Published in final edited form as:

Lung Cancer. 2017 December ; 114: 38–43. doi:10.1016/j.lungcan.2017.10.008.

Vasculature surrounding a nodule: a novel lung cancer biomarker

Xiaohua Wang¹, Joseph K. Leader¹, Renwei Wang², David Wilson^{2,3}, James Herman^{2,4}, Jian-Min Yuan^{2,5}, and Jiantao Pu^{1,6,*}

¹Department of Radiology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

²University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania, USA

³Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

⁴Division of Hematology/Oncology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

⁵Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

⁶Department of Bioengineering, University of Pittsburgh, Pittsburgh

Abstract

Purpose—To investigate whether the vessels surrounding a nodule depicted on non-contrast, low-dose computed tomography (LDCT) can discriminate benign and malignant screen detected nodules.

Materials and Methods—We collected a dataset consisting of LDCT scans acquired on 100 subjects from the Pittsburgh Lung Screening study (PLuSS). Fifty subjects were diagnosed with lung cancer and 50 subjects had suspicious nodules later proven benign. For the lung cancer cases, the location of the malignant nodule in the LDCT scans was known; while for the benign cases, the largest nodule in the LDCT scan was used in the analysis. A computer algorithm was developed to identify surrounding vessels and quantify the number and volume of vessels that were connected or near the nodule. A nonparametric receiver operating characteristic (ROC) analysis was performed based on a single nodule per subject to assess the discriminability of the surrounding vessels to provide a lung cancer diagnosis. Odds ratio (OR) were computed to determine the probability of a nodule being lung cancer based on the vessel features.

Corresponding Author and Guarantor of the entire manuscript: Jiantao Pu, Ph.D., Department of Radiology & Bioengineering, University of Pittsburgh, 3362 Fifth Avenue, Pittsburgh, PA 15213, Tel: (412)-641-2571, Fax: (412)-641-2582, puj@upmc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Author contributions

XW, JP: develop method, analyzed and interpreted data, manuscript preparation

JKL, JP: analyzed and interpreted data, manuscript preparation

RW: analyzed and interpreted data

DW, JH, JMY, and JP: designed and supervised the study, read and approved final manuscript

Conflicts of interest

The authors declare that there no conflict of interest.

Results—The areas under the ROC curves (AUCs) for vessel count and vessel volume were 0.722 (95% CI=0.616-0.811, $p < 0.01$) and 0.676 (95% CI= 0.565-0.772), respectively. The number of vessels attached to a nodule was significantly higher in the lung cancer group 9.7 (± 9.6) compared to the nonlung cancer group 4.0 (± 4.3)

Conclusion—Our preliminary results showed that malignant nodules are often surrounded by more vessels compared to benign nodules, suggesting that the surrounding vessel characteristics could serve as lung cancer biomarker for indeterminate nodules detected during LDCT lung cancer screening using only the information collected during the initial visit.

Keywords

lung cancer; vasculature; low dose CT; cancer screening

I. INTRODUCTION

Lung cancer remains the leading cause of cancer deaths in the United States (U.S.) and worldwide, exceeding the next three cancers combined [1]. The high mortality rate of lung cancer is in part reflective of the lack of physical symptoms in the early stages of disease leading to late diagnosis [2] and lack of lung cancer screening. The early work by Henschke et al 1999 [3] in the Early Lung Cancer Action Project (ELCAP) demonstrated the efficacy of using low-dose CT (LDCT) scans of the chest for lung cancer screening compared to chest x-ray. This work was followed-up by the larger National Lung Screening Trial (NLST) that observed a 20% reduction in lung cancer mortality when using LDCT exams for lung cancer screening compared to chest x-ray [4–5]. However, 24% of the NLST participants screened had indeterminate lung nodules that required follow-up, but 96% of these nodules were found to be non-cancerous (or false positives). These false positives may lead to harmful and/or costly unintended consequences (e.g., follow-up CT scans, positron emission tomography (PET)/CT exam, invasive biopsies) [6–7]. The high false positive rate and the associated over-diagnosis demonstrate the need to improve the efficacy of CT-based lung cancer screening.

In effort to reduce the devastating lung cancer burden, lung cancer screening using LDCT examination has become more common in the clinic and was recently approved for reimbursed in the U.S. healthcare system. The high prevalence of indeterminate nodules detected during LDCT screening is one challenging aspect of screening and will need to be addressed as the practice of lung screening grows [4]. Although there has been significantly more research effort in image processing focused on lung nodule detection compared to nodule diagnosis, investigators have worked on nodule diagnosis for more than 20 years using a variety of image processing and evaluation approaches [8–23]. Image features developed to discriminate benign and malignant nodules have included nodule morphology, nodule density, image texture, deep learning, and many others that were used in a variety of classifiers.

