Observational Study

Medicine

OPEN

Correlation of computed tomography quantitative parameters with tumor invasion and Ki-67 expression in early lung adenocarcinoma

Hao Dong, MD[a], Lekang Yin, PhD[b], Cuncheng Lou, MD[a], Junjie Yang, MD[c], Xinbin Wang, MD[a], Yonggang Qiu, MD[a,*]

Abstract

The purpose of the study is to investigate the correlation of computed tomography (CT) quantitative parameters with tumor invasion and Ki-67 expression in early lung adenocarcinoma.

The study involved 141 lesions in 141 patients with early lung adenocarcinoma. According to the degree of tumor invasion, the lesions were assigned into (adenocarcinoma in situ + minimally invasive adenocarcinoma) group and invasive adenocarcinoma (IAC) group. Artificial intelligence-assisted diagnostic software was used to automatically outline the lesions and extract corresponding quantitative parameters on CT images. Statistical analysis was performed to explore the correlation of these parameters with tumor invasion and Ki-67 expression.

The results of logistic regression analysis showed that the short diameter of the lesion and the average CT value were independent predictors of IAC. Receiver operating characteristic curve analysis identified the average CT value as an independent predictor of IAC with the best performance, with the area under the receiver operating characteristic curve of 0.893 ($P<.001$), and the threshold of –450 HU. Besides, the predicted probability of logistic regression analysis model was detected to have the area under the curve of 0.931 ($P<.001$). The results of Spearman correlation analysis showed that the expression level of Ki-67 had the highest correlation with the average CT value of the lesion ($r=0.403$, $P<.001$).

The short diameter of the lesion and the average CT value are independent predictors of IAC, and the average CT value is significantly positively correlated with the expression of tumor Ki-67.

Abbreviations: AAH = adenomatous hyperplasia, AI = artificial intelligence, AIS = adenocarcinoma in situ, AUC = area under the curve, CT = computed tomography, HRCT = high-resolution computed tomography, IAC = invasive adenocarcinoma, LUAD = lung adenocarcinoma, MIA = minimally invasive adenocarcinoma, ROC = receiver operating characteristic.

Keywords: computed tomography, Ki-67, lung adenocarcinoma, quantitative parameters, tumor invasion

1. Introduction

Lung cancer is the malignant tumor with the highest incidence and mortality worldwide.[1] Adenocarcinoma is the most common histologic type of lung cancer and its incidence has increased over the past few decades, accounting for more than 40% of the total nowadays.[2] In 2015, the World Health Organization adopted a new classification of lung adenocarcinoma (LUAD) according to the degree of tumor invasion, which was atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and (4) invasive adenocarcinoma (IAC).[3,4] The treatment options and prognoses of adenocarcinomas with different invasive degrees vary greatly. Existing studies showed that in patients with stage Ia lung cancer, the postoperative 5-year survival rate for AIS and

HD and LY contributed equally to this work.

This work was funded by the Policy Guidance Project of Major Science and Technology Plan for Social Development in Xiaoshan District, Hangzhou City of China (No. 2021309).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Radiology, First People's Hospital of Xiaoshan District, Hangzhou, Zhejiang, China, [b] Department of Radiology, Zhongshan Hospital, Fudan University, Shanghai, China, [c] Department of Pathology, First People's Hospital of Xiaoshan District, Hangzhou, Zhejiang, China.

[*] Correspondence: Yonggang Qiu, Department of Radiology, First People's Hospital of Xiaoshan District, Hangzhou, Zhejiang 311200, China (e-mail: bb46411545@sina.com).

How to cite this article: Dong H, Yin L, Lou C, Yang J, Wang X, Qiu Y. Correlation of computed tomography quantitative parameters with tumor invasion and Ki-67 expression in early lung adenocarcinoma. Medicine 2022;101:25(e29373).

Received: 19 November 2021 / Received in final form: 11 April 2022 / Accepted: 11 April 2022

http://dx.doi.org/10.1097/MD.0000000000029373

MIA could be close to 100%,[5] while the 5-year disease-free survival rate for IAC was only 74.6%.[6] In this context, it is particularly important to distinguish the pathological types of early LUAD before surgery.

