in patients with stable chest pain across Europe.

1. Introduction

Screening for lung cancer in high-risk groups using computed tomography (CT) with low-dose techniques is increasing based on the relative reduction in lung-cancer mortality demonstrated in the national lung cancer screening trial (NLST) and Nelson trials [1,2]. The debate has principally centered around nodule size criteria for further investigation [3] and the cost implementation of such screening programs, i.e., which patient groups have a high enough risk to benefit from CT screening and whether or not smoking cessation programs should be incorporated into CT programs [4]. The US Preventive Services Task Force has recommended annual chest CT screening for lung cancer in patients who are over 55 years of age, have had at least 30 pack years, and are active smokers or have quit smoking in the last 15 years [5].

Lung nodules are one of the commonest incidental findings on cardiac CT in patients with a low-intermediate pretest probability of suspected stable coronary artery disease [6]. No lung nodule management recommendations specifically exist for cardiac CT, despite many such patients referred for cardiac CT fulfilling the above age and lung-cancer risk criteria for CT lung-cancer screening. A major issue for cardiac CT is that it does not cover the entire lungs but only the lung parenchyma within the cardiac scan range. Therefore, recommendations such as the Lung-RADS and Fleischner models may not apply identically in clinical situations where cardiac CT is deemed appropriate [7]. There is no prospective data evaluating whether a full chest CT is required immediately following cardiac CT or whether it is sufficient to obtain a follow up scan. Although the most recent Fleischner nodule guidelines make recommendations for incidentally detected nodules on incomplete thoracic CT scans, they are based on CT lung-cancer screening programs [8] rather than cardiac CT trials.

Thus, we have as part of the prospective European multicentre DISCHARGE trial (www.dischargetrial.eu, [9]) initiated an effort to translate the Lung-RADS recommendations of the ACR [10] into a

Abbreviations: NLST, national lung cancer screening trial; ACR, American College of Radiology; eCRF, electronic clinical report form; LDCT, low-dose computed tomography

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Table 1
Modifications to the Lung-RADS algorithm for Cardiac CT in the DISCHARGE trial.

Category	Modification	Management Modifications
0	Not relevant in DISCHARGE	
1	None	
2	Nodule changed from 20 mm to 10 mm	If > 55 yo, ≥30 pack yrs or non-smoking Hx < 15yrs, LDCT in 12 months, if not, no LDCT F/U Changed time for unchanged Cat 3 and 4 nodules from ≥3 months to ≥18-24 months
3	Changed NSN from ≥20 mm to ≥10 mm	Perform whole chest LDCT
4a	None	Perform whole chest LDCT
4b	None	Perform whole chest contrast-enhanced CT
4x	None	Perform whole chest LDCT (Cat 3x) or contrast-enhanced CT (Cat 4x)

LDCT-low dose chest CT; pt-patient; F/U- follow up; NSN-non-solid nodule; yo-years old; Hx-history.

practical nodule management algorithm that is specifically designed for cardiac CT in patients that may share risk factors with patients suitable for lung cancer CT-screening [11]. The "Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease" (DISCHARGE) study is a pragmatic randomised controlled trial assessing the comparative effectiveness of cardiac CT and invasive coronary angiography for the detection of coronary artery disease in patients with a low-intermediate pre-test probability (10–60 %). It commenced patient recruitment in 2015 incorporating 26 clinical centres in 16 European countries with a sample size of 3546 patients. In this short communication we will describe the methodology by which the lung-RADS nodule management algorithm will be modified specifically for cardiac CT in the trial.

2. Methods

2.1. Background of the DISCHARGE trial

The number of randomized pragmatic trials comparing cardiac CT to invasive coronary angiography (ICA) is limited [12]. Therefore, the DISCHARGE trial was initiated to investigate in a randomized pragmatic study the comparative effectiveness of coronary CTA versus ICA in a multicenter setting across the continent of Europe. Details of the trial methodology have been published elsewhere [9]. In the DISCHARGE trial, patients with low-intermediate pre-test probability for obstructive CAD with stable chest pain will be randomized to coronary CTA or ICA and outcomes will be collected on one- and up to four-year follow-up.

2.2. Lung nodule model

As part of the trial, which commenced recruitment in 2015, it was realized that lung nodule detection would be inevitable, and a search of the literature was undertaken for lung nodule guidelines specific to cardiac CT. Our literature search returned no articles based on prospective data. Since many patients being evaluated for chest pain share similar demographics and risk factors for lung cancer such as smoking, the CT screening nodule guidelines issued by the American College of Radiology (ACR) were deemed most suitable [10,13]. The Lung-RADS and Fleischner nodule guidelines underwent updates (2019 and 2017 respectively) during the trial but we did not alter our modified nodule algorithm approach during the trial based on our external advisory board instructions.