The fact that tumor angiogenesis is critical to tumor viability and growth has been well recognized in biology as a hallmark of lung cancer risk, progression, and therapeutic efficacy [24]. An invasive, *ex vivo* procedure is the standard approach to assess tumor

angiogenesis that involves sampling the tumor to evaluate its microvascular density (MVD) and assess the metabolic burden of the supported tumor cells. Several imaging techniques have been developed to indirectly assess tumor angiogenesis by quantifying the level of perfusion or metabolic activity in the nodule (e.g., CT scan, dual energy CT scan, positron emission tomography (PET)/CT, and magnetic resonance imaging (MRI)) implementing various approaches (e.g., dynamic imaging, contrast-enhanced imaging, image texture analysis) [13, 25–31]. These techniques focus primarily on a tumor's internal micro-vascularity. Mori et al. 1990 [32] made one of the first observations of tumor angiogenesis on CT images outside the nodule and reported that pulmonary veins converged toward malignant nodules significantly more than towards benign nodules. Other reports in the literature support the idea that the vasculature converging towards or surrounding a nodule depicted on CT images may be related to lung cancer stage and pathology [33–37].

In this study, we investigated if the vessels surrounding a lung nodule could discriminate between benign and malignant nodules. Computer algorithms were developed to detect and quantify tube-like structures in the local environment surrounding a nodule depicted in non-contrast LDCT scans. Fifty paired CT scans with verified benign and malignant nodules acquired on different subjects were collected retrospectively from a lung cancer screening study to test whether the presence of vessels (i.e., tube-like structures) will be significant greater in the local environment of a malignant nodule compared to a benign nodule.

II. METHODS AND MATERIALS

A. Data sources

This study evaluated lung nodules depicted on lung cancer screening CT exams of the chest performed on participants in the Pittsburgh Lung Screening Study (PLuSS) [38]. PLuSS is a community-based research cohort that recruited 3,642 participants that were current and former smokers. Each PLuSS participant completed a questionnaire, underwent spirometry for pulmonary function testing (PFT), received a chest LDCT exam, and provided a blood sample. All of the 3,642 participants received a baseline LDCT scan, and 3,423 participants received a follow-up LDCT scan one-year later. The PLuSS extension study recruited a subset of 970 original PLuSS participants who received biennial LDCT scans and other procedures over nearly 16 years from the baseline procedures. From the 299 confirmed lung cancer cases we random selected 50 subjects with screen detected nodules between with a diameter between 0.4 and 4.0 cm. Additionally, from the 1,443 cases with confirmed benign nodules (detected at either baseline or follow-up) we randomly selected 50 subjects with screen detected nodules with a diameter between 0.4 and 4.0 cm as measured by a radiologist on CT images. The baseline LDCT scan or the LDCT scan with the first appearance of the lung nodule in either the benign or malignant cases was used in this study. In the lung cancer dataset, the tumor location was known. In the benign dataset, the largest nodule on the selected LDCT scan was used in the analysis. All participants provided written informed consent as approved by the University of Pittsburgh IRB (University of Pittsburgh IRB # 011171).

B. CT examination

The chest CT examinations were performed on a General Electric scanner (GE) without radiopaque contrast with the participants in a supine position and holding their breath at end-inspiration. The CT data were acquired using helical technique at a low radiation exposure (40 mAs) without tube current modulation. Contiguous CT images were reconstructed using GE's lung kernel at a 2.5 mm thickness.

C. Quantification of vasculature surrounding a nodule

We first used a computer algorithm [39–40] to automatically detect, segment, and compute dimensional statistics of manually identified nodules on LDCT images (Figure 1(A)-(B)). A sub-volume located at the center of the segmented with a size of $50 \times 50 \times 50 \text{ mm}^3$ was extracted. The blood vessels within the sub-volume were identified using another image processing algorithm as previously described [41], which was designed for automated detection of tubular structures in volumetric images. Finally, a skeletonization procedure [41] was used to extract the centerline of the identified vessels.

To quantify the vessels surrounding a nodule, only the vessels in the sub-volume that are connected or close enough to a nodule are evaluated. The distance and direction criterion used to determine whether a vessel skeleton surrounding a nodule was evaluated (the following criteria use vessel nomenclature in Figure 2):

1. a skeleton (e.g., V2) is attached directly to a nodule;
2. a skeleton (e.g., V6) is very close (e.g., 3 mm) to a nodule.
3. a skeleton's path is projected towards the center of a nodule and less than 5.0 mm from the nodule (e.g., V5). "Projecting toward" the nodule is defined as skeletons with an angle less than 15 degrees between the skeleton's trajectory and a line between the end of the skeleton and the nodule's center. As compared to (2), a direction condition is used to assure that the vessels, which might be disconnected due to existing image noises or the limit of image resolution, will be taken into account.