Ki-67 antigen is a nuclear-related antigen associated with cell proliferation. Higher proportions of positive Ki-67 expression indicate stronger proliferative ability of tumor cells but worse prognosis of patients.[7] Although, there were some studies reporting the associations of the pathological type of lung cancer and the computed tomography (CT) signs with the Ki-67 antigen expression,[8–10] the correlation between the quantitative parameters of CT and the Ki-67 antigen expression in LUAD to our knowledge has not been reported yet.

It is known that in patients with LUAD, the invasiveness of tumor and the expression level of Ki-67 are closely related to the prognosis. Here, artificial intelligence (AI)-assisted diagnostic software was applied to explore the correlation of CT quantitative parameters of early LUAD with the degree of invasion and Ki-67 expression. It aims to provide more accurate and valuable information for clinical diagnosis and treatment of early LUAD, help clinically optimize the treatment plan in a non-invasive way and improve the prognosis of patients.

2. Materials and methods

2.1. Patients

The clinical data of 141 patients with early LUAD who underwent surgical treatment at our institute from June 2017 to May 2020 were collected. There were 58 males and 80 females, aged from 28 to 82 years old, with an average age of 59 ± 11. There were 63 lesions in the AIS+MIA group (13 in AIS and 50 in MIA) and 78 lesions in the IAC group. Inclusion criteria: patients were pathologically diagnosed with LUAD; patients have preoperative chest high-resolution computed tomography (HRCT) images within 1 month before surgery; on HRCT, the long diameter of the lesion was less than 3 cm, and there was no lymph node or distant metastases. Overall preoperative stage $\leq T_1N_0M_0$; and immunohistochemical examination of Ki-67 expression level within 1 week after surgery. Exclusion criteria: a history of other malignant tumors or comorbidities; No preoperative HRCT image data; presence of image artifacts that might affect the observation of CT signs of the lesion; and presence of lymph node or distant metastases. This study was approved by the Ethics Committee of Xiaoshan First People's Hospital (Protocol Number: 2019-XS-013).

2.2. Inspection methods

Philips Brilliance 64-slice spiral CT machine was used for scanning. All patients received breath-hold training before scanning, and kept breath-hold while breathing calmly during scanning. The scanning range was from the tip to the bottom of the lung, including the axilla and chest wall on both sides. Scanning parameters: tube voltage 130 kV, tube current 300 mA, pitch 0.64, reconstruction layer thickness 1 mm, and reconstruction interval 1 mm.

2.3. CT quantitative parameters

The original image data were transmitted to the workstation and then imported into the AI-assisted diagnostic software (InferRead CT Lung, version: V9.5; Beijing Infervision), a tool that can automatically outline the lesion and extract useful quantitative parameters. The quantitative parameters were recorded by a senior radiologist, including long diameter, short diameter, average diameter, maximum CT value, minimum CT value, average CT value, and volume. The long diameter, short diameter, and average diameter are derived from the largest cross-section of the lesion, and the maximum CT value, minimum CT value, and average CT value are derived from voxels in 3 dimensions of the lesion.

2.4. Pathological diagnosis and Ki-67 evaluation

Pathological specimens were routinely fixed in 10% formalin and then paraffin-embedded. The tissue section of the largest section plain of the tumor was cut into a thickness of 4 mm and stained with hematoxylin and eosin. An experienced pathologist made the pathological diagnosis according to the latest World Health Organization classification of LUAD in 2015. Standard immunohistochemical staining method was performed with anti-Ki-67 antibodies (monoclonal mouse antibody MIB-1, 1:100 dilution). The positive expression of Ki-67 was quantitatively analyzed based on the brown stained particles located in the nucleus. The positive expression level of Ki-67 is divided into 4 grades: grade I: <5%; grade II: ≥5% and <10%; grade III: ≥10% and <20%; and grade IV: ≥20%.

2.5. Statistical analysis

The SPSS 23.0 software (SPSS Inc., Chicago, IL, USA) completed data processing and statistical analysis. The measurement data were analyzed in Shapiro-Wilk test for normality, and were represented by $x \pm s$ in case of normal distribution, or M (Q) otherwise. Between-group comparison was completed by the Mann-Whitney U test. Univariate combined with multivariate logistic regression model was used to screen the independent predictors of IAC and retain predicted probability values. Receiver operating characteristic (ROC) curve analysis was performed on each CT quantitative parameter and the predicted probability of the logistic regression model to obtain the area under the curve (AUC) for sensitivity, specificity and cut-off. The correlation between CT quantitative parameters and Ki-67 expression adopted Spearman correlation analysis method, and the correlation coefficient was calculated. $P < .05$ indicates that the difference is statistically significant.