2.3. Working group

A working group was formed for the evaluation of the lung nodule algorithm headed by RH, JD, MD before discussion with the principal investigators of all 16 DISCHARGE countries [9]. Modifications of Lung-RADS to cardiac CT were considered and implemented into an electronic clinical report form (eCRF) which included the McWilliams calculator [14]. The DISCHARGE trial team collaboratively adjusted the Lung-RADS recommendations specifically to the needs of cardiac CT with assistance and external oversight of two international experts on low-dose chest CT for lung cancer screening (EK and HUK). The working group presented the modified nodule guidelines to and received feedback from the entire 16-country DISCHARGE consortium on implementing the recommendations to a cardiac CT specific patient population. Sites will upload nodule details using the trial website eCRF with the following details: (i) nodule versus mass, (ii) number if nodules, (iii) solid/part-solid/non-solid, (iv) longest and shortest diameter, (v) upper lobe location, (vi) spiculations, (vii) lymphadenopathy and (viii) rapidly enlarging GGN. Additionally, patient demographics such as > 30 pack years and age will be inputted into the eCRF. Efforts will made by all sites to compare the cardiac CT with any previous imaging to assess for nodule stability.

2.4. Nodule measurements

Use of maximum intensity projections (8–10 mm slab thickness) at lung window settings will be encouraged for both cardiac CT and all subsequent follow-up chest CT lung nodule reads [15]. For nodule size measurements, the Lung-RADS recommendation of averaging two diameters (long + short) will be calculated and automatically rounded to one decimal place by an electronic clinical report form (eCRF). Nomenclature such as 'ground-glass' and 'nodule' were based on definitions from the glossary of terms for thoracic imaging [16]. Nodule growth will be defined as a mean > 1.5 mm.

3. Results

Modifications to the Lung-RADS paradigm were made for categories 2-4× (Table 1, Fig. 1). Categories 0 and 1 will be deemed that no follow-up is required. For category 2 nodules, the subgroup of non-solid nodules measuring < 20 mm, or ≥20 mm and unchanged, the size was reduced to < 10 mm, or ≥10 mm and unchanged on the basis of an increased incidence of malignancy in this nodule subcategory [17]. We removed the term 'slowly growing' from this category. Because Lung-RADS assumes a predetermined set of clinical variables as part of lung cancer screening but patients undergoing cardiac CT may not fulfill such criteria, we will include a specific clinical set of variables in this category such that if patients were > 55 years old, had a ≥30 pack year smoking history or < 15 years as a non-smoker they would undergo a follow-up LDCT in 12 months. If patients are negative for these demographics, no follow-up LDCT will be undertaken. Furthermore, some category 3 and 4 nodules that remain stable will also be included in category 2, but we changed the time interval for stability from > 3 months to 18 and 27 months, respectively.

For category 3 nodules, the subgroup of non-solid nodules was changed from ≥20 mm to ≥10 mm for similar reasons as category 2. Nodules on cardiac CT classified as category 3 or 4 will all undergo a completion whole chest LDCT. The low dose chest CT protocol recommended by the ACR will be used in the DISCHARGE trial. Specifically, this involves non-contrast multidetector CT with 16 slices