Skeletons that are within the sub-volume but do not meet the above criterion are not evaluated, such as the skeletons V1, V3, and V4 in Figure 3. Computation of the volume of vessels surrounding a nodule included all vessels in the sub-volume, regardless of contact (or projected contact) to a nodule. It is notable that only the skeletons at the end of the vessels are considered and those with a length less than 3.5 mm are discarded. For example, the skeleton V1 is not considered in the quantification.

D. Data Analysis

Group level comparisons were evaluated using Chi-square for categorical or nominal variables and Student's T-test for continuous variables of subject demographics, clinical characteristics, and image features. Correlation between the surrounding vessel features was tested with the Pearson Correlation coefficient (PCC). The hypothesis that the vessels surrounding a nodule will be greater in the lung cancer group compared to the non-lung cancer group was tested using a one-tailed T-test. Odds ratio (OR) and 95% confidence

interval (CI) for lung cancer were estimated for categories of CT-depicted nodule and surrounding vessel characteristics using dichotomized data. A receiver operating characteristic (ROC) analysis was performed to evaluate the ability of the surrounding vessel features to discriminate between benign and malignant nodules. In all analyses, a p-value less than 0.05 was considered statistically significant. The analyses were performed using SPSS Version 24.

III. RESULTS

There were no significant differences in the demographics between the lung cancer and non-lung cancer groups in terms of gender, age, smoking status, and smoking history (Table 1). Additionally, there were also not significant differences in lung disease associated with smoking such as physician-diagnosed emphysema and chronic obstructive pulmonary disease (COPD) assessed using the Global Initiative for COPD [35]. Although the lung nodules in the lung cancer group were on average slightly larger than the non-lung cancer group, the difference did not reach statistical significance (Table 1). The mean lung nodule diameter in the lung cancer and non-lung cancer groups were 1.4 (± 0.6) cm and 1.0 (± 0.6) cm, respectively, measured on CT images by a radiologist. Finally, there was no significant difference between the number of solid and part-solid nodules in the two groups.

The number of vessels attached to a nodule was significantly higher in the lung cancer group 9.7 (± 9.6) compared to the non-lung cancer group 4.0 (± 4.0) (Fig. 3, Table 2). However, the volume of vessels surrounding the nodules was not significant between the two groups. Vessel count and vessel volume were significantly correlated (PCC = 0.613, $p < 0.05$). In the lung cancer group, nodule size was significantly correlated to vessel count (PCC = 0.396, $p < 0.05$) and vessel volume (PCC = 0.320, $p < 0.05$), but the correlation was weak and nodules size only accounted for 16% and 10% of the variance in vessel count and vessel volume, respectively. Similarly in the non-lung cancer group, nodule size was significantly correlated to vessel count (PCC = 0.462, $p < 0.05$) and vessel volume (PCC = 0.443, $p < 0.05$), but the correlation was also weak and nodules size only accounted for 21% and 20% of the variance in vessel count and vessel volume, respectively.

When the surrounding vessel data was dichotomized there were significantly greater odds ratios (OR) that a nodule was malignant when the vessel count was greater than or equal to 2 and vessel volume was greater than 0.17 ml, OR = 4.0 [lower 95% confidence limit (LCL) = 1.2, upper 95% confidence limit (UCL) = 13.4] and 6.0 [LCL = 2.0, UCL = 17.7], respectively. In the dichotomized data, vessel count and vessel volume had a sensitivity of 92.0% and 90.0%, respectively, and a specificity of 26.0% and 40.0%, respectively. Both surrounding vessel features had a modest ability to discriminate benign and malignant nodules in the ROC analysis (Figure. 4). The area under the curve for vessel count and vessel volume were 0.722 [LCL = 0.616, UCL = 0.811] and 0.676 [LCL = 0.565, UCL = 0.772], which were not significantly different.