3. Results

3.1. CT quantitative parameters in AIS+MIA vs IAC

The long diameter ($P < .001$), short diameter ($P < .001$), average diameter ($P < .001$) of the lesion, and the maximum CT value ($P < .001$), minimum CT value ($P < .001$), average CT value ($P < .001$), and volume ($P < .001$) between the 2 groups were statistically different (Table 1). Representative images on HRCT, pathology, and Ki-67 immunostaining results of LUAD with different invasion degrees are shown in Figures 1–3.

3.2. Logistic regression analysis of AIS+MIA and IAC

The statistically significant variables in the univariate analysis were further analyzed in binary logistic regression analysis. The results showed that the short diameter of the lesion and the average CT value were independent predictors of IAC (Table 2).

Table 1

Comparison of CT quantitative parameters between AIS+MIA and IAC.

	AIS+MIA (n=63)	IAC (n=78)	Z	P
Long diameter (mm)	10 (7)	17 (7)	–6.297	<.001
Short diameter (mm)	8 (6)	13 (6)	–6.255	<.001
Average diameter (mm)	9 (6)	15 (6)	–6.317	<.001
Maximum CT value (HU)	86 (367)	254 (132)	–4.989	<.001
Minimum CT value (HU)	–782 (69)	–504 (344)	–7.645	<.001
Average CT value (HU)	–568 (169)	–189 (365)	–8.018	<.001
Volume (mm^3)	411 (676)	1247 (1736)	–6.028	<.001

AIS = adenocarcinoma in situ, CT = computed tomography, IAC = invasive adenocarcinoma, MIA = minimally invasive adenocarcinoma.

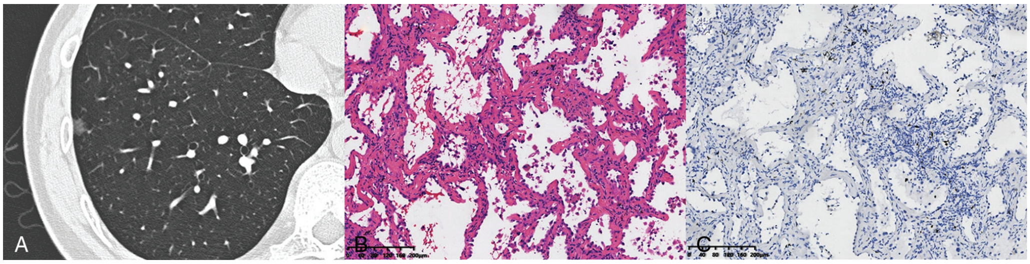

Figure 1. Image, pathology, and immunohistochemistry of pure ground glass nodules in the lower lobe of the right lung (male, 36 years old). (A) HRCT plain scan of the transverse lung window shows that the lesion is located in the lower lobe of the right lung. The long diameter is 8 mm, the average CT value is –646 HU, and the volume is 220 mm^3. (B) Surgical pathology confirms adenocarcinoma in situ (AIS) (HE × 100). (C) Immunohistochemical map, magnification × 100, and Ki-67 expression level is 1%. CT = computed tomography, HE = hematoxylin and eosin, HRCT = high-resolution computed tomography.

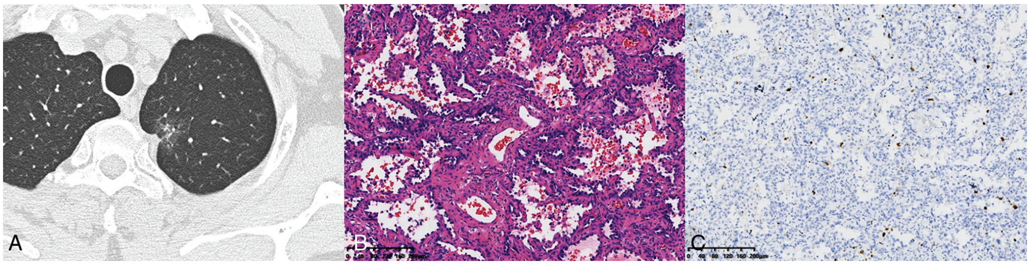

Figure 2. Image, pathology, and immunohistochemistry of mixed ground glass nodules in the superior lobe of the left lung (male, 58 years old). (A) HRCT plain scan of the transverse lung window shows that the lesion is located in the superior lobe of the left lung. The long diameter is 23 mm, the average CT value is –569 HU and the volume is 2998 mm^3. (B) Surgical pathology confirms minimally invasive adenocarcinoma (MIA) (HE × 100). (C) Immunohistochemical map, magnification × 100, and Ki-67 expression level is 7%. CT = computed tomography, HE = hematoxylin and eosin, HRCT = high-resolution computed tomography.