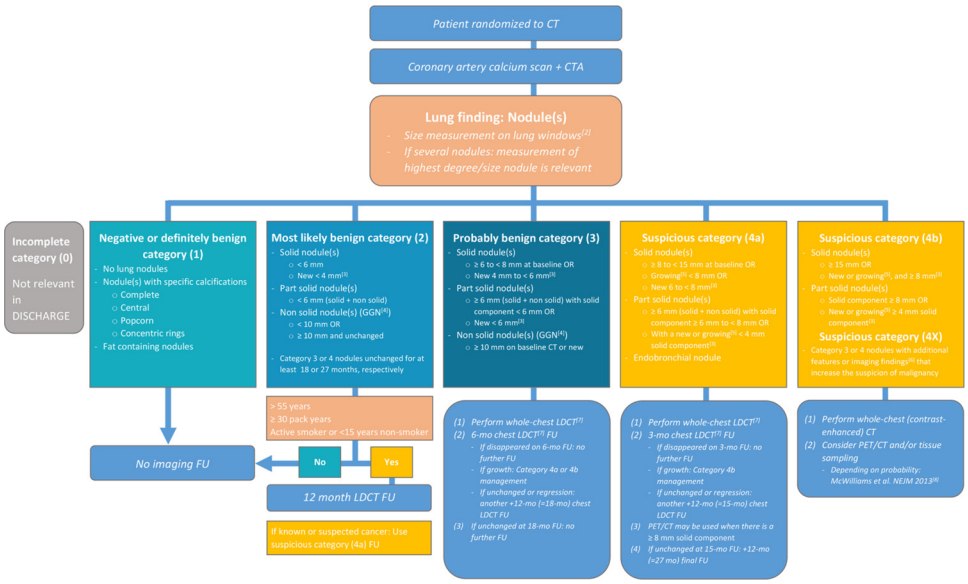

Fig. 1. Management of lung nodules in DISCHARGE[1].
(1) Based on modifications to the Lung-RADS algorithm.
(2) Mean diameter of longest and shortest diameters.
(3) If prior was available.
(4) Based on definitions from the glossary of terms for thoracic imaging (Hansell et al Radiology 2010).
(5) Growth defined as > 1.5 mm.
(6) Risk factor examples include Risk features: Spiculation, mediastinal lymph nodes > 1 cm small diameter, GGN that doubles in size in one year.
(7) See main text for protocol details.
(8) eCRF provides "Brock' likelihood of malignancy calculation.

or greater, gantry rotation of < 500 ms, helical technique and full inspiration with slice thickness of < 2.5 mm [10].

Patients with nodules belonging to categories 4a, 4b and 4x will have specific management algorithms assigned depending on the appearance of the nodule or its behavior on subsequent follow-up LDCT. This will include the use of PET-CT and/or tissue biopsy, depending on the likelihood of malignancy. The eCRF allows a calculation of malignancy likelihood based on the McWilliams calculator (Fig. 2) [14]. The 4x category will include additional features "that increase the suspicion of malignancy." These include findings such as nodule spiculation, enlarged mediastinal lymph nodes or upper lobe nodule location [18].

As for all nodule recommendations, it will be emphasized that whenever there is doubt that these recommendations do not represent best care for an individual patient, DISCHARGE sites will be instructed to provide best individual patient care. A hypothetical example of a part-solid nodule is provided (Fig. 2A–D) to illustrate use of the DISCHARGE eCRF and its potential data entry points for an incidentally detected lung nodule(s) on cardiac CT in the trial. For our hypothetical part-solid nodule, data entry (Fig. 2A) facilitates diameter inputs of the total as well as the solid component of the nodule. Specific 4x features are also available for input as well as patient risk factors (Fig. 2B). These inputs allow sites to choose an appropriate Lung-RADS category and also provides a link to the McWilliams calculator (Fig. 2C) to allow a likelihood of malignancy calculation. In our hypothetical example the nodule in question is a 4X nodule and would undergo a percutaneous CT guided biopsy to confirm malignancy. The eCRF has the facility to allow an upload of the pathology report (Fig. 2D) for verification.

4. Discussion

The DISCHARGE project is a European multi-centre pragmatic trial aiming to assess the comparative effectiveness of CT compared to ICA in patients with stable chest pain and an intermediate probability of coronary artery disease. One of several secondary objectives of this project is the development and prospective evaluation of a lung nodule management algorithm specific to cardiac CT. Currently, there are no lung nodule recommendations that fulfill this. Five major nodule recommendations (PanCan, Lung-RADS, NCCN, BTS and Fleischner) [8,10,14,19,20] apply to contemporaneous nodule management, but none have specifically been designed to address cardiac CT. Since lung nodules are one of the most common incidental findings on cardiac CT, this represents a real-life management issue for cardiothoracic radiologists [21]. Overly conservative and non-evidence-based approaches to lung nodule management can potentially lead to over-investigation, increased patient anxiety and lead- and over-diagnosis bias [22,23]. The DISCHARGE trial offers an opportunity to develop nodule management algorithms specific to cardiac CT based on a large spectrum of European patients from across the continent.

Patients referred for cardiac CTA will frequently have similar demographics and/or risk factors to patients undergoing LDCT lung cancer screening. For example, the age range of patients in the NLST was between 55–77, comparable to several recently published large cardiac CT trials [24–26]. Several risk factors, particularly smoking, are frequently seen in both patient populations, for example in the PROMISE trial the smoking prevalence of low-intermediate patients being investigated for CAD was approximately 50 % [25]. This led us to believe that combining the lung-RADS algorithm with the McWilliams calculator would be most suitable for our study population, since it has proven robust in malignancy prediction in other models [27].