IV. DISCUSSION

Our study suggests that the vessels converging towards or surrounding an indeterminate nodule is an important image biomarker for discriminating benign and malignant lung nodules during lung cancer screening. To our knowledge, this is the first investigation to quantify the vessels surrounding a nodule depicted on non-contrast LDCT images and its relation to malignancy. The two features individually investigated, which were the number of vessels connected to and volume of vessels surrounding a nodule, both demonstrated a modest ability to discriminate benign and malignant nodules in LDCT scans. Although the LDCT protocol is suboptimal for the sophisticated computer analysis performed, we believe it is important to evaluate the performance of the algorithm in assessing indeterminate nodules in a lung cancer screening dataset given the increasing availability of lung cancer screening by LDCT examinations. Our goal is to reduce the follow-up procedures initiated during LDCT lung screening using the data collected during the initial screening visit.

The count of vessels connected to a nodule and the volume of vessels surrounding a nodule used as quantified image features in this study were strongly correlated. In a dichotomized dataset, to achieve greater than 90% sensitivity vessel count and vessel volume had specificities of 40.0% and 26.0%, respectively. In general, it was easier to maintain a high sensitivity without reducing specificity too much when dichotomizing the vessel count compared to the vessel volume. This finding may in part be due to the fact that we did not separate pulmonary arteries and veins. Mori et al. 1990 [35] observed that the count of arteries converging towards a nodule was not significantly different between malignant and nodules, but that the count of veins was significantly greater in malignant compared to benign nodules. In our study, malignant nodules had a significantly higher count of attached vessels compared to benign nodules. Similarly, all of malignant nodules and 88% of the benign nodules in the Mori et al study had arteries attached, but 93% of the malignant nodules and only 13% of benign nodules had veins attached. The vessel volume surrounding a nodule feature only required the presence of a vessel in the sub-volume around a nodule and did not require attachment or convergence toward the nodule. Consequently, most malignant nodules had a high vessels volume as did a high percentage of benign nodules. Gao et al. [36] reported that 49 % of malignant and 90% benign ground glass nodules had vessels by-pass or pass through the nodules on CT images, but that 51% of the malignant nodules had distorted, dilated, or complicated vessel appearance near the nodules. They did not find a difference between the presence of arteries and veins.

The two features we developed and investigated proved to have modest power to discriminate between benign and malignant nodules, but performed slightly different, which suggests that a combination of the two features may improve discriminatory performance. Our study used lung cancer screening non-contrast LDCT scans to assess indeterminate nodules, while other studies reporting on vessel convergence [16, 20] that used diagnostic CT scans. One common observation in this and other studies is that vessel depiction on CT images provides information that can be utilized to discriminate benign and malignant nodules, but it is a complex association.

In addition to assisting in the evaluation of screen-detected pulmonary nodules, our surrounding vessel CT image features may also have an important role in predicting disease course and treatment efficacy. In a histopathological study of cohort of 86 cancer cases, Rigau et al. [34] investigated peritumoral and intratumoral vascular invasion of lung tumors. The presence of vascular invasion of the tumor was significantly related to a decreased length of event free survival and in early stage cancer increased incidence of metastatic relapse. Although this was a microscopic study, it is possible that our surrounding vessel feature based on CT images could act as a surrogate marker of vascular invasion of a tumor. Since several lung cancer treatment regimens target tumor angiogenesis [42], surrounding vessel image features appear well suited to assist in quantifying response to these types of treatments. Specifically, we believe a decrease in the vessels connected to or surrounding a nodule in serial CT scans may provide evidence that the tumor is receiving and/or demanding less nourishment to grow and metastasize or more importantly halting growth. Both of these applications would require higher quality CT scans with the possible addition of contrast-enhancement (e.g., iodine contrast) to improve depiction of the vascular system compared to non-contrast LDCT lung cancer screening scans.

Although many investigators have used diagnostic CT scans to diagnose indeterminate nodules [9–11, 13–16, 17–23], another group also used computer analysis of LDCT scans from a lung cancer screening program to discriminate benign and malignant nodules [13, 16]. In their initial study, 7 features (out of 43) were used in a linear discriminate analysis and an AUC of 0.846 was achieved for discriminating benign and malignant nodules [12]. In the follow-up study, a massive training artificial neural network was used on the same dataset and performance improved to AUC= 0.875 for the nontraining cases and 0.882 for the entire dataset [13]. Although the performance of our two features was not as high as the above more complex studies, our study evaluated two image features independently and achieved a modest performance for each feature (AUC = 0.722 and 0.676). How our features will perform in combination with other features in a sophisticated classification process will be investigated in the future.