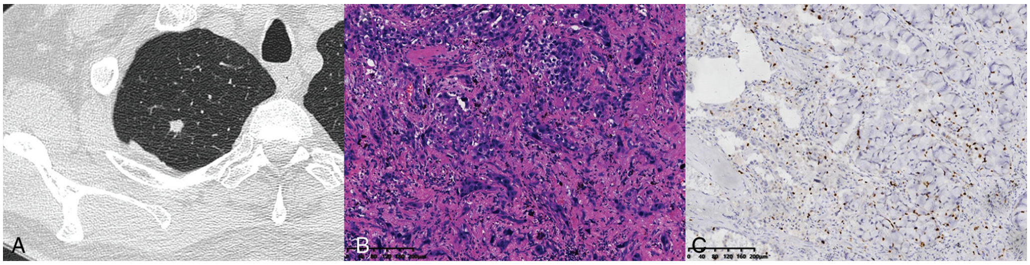

Figure 3. Image, pathology, and immunohistochemistry of solid nodules in the superior lobe of the right lung (male, 59 years old). (A) HRCT plain scan of the transverse lung window shows that the lesion is located in the superior lobe of the right lung. The long diameter is 8 mm, the average CT value is –77 HU, and the volume is 279 mm^3. (B) Surgical pathology confirms invasive adenocarcinoma (IAC) (HE × 100). (C) Immunohistochemical map, magnification × 100, and Ki-67 expression level is 30%. CT = computed tomography, HE = hematoxylin and eosin, HRCT = high-resolution computed tomography.

Table 2

Logistic regression analysis results of AIS+MIA and IAC.

Covariate	B	SE	Wald	*P*	OR	95%CI
Short diameter	0.332	0.083	15.863	.000	1.394	1.184–1.641
Average CT value	0.010	0.002	26.083	.000	1.010	1.006–1.014
Constant	0.880	1.189	0.547	.459	2.410	–

AIS = adenocarcinoma in situ, CT = computed tomography, IAC = invasive adenocarcinoma, MIA = minimally invasive adenocarcinoma.

Table 3

ROC curve analysis for CT quantitative parameter and predicted probability to identify AIS+MIA and IAC.

	Threshold	AUC	Sensitivity	Specificity	*P*
Long diameter (mm)	10.5	0.808	92.3	55.6	<.001
Short diameter (mm)	9.5	0.806	84.6	66.7	<.001
Average diameter (mm)	10.5	0.809	87.2	63.5	<.001
Maximum CT value (HU)	154	0.745	80.8	65.1	<.001
Minimum CT value (HU)	–635	0.875	64.1	94.8	<.001
Average CT value (HU)	–450	0.893	79.5	82.5	<.001
Volume (mm^3)	533	0.796	85.9	58.7	<.001

AIS = adenocarcinoma in situ, AUC = area under the curve, CT = computed tomography, IAC = invasive adenocarcinoma, MIA = minimally invasive adenocarcinoma, ROC = receiver operating characteristic.

3.3. ROC curve analysis for CT quantitative parameters and the predicted probability of logistic regression analysis model to distinguish AIS+MIA from IAC

The AUC values of the long diameter, short diameter, average diameter, maximum CT value, minimum CT value, average CT value, and volume were 0.808, 0.806, 0.809, 0.745, 0.875, 0.893, and 0.796, respectively. The AUC of the average CT value was the highest, with the cut-off of –450 HU, the sensitivity of 79.5%, and the specificity of 82.5%. Besides, the AUC of the predicted probability value was 0.931, with the sensitivity of 89.7% and the specificity of 85.7% (Table 3 and Fig. 4).