Two major issues exist for lung nodules detected incidentally on cardiac CT, one is whether patients should undergo a completion CT of the entire chest and the other is whether nodules require any follow-up, either with or without contrast. We modified the lung-RADS recommendations to address these issues and will evaluate the safety and efficacy of the modifications during the DISCHARGE trial. We omitted whole chest CT or follow up in categories 1 and 2 (Table 1) based on malignancy probabilities of < 1% for these groups, but we provided patient demographics such as smoking as additional factors in this category to provide guidance to cardiothoracic radiologists in real-world practice. We also aim to reduce the health burden on health sectors across Europe whilst minimizing patient harm. Since CT lung cancer screening programs are evolving beyond nodule evaluation alone to additional smoking-related entities such as emphysema [28] and cardiovascular health [29], analysis of the DISCHARGE trial data beyond nodule assessment may provide unique insights into how these entities influence each other and how they should be scored and managed.

Several nodule size adjustments were made to reflect the evolving situation in nodule evaluation in lung cancer investigation. Since publication of the Lung-RADS algorithm, subsequent papers have shown an increased likelihood of malignancy for smaller sub-solid nodules. In the NLST, 2% of category 2 sub-solid nodules subsequently developed malignancy [11]. Similarly, in a paper by Kakinuma et al. that assessed non-solid nodules, approximately 10% grew and 1% developed into invasive adenocarcinomas or minimally invasive adenocarcinomas [17]. Thus, it became clear that lower thresholds for managing non-solid nodules seemed prudent for cardiac CT in a non-screening