Two recent studies applied the burgeoning deep learning approach to classify nodules as benign or malignant and both studies report good performance with AUCs of 0.946 [22] and 0.899 [23]. However, nodule status (i.e., benign or malignant) was determined by subjective visual rating of radiologist and it appears there were more diagnostic CT scans than LDCT scans in the dataset. There is a large variability in radiologists agreement in nodule detection and diagnosis [13, 43–44], which indicates that studies based on radiologists interpretation are based on an approximation of truth. Therefore, matching a radiologist subjective assessment of indeterminate nodules may not be the ultimate target because radiologists often recommend additional follow-up procedures (e.g., follow-up imaging, biopsy) to conclusively determine nodule status. Ultimately, if a set (or single) of image features could rule-out indeterminate nodules detected on a screening LDCT scan, then such a feature set would eliminate a lot of unnecessary follow-up and potentially harmful procedure.

There are several limitations to our preliminary study. First, non-contrast LDCT scans (40 mAs) reconstructed at relatively thick (2.5mm) images for lung cancer screening were used in the study, which are suboptimal for the task of quantifying the vessels surrounding a

nodule. Although some of our algorithm development was performed on higher quality CT scans (higher radiation exposure and thinner images), we believe that in light of the recent increase in lung cancer screening it was important to evaluate the performance of the surrounding vessel features in non-contrast LDCT scans. To overcome the potential for poor resolution of small vessel in the low-dose images, we used several direction and distance criterion (Section II.B) to detect and quantify the vessels. Therefore, we believe this study represent the nadir performance regarding the discrimination of benign and malignant nodules. Second, we are developing several other image features to quantify the vasculature surrounding a nodule (e.g., tortuosity, spatial crossing pattern) in higher quality CT scans. In the future, including all the vasculature image features in a model may improve the ability to determine nodule malignancy compared to the present study. But, this study represents the current performance of our algorithm in LDCT scans. Third, we did not control for nodule size in the computation of the surrounding vessel features. This may have introduced a bias into the surrounding vessel count and volume results.. However, we do not think the absence of controlling for nodule size had a significant influence in our study because the correlations between nodule size and surrounding vessel count and volume were weak and nodule size was not significantly different between the two groups. Fourth, the sample size was small (n=100), but it was balanced between benign and malignant cases and the LDCT protocol was the same for all subjects. Finally, this was a study of cases from a single institution and may or may not be generalizable to other institutions.

V. CONCLUSION

Inspired by the role of angiogenesis in tumor growth and metastasis, we found that the vessels surrounding a nodule depicted on CT images are a potential lung cancer biomarker. Our morphology based image features that quantified the surrounding vessels were significantly different in the lung group compared to the non-lung cancer group despite testing with suboptimal CT image. Since our findings were observed using suboptimal lung cancer screening non-contrast LDCT exams, it provides a preliminary indication that our approach to quantify a nodule's surrounding vessels may have a role in evaluation of indeterminate nodules detected during lung cancer screening. We believe that any tool (or image features) that has a high sensitivity with even a modest specificity for discriminating indeterminate nodules as benign or malignant based on the data collected during the initial screening visit could improve the efficacy of lung cancer screening.

Acknowledgments

This work is supported in part by National Institutes of Health (NIH) Grants R21-CA197493, R01-HL096613, the University of Pittsburgh Cancer Institute's Specialized Program of Research Excellence (SPORE) in Lung Cancer (NCI P50-CA90440), the Cancer Center Core Grant (NCI 2P30 CA047904), and NSF- 81641075.

References

1. Cancer Facts & Figures 2014. [Accessed October 2014] American Cancer Society. 2014. Available at <http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151pdf>
2. Flehinger BJ, Kimmel M, Melamed MR. Survival from early lung cancer: implications for screening. *Chest*. 1992; 101:1013–1018. [PubMed: 1313349]

3. Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, Libby DM, Pasmantier MW, Koizumi J, Altorki NK, Smith JP. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet*. 1999; 354(9173):99–105. [PubMed: 10408484]
4. Aberle DR, DeMello S, Berg CD, et al. National Lung Screening Trial Research Team. Results of the two incidence screenings in the National Lung Screening Trial. *N Engl J Med*. 2013; 369:920–31. [PubMed: 24004119]
5. National Lung Screening Trial Research Team. The National Lung Screening Trial: overview and study design. *Radiology*. 2011; 258:243–53. [PubMed: 21045183]
6. Park ER, Gareen IF, Jain A, et al. Examining whether lung screening changes risk perceptions: National Lung Screening Trial participants at 1-year follow-up. *Cancer*. 2013; 119:1306–13. [PubMed: 23280348]
7. Thalanayar PM, Altintas N, Weissfeld JL, Fuhrman CR, Wilson DO. Indolent Potentially Inconsequential Lung Cancers in the Pittsburgh Lung Screening Study (PLuSS). *Ann Am Thorac Soc*. 2015; 12(8):1193–96. [PubMed: 26107281]
8. Gurney JW, Swensen SJ. Solitary pulmonary nodules: determining the likelihood of malignancy with neural network analysis. *Radiology*. 1995; 196(3):823–9. [PubMed: 7644650]
9. McNitt-Gray MF, Hart EM, Wyckoff N, Sayre JW, Goldin JG, Aberle DR. A pattern classification approach to characterizing solitary pulmonary nodules imaged on high resolution CT: preliminary results. *Medical Physics*. 1999; 26(6):880–8. [PubMed: 10436888]
10. Nakamura K, Yoshida H, Engelmann R, MacMahon H, Katsuragawa S, Ishida T, Ashizawa K, Doi K. Computerized analysis of the likelihood of malignancy in solitary pulmonary nodules with use of artificial neural networks. *Radiology*. 2000; 214(3):823–30. [PubMed: 10715052]
11. Matsuki Y, Nakamura K, Watanabe H, Aoki T, Nakata H, Katsuragawa S, Doi K. Usefulness of an artificial neural network for differentiating benign from malignant pulmonary nodules on high-resolution CT: evaluation with receiver operating characteristic analysis. *AJR: American Journal of Roentgenology*. 2002; 178(3):657–63. [PubMed: 11856693]
12. Aoyama M, Li Q, Katsuragawa S, Li F, Sone S, Doi K. Computerized scheme for determination of the likelihood measure of malignancy for pulmonary nodules on low-dose CT images. *Medical Physics*. 2003; 30(3):387–94. [PubMed: 12674239]
13. Li F, Aoyama M, Shiraishi J, Abe H, Li Q, Suzuki K, Engelmann R, Sone S, Macmahon H, Doi K. Radiologists' performance for differentiating benign from malignant lung nodules on high-resolution CT using computer-estimated likelihood of malignancy. *AJR: American Journal of Roentgenology*. 2004; 183(5):1209–15. [PubMed: 15505279]
14. Matsuoka S, Kurihara Y, Yagihashi K, Niimi H, Nakajima Y. Peripheral solitary pulmonary nodule: CT findings in patients with pulmonary emphysema. *Radiology*. 2005; 235(1):266–73. [PubMed: 15716392]
15. Shah SK, McNitt-Gray MF, Rogers SR, Goldin JG, Suh RD, Sayre JW, Petkovska I, Kim HJ, Aberle DR. Computer aided characterization of the solitary pulmonary nodule using volumetric and contrast enhancement features. *Academic Radiology*. 2005; 12(10):1310–9. [PubMed: 16179208]
16. Suzuki K, Li F, Sone S, Doi K. Computer-aided diagnostic scheme for distinction between benign and malignant nodules in thoracic low-dose CT by use of massive training artificial neural network. *IEEE Transactions on Medical Imaging*. 2005; 24(9):1138–50. [PubMed: 16156352]
17. Way TW, Sahiner B, Chan HP, Hadjiiski L, Cascade PN, Chughtai A, Bogot N, Kazerooni E. Computer-aided diagnosis of pulmonary nodules on CT scans: improvement of classification performance with nodule surface features. *Medical Physics*. 2009; 36(7):3086–98. [PubMed: 19673208]
18. Iwano S, Nakamura T, Kamioka Y, Ikeda M, Ishigaki T. Computer-aided differentiation of malignant from benign solitary pulmonary nodules imaged by high-resolution CT. *Computerized Medical Imaging and Graphics*. 2008; 32(5):416–22. [PubMed: 18501556]
19. Chen H, Xu Y, Ma Y, Ma B. Neural network ensemble-based computer-aided diagnosis for differentiation of lung nodules on CT images: clinical evaluation. *Academic Radiology*. 2010; 17(5):595–602. [PubMed: 20167513]