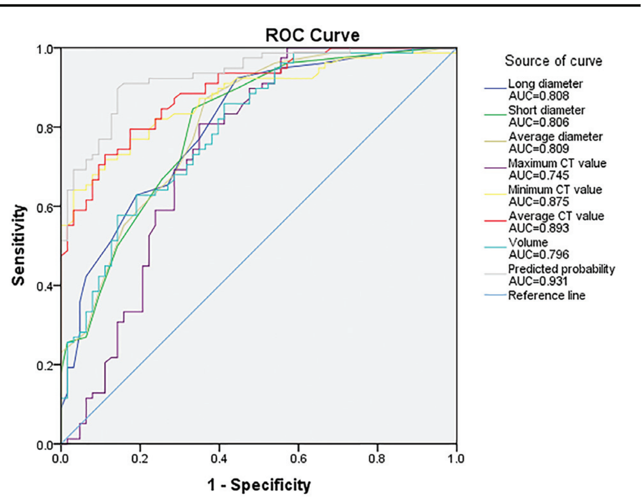

Figure 4. The ROC curves of each CT quantitative parameter and the predicted probability of logistic regression analysis to identify the degree of invasion of early lung adenocarcinoma. CT = computed tomography, ROC = receiver operating characteristic.

3.4. Correlation between CT quantitative parameters and Ki-67 expression level

There were 84 lesions with grade I Ki-67 expression (AIS = 12, MIA = 39, and IAC = 33), 33 lesions with grade II (AIS = 1, MIA = 10, and IAC = 22), 14 lesions with grade III (MIA = 1 and IAC = 13), and 10 lesions with grade IV (IAC = 10). The statistical results showed that the expression level of Ki-67 had the highest correlation with the average CT value of the lesion (r = 0.403, *P* < .001) (Table 4).

4. Discussion

Surgical resection is the most important and effective treatment for early LUAD. Some studies believed that patients with AIS or MIA are suitable for segmental resection,[11] while patients with IAC require total lobectomy.[12] Segmental resection can preserve more functional lung parenchyma in patients. However, there is no significant difference between segmental resection and lobectomy for early lung cancer in survival and complication rates.[13,14] It can be seen that, distinguishing the subtypes of LUAD not only affects the judgment of patient's prognosis, but also correlates to the selection of surgical methods. The traditional imaging diagnosis method is to comprehensively determine the nature of the lesion by observing the growth pattern, size, density, and other characteristics. However, the experience of the reading physician makes certain effects since the measurement is tedious and time-consuming, besides, the size and density of the lesion measured manually lack accuracy and repeatability.[15,16] In this study, AI-assisted diagnostic software was used. It can directly and automatically outline the lesion and accurately quantify its various indicators, which reduces the error of manual measurement and has high repeatability and reliability.

This study showed that there were statistical differences in the CT quantitative parameters between AIS+MIA and IAC. The

Table 4

Relevance of CT quantitative parameters and Ki-67 expression.

	Grade I (n=84)	Grade II (n=33)	Grade III (n=14)	Grade IV (n=10)	r	P
Long diameter (mm)	13 (8)	16 (9)	17 (7)	15 (11)	0.202	.016
Short diameter (mm)	10 (6)	12 (5)	12 (6)	12 (6)	0.189	.025
Average diameter (mm)	12 (7)	14 (7)	15 (7)	13.5 (8)	0.210	.012
Maximum CT value (HU)	194 (262)	239 (338)	259 (138)	263 (131)	0.182	.031
Minimum CT value (HU)	–759 (154)	–650 (426)	–640 (285)	–387 (121)	0.381	<.001
Average CT value (HU)	–502 (254)	–370 (520)	–342 (391)	–73 (82)	0.403	<.001
Volume (mm^3)	713 (934)	1004 (1594)	1367 (2184)	1484 (2472)7	0.243	.004

CT = computed tomography.

short diameter of the lesion and the average CT value were independent predictors of IAC. The ROC curve analysis results showed that the average CT value in univariate analysis was the best predictor of IAC, with an AUC of 0.893 and a cut-off of –450 HU. Although, the size and volume also had a high AUC and showed a high sensitivity, the low specificity led to a greater possibility of false positives. Using the average CT value to predict the degree of tumor invasion in LUAD may lead to different outcomes. For instance, Wu et al[17] believed that the average CT value was an independent variable for predicting the invasiveness of stage Ia lung cancer and helped distinguish AAH +AIS from MIA+IAC with a cut-off of –469 HU. Eguchi et al[18] showed that the CT cut-off values of AIS, MIA, and IAC were about –650 HU, –625 HU and –560 HU, respectively. Contrarily, Han et al[19] believed that the average CT value was poor in identifying and diagnosing AIS+MIA and IAC. We believe that the discrepancy among different studies is related to the difference in the scanning equipment on the one hand and the lack of a unified and standardized measurement method for CT values on the other hand. In this study, the average CT value was automatically measured by an AI-assisted diagnostic software, which can better overcome the error caused by manual measurement.