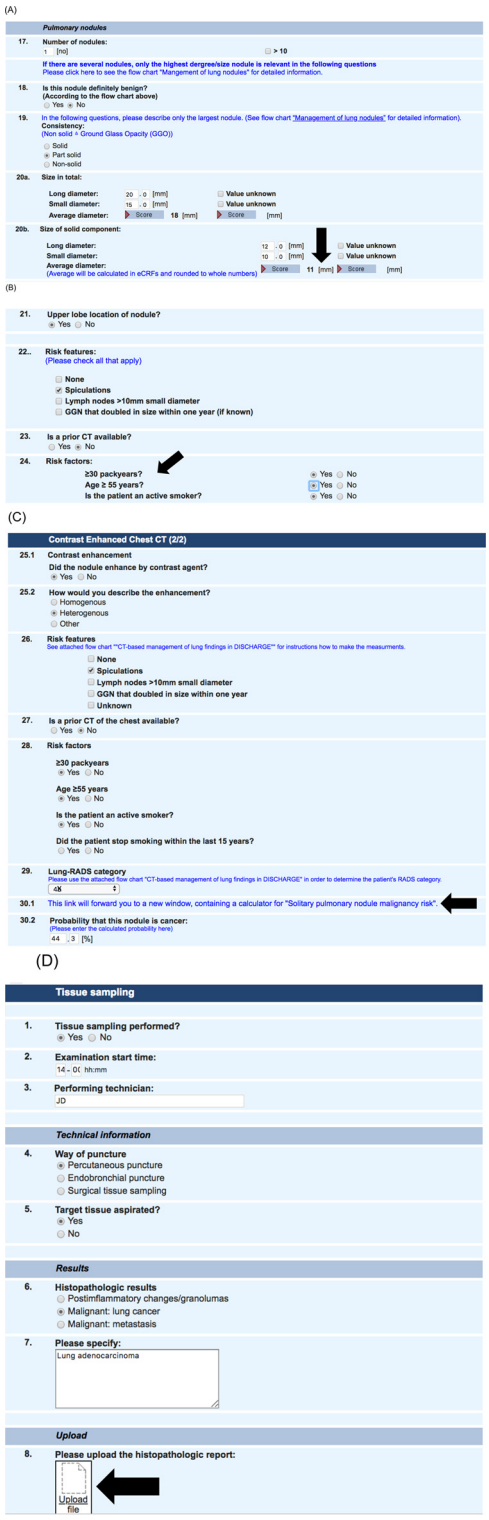

Fig. 2. Subsections of the eCRF showing lung nodule data entry inputs along modified pathways specific for cardiac CT. A hypothetical example of an incidentally detected part-solid nodule on cardiac CT is provided. (A) The eCRF automatically calculates mean nodule size (arrow) from inputted long and short diameters. (B) Additional features suggestive of malignancy along with patient risk factors (arrow) can be inputted. In this hypothetical example the nodule would fulfill criteria for a Lung-RADS category 4x nodule. (C) A whole chest contrast-enhanced CT is recommended for this category, the findings of which can be inputted and the McWilliams calculator is available via an online link (arrow) to obtain a likelihood of nodule malignancy. In our hypothetical example it calculates a malignancy likelihood of 44.3 %. (D) For a nodule with a 44.3 % likelihood of malignancy a percutaneous CT-guided biopsy to obtain confirmation of malignancy can be inputted. The pathology report can be uploaded to the eCRF (arrow).

population [30].

Nodule cut-offs for including nodules < 6 mm in category 2 is likely to result in a small number of false negative cardiac CT results. In a study by Pinsky et al. the NLST data was reanalyzed and compared to the Lung-RADS algorithm. At baseline, the false-positive result rate for Lung-RADS was 12.8% versus 26.6% for the NLST; after baseline, the false-positive result rate was 5.3% for Lung-RADS versus 21.8% for the NLST. Baseline sensitivity was 84.9% for Lung-RADS versus 93.5% for the NLST, and sensitivity after baseline was 78.6% for Lung-RADS versus 93.8% for the NLST. Whether similar diagnostic test performance will be seen when applied to lower risk groups referred for other tests such as cardiac CT across Europe is currently unknown. Several studies that have applied existing nodule guidelines (Fleischner, BTS) to cardiac CT in patients with acute coronary syndrome [31] and stable chest pain [22] have shown a reduction in number of follow-up studies with no missed malignancies. Studies assessing the McWilliams calculator outside of CT lung cancer screening populations have shown it to have a high predictive discrimination of potentially malignant and benign nodules when validated in an unselected, heterogeneous clinical population [32]. Results of the DISCHARGE trial will provide an insight into the applicability of modified Lung-RADS and the McWilliams calculator to patient populations undergoing cardiac CT and provide further information on the likely benefits but also potential drawbacks of the management of lung nodules detected by cardiac CT.

The DISCHARGE trial provides a unique opportunity to study the Lung-RADS algorithmic approach applied to cardiac CT across a wide range of cultures and countries in a pragmatic trial setting. While single center and national studies provide answers to these questions at a domestic level, it is hoped in the DISCHARGE trial that continental trends across all sites may allow insights into the applicability of a modified Lung-RADS algorithm to patient populations beyond the CT lung cancer screening models and assess cultural and demographics differences influencing nodule detection and management at a unique societal and population level.

Declaration of Competing Interest

All authors have no conflict of interest related to this work.

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CRediT authorship contribution statement

Robert Haase: Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Jonathan D. Dodd:** Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Hans-Ulrich Kauczor:** Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Ella A. Kazerooni:** Supervision, Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Marc Dewey:** Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition.

References

[1] T. National Lung Screening Trial Research, D.R. Aberle, A.M. Adams, C.D. Berg, W.C. Black, J.D. Clapp, R.M. Fagerstrom, I.F. Gareen, C. Gatsonis, P.M. Marcus, J.D. Sicks, Reduced lung-cancer mortality with low-dose computed tomographic screening, N. Engl. J. Med. 365 (5) (2011) 395–409, https://doi.org/10.1056/NEJMoa1102873.

[2] H.J. de Koning, C.M. van der Aalst, P.A. de Jong, E.T. Scholten, K. Nackaerts, M.A. Heuvelmans, J.J. Lammers, C. Weenink, U. Yousaf-Khan, N. Horeweg, S. van' t Westeinde, M. Prokop, W.P. Mali, F.A.A. Mohamed Hoesein, P.M.A. van Ooijen, J. Aerts, M.A. den Bakker, E. Thunnissen, J. Verschakelen, R. Vliegenthart, J.E. Walter, K. Ten Haaf, H.J.M. Groen, M. Oudkerk, Reduced lung-cancer mortality with volume CT screening in a randomized trial, N. Engl. J. Med. 382 (6) (2020) 503–513, https://doi.org/10.1056/NEJMoa1911793.

[3] J. Chin, T. Syrek Jensen, L. Ashby, J. Hermansen, J.D. Hutter, P.H. Conway, Screening for lung cancer with low-dose CT–translating science into medicare coverage policy, N. Engl. J. Med. 372 (22) (2015) 2083–2085, https://doi.org/10.1056/NEJMp1502598.