20. Lee MC, Boroczky L, Sungur-Stasik K, Cann AD, Borczuk AC, Kawut SM, Powell CA. Computer-aided diagnosis of pulmonary nodules using a two-step approach for feature selection and classifier ensemble construction. *Artificial Intelligence in Medicine*. 2010; 50(1):43–53. [PubMed: 20570118]
21. Emaminejad N, Qian W, Guan Y, Tan M, Qiu Y, Liu H, Zheng B. Fusion of Quantitative Image and Genomic Biomarkers to Improve Prognosis Assessment of Early Stage Lung Cancer Patients. *IEEE Transactions on Biomedical Engineering*. 2016; 63(5):1034–43. [PubMed: 26390440]
22. Nibali A, He Z, Wollersheim D. Pulmonary nodule classification with deep residual networks. *International Journal of Computer Assisted Radiology and Surgery*. 2017
23. Sun W, Zheng B, Qian W. Automatic feature learning using multichannel ROI based on deep structured algorithms for computerized lung cancer diagnosis. *Computers in Biology and Medicine*. 2017 in press.
24. Angiogenesis. [Accessed October 2014] National Cancer Institute. 2014. Available at <http://www.cancer.gov/cancertopics/understandingcancer/angiogenesis>
25. Baxa J, Vondrakova A, Matouskova T, Ruzickova O, Schmidt B, Flohr T, et al. Dual-phase dual-energy CT in patients with lung cancer: assessment of the additional value of iodine quantification in lymph node therapy response. *Eur Radiol*. 2014; 24(8):1981–8. [PubMed: 24895031]
26. Harders SW, Madsen HH, Nellesmann HM, Rasmussen TR, Thygesen J, Hager H, et al. Dynamic contrast-enhanced CT in suspected lung cancer: quantitative results. *Br J Radiol*. 2013; 86(1031): 20130257. [PubMed: 24029629]
27. Steinert HC. PET and PET-CT of lung cancer. *Methods Mol Biol*. 2011; 727:33–51. [PubMed: 21331927]
28. Tateishi U, Kusumoto M, Nishihara H, Nagashima K, Morikawa T, Moriyama N. Contrast-enhanced dynamic computed tomography for the evaluation of tumor angiogenesis in patients with lung carcinoma. *Cancer*. 2002; 95(4):835–42. [PubMed: 12209728]
29. Chae EJ, Song JW, Krauss B, Song KS, Lee CW, Lee HJ, et al. Dual-energy computed tomography characterization of solitary pulmonary nodules. *J Thorac Imaging*. 2010; 25(4):301–10. [PubMed: 21042068]
30. Schmid-Bindert G, Henzler T, Chu TQ, Meyer M, Nance JW Jr, Schoepf UJ, et al. Functional imaging of lung cancer using dual energy CT: how does iodine related attenuation correlate with standardized uptake value of 18FDG-PET-CT? *Eur Radiol*. 2012; 22(1):93–103. [PubMed: 21822784]
31. Li Y, Yang ZG, Chen TW, Chen HJ, Sun JY, Lu YR. Peripheral lung carcinoma: correlation of angiogenesis and first-pass perfusion parameters of 64-detector row CT. *Lung Cancer*. 2008; 61(1): 44–53. [PubMed: 18055062]
32. Mori K, Saitou Y, Tominaga K, Yokoi K, Miyazawa N, Okuyama A, Sasagawa M. Small nodular lesions in the lung periphery: new approach to diagnosis with CT. *Radiology*. 1990; 177(3):843–849. [PubMed: 2243999]
33. Wang Y, Liang KR, Liu XG, Wang JA, Kang JH, Liang MZ. Relationship between peripheral lung cancer and the surrounding bronchi, pulmonary arteries, pulmonary veins: a multidetector CT observation. *Clin Imaging*. 2011; 35(3):184–92. [PubMed: 21513854]
34. Rigau V, Molina TJ, Chaffaud C, Huchon G, Audouin J, Chevret S, et al. Blood vessel invasion in resected non small cell lung carcinomas is predictive of metastatic occurrence. *Lung Cancer*. 2002; 38(2):169–76. [PubMed: 12399129]
35. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, Rodriguez-Roisin R. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2013; 187(4):347–65. [PubMed: 22878278]
36. Gao F, Li M, Ge X, Zheng X, Ren Q, Chen Y, Lv F, Hua Y. Multi-detector spiral CT study of the relationships between pulmonary ground-glass nodules and blood vessels. *Eur Radiol*. 2013; 23(12):3271–3277. [PubMed: 23832317]
37. Yang Z, Sone S, Takashima S, Li F, Honda T, Yamada T. Small peripheral carcinomas of the lung: thin-section CT and pathologic correlation. *Eur Radiol*. 1999; 9(9):1819–1825. [PubMed: 10602957]