Ki-67 has been widely used in pathology to determine the growth rate of tumor cells.[20] It exists in the cell nucleus and can be expressed in G1, S, G2, and M phases of the cell cycle, but not in G0 phase, demonstrating its role as an indicator of cell proliferative ability. Previous studies confirmed that the stronger the proliferation of LUAD tumor cells, the worse the prognosis,[21] while a meta-analysis indicated that the expression level of Ki-67 was significantly related to the prognosis of patients with non-small cell lung cancer and high expression indicated a poor prognosis.[22] Immunohistochemistry is the conventional method to detect Ki-67 expression, but it requires specimens which must be obtained by invasive methods such as biopsy or surgery. If the expression level of Ki-67 can be accurately predicted based on the CT quantitative parameters of early LUAD, it will help clinically optimize the treatment plan in a non-invasive way and improve the prognosis of patients.

Among the 141 lesions included in this study, most of them had Ki-67 expression less than 5% (84/141), indicating low expression level of Ki-67 in early LUAD in general. Besides, cases with Ki-67 expression greater than 20% were all IAC (10/10). As the degree of invasion increased, the expression of Ki-67 correspondingly increased, which may be related to the more vigorous cell proliferation in LUAD of higher malignancy. A study reported that the short diameter of the lesion was an independent predictor of the high expression of Ki-67.[23] The results of the present study showed that the expression level of Ki-67 had a high correlation with the average CT value of the lesion, which may be due to the presence of ground glass components in a large part of early adenocarcinoma. Among the 141 lesions included in this study, 118 cases were ground glass nodules. The generation of ground glass density shadow is related to the growth of tumor cells along the alveolar wall without causing alveolar collapse. With the increase of Ki-67 expression, the tumor cell proliferation speeds up, which causes alveolar wall collapse resulting in the disappearance of the original air in the alveolar cavity and the reduction of intercellular space. In this context, it may first show an increase in the density of the lesion rather than an increase in diameter and volume.

Our research has several limitations. First, since this is a single-center retrospective study, there may be an inevitable selection bias. Second, the sample size is relatively small. In subsequent studies, we will use a larger sample size to conduct a multicenter study to address this issue.

In summary, the CT quantitative parameters of early LUAD have a certain correlation with the degree of tumor invasion and the expression level of Ki-67. The short diameter of the lesion and the average CT value are independent predictors of IAC. The average CT value is positively correlated with the Ki-67 expression in tumor. Therefore, in the absence of biopsy and surgery, CT quantitative parameters can indirectly assess the degree of tumor invasion and proliferative activity of LUAD, which facilitates clinical diagnosis and treatment of LUAD and helps judge the prognosis.

Acknowledgments

We sincerely acknowledge Mr Lekang Yin from the Radiology Department of Zhongshan Hospital Affiliated to Fudan University for guiding us.

Author contributions

Conceptualization: Hao Dong.
Data curation: Hao Dong, Junjie Yang, Xinbin Wang, Yonggang Qiu.
Formal analysis: Hao Dong.
Methodology: Hao Dong.
Project administration: Cuncheng Lou, Yonggang Qiu.
Resources: Junjie Yang.
Writing – original draft: Hao Dong.
Writing – review & editing: Hao Dong, Lekang Yin, Yonggang Qiu.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

[2] Kuhn E, Morbini P, Cancellieri A, Damiani S, Cavazza A, Comin CE. Adenocarcinoma classification: patterns and prognosis. Pathologica 2018;110:5–11.

[3] Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015;10:1243–60.

[4] Petersen I, Warth A. Lung cancer: developments, concepts, and specific aspects of the new WHO classification. J Cancer Res Clin Oncol 2016;142:895–904.

[5] Zhou J, Li Y, Zhang Y, et al. Solitary ground-glass opacity nodules of stage IA pulmonary adenocarcinoma combination of 18 F-FDGPET/CT and high-resolution computed tomography features to predict invasive adenocarcinoma. Oncotarget 2017;8:23312–21.