[4] H.U. Kauczor, L. Bonomo, M. Gaga, K. Nackaerts, N. Peled, M. Prokop, M. Remy-Jardin, O. von Stackelberg, J.P. Sculier, R. European Society of, S. European Respiratory, ESR/ERS white paper on lung cancer screening, Eur. Respir. J. 46 (1) (2015) 28–39, https://doi.org/10.1183/09031936.00033015.

[5] V.A. Moyer, U.S.P.S.T. Force, Screening for lung cancer: U.S. Preventive services task force recommendation statement, Ann. Intern. Med. 160 (5) (2014) 330–338, https://doi.org/10.7326/M13-2771.

[6] P. Karius, A. Lembcke, F.C. Sokolowski, I.D.P. Gandara, A. Rodriguez, B. Hamm, M. Dewey, Extracardiac findings on coronary computed tomography angiography in patients without significant coronary artery disease, Eur. Radiol. 29 (4) (2019) 1714–1723, https://doi.org/10.1007/s00330-018-5688-4.

[7] A.J. Taylor, M. Cerqueira, J.M. Hodgson, D. Mark, J. Min, P. O'Gara, G.D. Rubin, F. American College of Cardiology Foundation Appropriate Use Criteria Task, T. Society of Cardiovascular Computed, R. American College of, A. American Heart, E. American Society of, C. American Society of Nuclear, I. North American Society for Cardiovascular, A. Society for Cardiovascular, Interventions, R. Society for Cardiovascular Magnetic, ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010, Appropriate use criteria for cardiac computed tomography. A report of the American college of cardiology foundation appropriate use criteria task force, the society of cardiovascular computed tomography, the American college of radiology, the American heart association, the American society of echocardiography, the American society of nuclear cardiology, the north American society for cardiovascular imaging, the society for cardiovascular angiography and interventions, and the society for cardiovascular magnetic resonance, J. Cardiovasc. Comput. Tomogr. 4 (6) (2010) 1–33, https://doi.org/10.1016/j.jcct.2010.11.001 407.

[8] H. MacMahon, D.P. Naidich, J.M. Goo, K.S. Lee, A.N.C. Leung, J.R. Mayo, A.C. Mehta, Y. Ohno, C.A. Powell, M. Prokop, G.D. Rubin, C.M. Schaefer-Prokop, W.D. Travis, P.E. Van Schil, A.A. Bankier, Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017, Radiology 284 (1) (2017) 228–243, https://doi.org/10.1148/radiol.2017161659.

[9] A.E. Napp, R. Haase, M. Laule, G.M. Schuetz, M. Rief, H. Dreger, G. Feuchtner, G. Friedrich, M. Spacek, V. Suchanek, K. Fuglsang Kofoed, T. Engstroem, S. Schroeder, T. Drosch, M. Gutberlet, M. Woinke, P. Maurovich-Horvat, B. Merkely, P. Donnelly, P. Ball, J.D. Dodd, M. Quinn, L. Saba, M. Porcu, M. Francone, M. Mancone, A. Erglis, L. Zvaigzne, A. Jankauskas, G. Sakalyte, T. Haran, M. Ilnicka-Suckiel, N. Bettencourt, V. Gama-Ribeiro, S. Condrea, I. Benedek, N. Cemerlic Adjic, O. Adjic, J. Rodriguez-Palomares, B. Garcia Del Blanco, G. Roditi, C. Berry, G. Davis, E. Thwaite, J. Knuuti, M. Pietila, C. Kepka, M. Kruk, R. Vidakovic, A.N. Neskovic, I. Diez, I. Lecumberri, J. Geleijns, C. Kubiak, A. Strenge-Hesse, T.H. Do, F. Fromel, I. Gutierrez-Ibarluzea, G. Benguria-Arrate, H. Keiding, C. Katzer, J. Muller-Nordhorn, N. Rieckmann, M. Walther, P. Schlattmann, M. Dewey, D.T. Group, Computed tomography versus invasive coronary angiography: design and methods of the pragmatic randomised multicentre DISCHARGE trial, Eur. Radiol. 27 (7) (2017) 2957–2968, https://doi.org/10.1007/s00330-016-4620-z.

[10] American College of Radiology, Lung-RADS, (2014) Available via http://www.acr.org/Quality-Safety/Resources/LungRADS . (Accessed Accessed 01 June 2018.