38. Wilson DO, Weissfeld JL, Fuhrman CR, Fisher SN, Balogh P, Landreneau RJ, Luketich JD, Siegfried JM. The Pittsburgh Lung Screening Study (PLuSS): outcomes within 3 years of a first computed tomography scan. *Am J Respir Crit Care Med*. 2008 Nov 1; 178(9):956–61. [PubMed: 18635890]
39. Pu J, Zheng B, Leader JK, Wang XH, Gur D. An automated CT based lung nodule detection scheme using geometric analysis of signed distance field. *Med Phys*. 2008; 35:3453–61. [PubMed: 18777905]
40. Pu J, Paik DS, Meng X, Roos JE, Rubin DG. Shape “break-and-repair” strategy and its application to computerized medical image segmentation. *IEEE Trans. Visualization and Computer Graphics*. 2011; 17:115–124. [PubMed: 21071791]
41. Pu J, Fuhrman C, Good WF, Sciurba FC, Gur D. A differential geometric approach to automated segmentation of human airway tree. *IEEE Trans Med Imaging*. 2011; 30:266–78. [PubMed: 20851792]
42. Custodio A, de Castro J. Strategies for maintenance therapy in advanced non-small cell lung cancer: current status, unanswered questions and future directions. *Crit Rev Oncol Hematol*. 2012; 82(3):338–60. [PubMed: 21908201]
43. Armato SG 3rd, McNitt-Gray MF, Reeves AP, Meyer CR, McLennan G, Aberle DR, Kazerooni EA, MacMahon H, van Beek EJ, Yankelevitz D, Hoffman EA, Henschke CI, Roberts RY, Brown MS, Engelmann RM, Pais RC, Piker CW, Qing D, Kocherginsky M, Croft BY, Clarke LP. The Lung Image Database Consortium (LIDC): an evaluation of radiologist variability in the identification of lung nodules on CT scans. *Academic Radiology*. 2007; 14(11):1409–21. [PubMed: 17964464]
44. Young S, Lo P, Kim G, Brown M, Hoffman J, Hsu W, Wahi-Anwar W, Flores C, Lee G, Noo F, Goldin J, McNitt-Gray M. The effect of radiation dose reduction on computer-aided detection (CAD) performance in a low-dose lung cancer screening population. *Medical Physics*. 2017; 44(4):1337–46. [PubMed: 28122122]

Highlights

- Fifty-paired LDCT scans with benign / malignant lung cancer were collected
- Computerized schemes to quantify the vasculatures around a nodule were used.
- Malignant nodules are often surrounded by more vessels than benign nodules.

Figure 1.

The basic steps for the extraction of the vasculature surrounding a nodule. (A) a LDCT scan and the delineated boundary of a nodule, (B) the 3D visualization of the nodule in A and its surrounding vasculature, (C) a zoomed-in visualization of the nodule and its surrounding structures, (D) the skeletons / centerlines of the vasculature in (C).

Figure 2.

Illustration of how the vasculature measures were computed. The shadowed region indicates a nodule, and the lines (i.e., V1 – V6) indicate the vessel skeletons. The red lines (i.e., V2, V5, and V6) are classified as surrounding vessels, because V2 is directly attached to the nodule, V5 is close to the nodule and at same time projected towards the center of the nodule, V6 is very close to the nodule. The blue ones (i.e., V1, V3, and V4) are not classified as surrounding vessels since they do not meet the defined criteria.

Figure 3.
Three-dimensional visualization of the vessels surrounding two nodules: (A)-(B) malignant tumor. (C)-(D) benign nodule.

Figure 4. Receiver operator characteristic analysis of vessel count (solid line) and vessel volume (dotted line) to discriminate benign and malignant nodules. Area under the curve and 95% confidence interval for vessel count and vessel volume were 0.695 [0.588-0.787] and 0.663 [0.556-0.759], respectively.

Table 1

Subject demographics

	lung cancer (n=50)	non-lung cancer (n=50) ^I
Male, n (%)	25 (50)	29 (58)
Age, mean yrs (SD)	63.7 (7.0)	65.4 (7.0)
Current smoker, n (%)	32 (64)	25 (50)
Smoking history, mean pack-years (SD)	60.6 (24.3)	62.0 (23.5)
Emphysema, n (%)	35 (70)	34 (68)
GOLD score, n (%)		
mild COPD	7 (14)	11 (22)
moderate COPD	22 (44)	10 (20)
severe COPD	6 (12)	11 (22)
very severe COPD	0 (0)	0 (0)
No COPD, n (%)	15 (30)	18 (36)
Nodule diameter, mean cm (SD)	1.4 (0.6)	1.0 (0.6)
Nodule type, n (%)		
Solid	27 (54)	41 (82)
Part-solid	23 (46)	9 (18)

^INo p-values were less than 0.05

GOLD – Global Initiative for Chronic Obstructive Lung Disease; COPD – chronic obstructive pulmonary disease

Table 2

Characteristics of vessels surrounding the nodule

	lung cancer (n=50)	non-lung cancer (n=50)
Vessel volume, mean ml (SD)	1.2 (1.7)	0.8 (1.7)
Vessel count, mean count (SD)	9.7 (9.6)	4.0 (4.3) ^I

^I
p-value < 0.05