[6] Boland JM, Froemming AT, Wampfler JA, et al. Adenocarcinoma in situ, minimally invasive adenocarcinoma, and invasive pulmonary adenocarcinoma—analysis of interobserver agreement, survival, radiographic characteristics, and gross pathology in 296 nodules. Hum Pathol 2016;51:41–50.

[7] Lin L, Cheng J, Tang D, et al. The associations among quantitative spectral CT parameters, Ki-67 expression levels and EGFR mutation status in NSCLC. Sci Rep 2020;10:3436.

[8] Wen S, Zhou W, Li CM, et al. Ki-67 as a prognostic marker in early-stage non-small cell lung cancer in Asian patients: a meta-analysis of published studies involving 32 studies. BMC Cancer 2015;15:520.

[9] Xu J, Liu P, Da J, Hao J, Peng W, Sun G. Prognostic value of Ki-67 in stage I non-small-cell lung cancer: a meta-analysis involving 1931 patients. Pathol Res Pract 2019;215:855–60.

[10] Yan J, Wang H, Zhou H, He H, Qiu L, Wang Z. Correlation between expression of Ki-67 and MSCT signs in different types of lung adenocarcinoma. Medicine (Baltimore) 2020;99:e18678.

[11] Altorki NK, Wang X, Wigle D, et al. Perioperative mortality and morbidity after sublobar versus lobar resection for early-stage non-small-cell lung cancer: post-hoc analysis of an international, randomised, phase 3 trial (CALGB/Alliance 140503). Lancet Respir Med 2018;6:915–24.

[12] Altorki NK, Yip R, Hanaoka T, et al. Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules. J Thorac Cardiovasc Surg 2014;147:754–64.

[13] Charloux A, Quoix E. Lung segmentectomy: does it offer a real functional benefit over lobectomy? Eur Respir Rev 2017;26:170079.

[14] Chang CC, Yen YT, Lin CY, Chen YY, Huang WL, Tseng YL. Single-port video-assisted thoracoscopic surgery subsegmentectomy: the learning curve and initial outcome. Asian J Surg 2020;43:625–32.

[15] Weikert T, Akinci D'Antonoli T, Bremerich J, Stieltjes B, Sommer G, Sauter AW. Evaluation of an AI-powered lung nodule algorithm for detection and 3D segmentation of primary lung tumors. Contrast Media Mol Imaging 2019;2019:1545747.

[16] Prayer F, Röhrich S, Pan J, Hofmanninger J, Langs G, Prosch H. Künstliche Intelligenz in der Bildgebung der Lunge [Artificial intelligence in lung imaging] [in German]. Radiologe 2020;60:42–7.

[17] Wu H, Liu C, Xu M, et al. A retrospective study of mean computed tomography value to predict the tumor invasiveness in AAH and clinical stage Ia lung cancer. Zhongguo Fei Ai Za Zhi 2018;21:190–6.

[18] Eguchi T, Yoshizawa A, Kawakami S, et al. Tumor size and computed tomography attenuation of pulmonary pure ground-glass nodules are useful for predicting pathological invasiveness. PLoS One 2014;9:e97867.

[19] Han L, Zhang P, Wang Y, et al. CT quantitative parameters to predict the invasiveness of lung pure ground-glass nodules (pGGNs). Clin Radiol 2018;73:504.e1–7.

[20] Jakobsen JN, Sørensen JB. Clinical impact of ki-67 labeling index in non-small cell lung cancer. Lung Cancer 2013;79:1–7.

[21] Warth A, Cortis J, Soltermann A, et al. Tumour cell proliferation (Ki-67) in non-small cell lung cancer: a critical reappraisal of its prognostic role. Br J Cancer 2014;111:1222–9.

[22] Wei DM, Chen WJ, Meng RM, et al. Augmented expression of Ki-67 is correlated with clinicopathological characteristics and prognosis for lung cancer patients: an up-dated systematic review and meta-analysis with 108 studies and 14,732 patients. Respir Res 2018;19:150.

[23] Zhou B, Xu J, Tian Y, Yuan S, Li X. Correlation between radiomic features based on contrast-enhanced computed tomography images and Ki-67 proliferation index in lung cancer: a preliminary study. Thorac Cancer 2018;9:1235–40.