[11] K. Chung, C. Jacobs, E.T. Scholten, O.M. Mets, I. Dekker, M. Prokop, B. van Ginneken, C.M. Schaefer-Prokop, Malignancy estimation of Lung-RADS criteria for subsolid nodules on CT: accuracy of low and high risk spectrum when using NLST nodules, Eur. Radiol. 27 (11) (2017) 4672–4679, https://doi.org/10.1007/s00330-017-4842-8.

[12] M.K. Doris, D.E. Newby, How should CT coronary angiography be integrated into the management of patients with chest pain and how does this affect outcomes? Eur. Heart J. Qual. Care Clin. Outcomes 2 (2) (2016) 72–80, https://doi.org/10.1093/ehjqcco/qcv027.

[13] P.F. Pinsky, D.S. Gierada, W. Black, R. Munden, H. Nath, D. Aberle, E. Kazerooni, Performance of Lung-RADS in the national lung screening trial: a retrospective assessment, Ann. Intern. Med. 162 (7) (2015) 485–491, https://doi.org/10.7326/M14-2086.

[14] A. McWilliams, M.C. Tammemagi, J.R. Mayo, H. Roberts, G. Liu, K. Soghrati, K. Yasufuku, S. Martel, F. Laberge, M. Gingras, S. Atkar-Khattra, C.D. Berg, K. Evans, R. Finley, J. Yee, J. English, P. Nasute, J. Goffin, S. Puksa, L. Stewart, S. Tsai, M.R. Johnston, D. Manos, G. Nicholas, G.D. Goss, J.M. Seely, K. Amjadi, A. Tremblay, P. Burrowes, P. MacEachern, R. Bhatia, M.S. Tsao, S. Lam, Probability of cancer in pulmonary nodules detected on first screening CT, N. Engl. J. Med. 369 (10) (2013) 910–919, https://doi.org/10.1056/NEJMoa1214726.

[15] R. Valencia, T. Denecke, L. Lehmkuhl, F. Fischbach, R. Felix, F. Knollmann, Value of axial and coronal maximum intensity projection (MIP) images in the detection of pulmonary nodules by multislice spiral CT: comparison with axial 1-mm and 5-mm slices, Eur. Radiol. 16 (2) (2006) 325–332, https://doi.org/10.1007/s00330-005-2871-1.

[16] D.M. Hansell, A.A. Bankier, H. MacMahon, T.C. McLoud, N.L. Muller, J. Remy, Fleischner Society: glossary of terms for thoracic imaging, Radiology 246 (3) (2008) 697–722, https://doi.org/10.1148/radiol.2462070712.

[17] R. Kakinuma, Y. Muramatsu, M. Kusumoto, T. Tsuchida, K. Tsuta, A.M. Maeshima, H. Asamura, N. Moriyama, Solitary pure ground-glass nodules 5 mm or smaller: frequency of growth, Radiology 276 (3) (2015) 873–882, https://doi.org/10.1148/radiol.2015141071.

[18] K. Chung, C. Jacobs, E.T. Scholten, J.M. Goo, H. Prosch, N. Sverzellati, F. Ciompi, O.M. Mets, P.K. Gerke, M. Prokop, B. van Ginneken, C.M. Schaefer-Prokop, Lung-RADS category 4X: does it improve prediction of malignancy in subsolid nodules? Radiology 284 (1) (2017) 264–271, https://doi.org/10.1148/radiol.2017161624.

[19] National Comprehensive Cancer Network Guidelines, Lung Cancer Screening, (2017) Available via https://www.nccn.org/patients/guidelines/lung_screening/files/assets/basic-html/page-1.html# . (Accessed Accessed 01 June 2018.

[20] M.E. Callister, D.R. Baldwin, A.R. Akram, S. Barnard, P. Cane, J. Draffan, K. Franks, F. Gleeson, R. Graham, P. Malhotra, M. Prokop, K. Rodger, M. Subesinghe, D. Waller, I. Woolhouse, G. British thoracic society pulmonary nodule guideline development, C. British thoracic society standards of care, British thoracic society guidelines for the investigation and management of pulmonary nodules, Thorax 70 (Suppl. (2)) (2015), https://doi.org/10.1136/thoraxjnl-2015-207168 ii1-ii54l.

[21] P. Karius, G.M. Schuetz, P. Schlattmann, M. Dewey, Extracardiac findings on coronary CT angiography: a systematic review, J. Cardiovasc. Comput. Tomogr. 8 (3) (2014) 174–182, https://doi.org/10.1016/j.jcct.2014.04.002 e1-6l.

[22] M.C. Williams, A. Hunter, A.S.V. Shah, J. Dreisbach, J.R. Weir McCall, M.T. Macmillan, R. Kirkbride, F. Hawke, A. Baird, S. Mirsadraee, E.J.R. van Beek, D.E. Newby, G. Roditi, Impact of noncardiac findings in patients undergoing CT coronary angiography: a substudy of the Scottish computed tomography of the heart (SCOT-HEART) trial, Eur. Radiol. 28 (6) (2018) 2639–2646, https://doi.org/10.1007/s00330-017-5181-5.

[23] R.S. Wiener, M.K. Gould, C.G. Slatore, B.G. Fincke, L.M. Schwartz, S. Woloshin, Resource use and guideline concordance in evaluation of pulmonary nodules for cancer: too much and too little care, JAMA Intern. Med. 174 (6) (2014) 871–880, https://doi.org/10.1001/jamainternmed.2014.561.

[24] S.-H. investigators, CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial, Lancet 385 (9985) (2015) 2383–2391, https://doi.org/10.1016/S0140-6736(15)60291-4.

[25] U. Hoffmann, M. Ferencik, J.E. Udelson, M.H. Picard, Q.A. Truong, M.R. Patel, M. Huang, M. Pencina, D.B. Mark, J.F. Heitner, C.B. Fordyce, P.A. Pellikka, J.C. Tardif, M. Budoff, G. Nahhas, B. Chow, A.S. Kosinski, K.L. Lee, P.S. Douglas, P. Investigators, Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial (Prospective multicenter imaging study for evaluation of chest pain), Circulation 135 (24) (2017) 2320–2332, https://doi.org/10.1161/CIRCULATIONAHA.116.024360.

[26] M. Dewey, M. Rief, P. Martus, B. Kendziora, S. Feger, H. Dreger, S. Priem, F. Knebel, M. Bohm, P. Schlattmann, B. Hamm, E. Schonenberger, M. Laule, E. Zimmermann, Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial, BMJ 355 (2016), https://doi.org/10.1136/bmj.i5441 i5441l.

[27] H.M. Marshall, H. Zhao, R.V. Bowman, L.H. Passmore, E.M. McCaul, I.A. Yang, K.M. Fong, The effect of different radiological models on diagnostic accuracy and lung cancer screening performance, Thorax 72 (12) (2017) 1147–1150, https://doi.org/10.1136/thoraxjnl-2016-209624.

[28] Y. Liu, H. Wang, Q. Li, M.J. McGettigan, Y. Balagurunathan, A.L. Garcia, Z.J. Thompson, J.J. Heine, Z. Ye, R.J. Gillies, M.B. Schabath, Radiologic features of small pulmonary nodules and lung cancer risk in the national lung screening trial: a nested case-control study, Radiology 286 (1) (2018) 298–306, https://doi.org/10.1148/radiol.2017161458.

[29] K.C. Lee, H.S. Yong, J. Lee, E.Y. Kang, J.O. Na, Is the epicardial adipose tissue area on non-ECG gated low-dose chest CT useful for predicting coronary atherosclerosis in an asymptomatic population considered for lung cancer screening? Eur. Radiol. (2018), https://doi.org/10.1007/s00330-018-5562-4.

[30] O.M. Mets, P.A. de Jong, E.T. Scholten, K. Chung, B. van Ginneken, C.M. Schaefer-Prokop, Subsolid pulmonary nodule morphology and associated patient characteristics in a routine clinical population, Eur. Radiol. 27 (2) (2017) 689–696, https://doi.org/10.1007/s00330-016-4429-9.

[31] J.E. Scholtz, M.T. Lu, S. Hedgire, N.M. Meyersohn, G.R. Oliveira, A.M. Prabhakar, R. Gupta, M.K. Kalra, J.O. Shepard, U. Hoffmann, B.B. Ghoshhajra, Incidental pulmonary nodules in emergent coronary CT angiography for suspected acute coronary syndrome: impact of revised 2017 Fleischner Society Guidelines, J. Cardiovasc. Comput. Tomogr. 12 (1) (2018) 28–33, https://doi.org/10.1016/j.jcct.2017.11.005.

[32] K. Chung, O.M. Mets, P.K. Gerke, C. Jacobs, A.M. den Harder, E.T. Scholten, M. Prokop, P.A. de Jong, B. van Ginneken, C.M. Schaefer-Prokop, Brock malignancy risk calculator for pulmonary nodules: validation outside a lung cancer screening population, Thorax (2018), https://doi.org/10.1136/thoraxjnl-2017-211372.