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The Use of CT Pattern in Differentiating Non-invasive, Minimally Invasive and Invasive Variants of Lung Adenocarcinoma

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Abstract. *Background/Aim: This study determined whether computed tomography (CT) is an appropriate means by which to differentiate non-invasive and minimally invasive forms of pulmonary adenocarcinoma from the invasive variant. Patients and Methods: A total of 64 patients (38 men and 26 women, aged 42-76, mean age 64), who underwent surgery for pulmonary adenocarcinoma and a chest CT no less than 1 month before surgery, were included in the study. Lesions exhibiting ground glass opacity or ground glass opacity with a solid component of 5 mm or smaller, were defined as minimally invasive or non-invasive adenocarcinomas. CT findings were correlated with histopathological examination. Results: Distinguishing minimally invasive and non-invasive adenocarcinoma from invasive adenocarcinoma using CT was achieved with a sensitivity of 77.7%, a specificity of 97.8%, a positive predictive value of 93.3%, and a negative predictive value of 91.8%. Conclusion: CT can be useful in assessing the degree of invasiveness of pulmonary adenocarcinoma and is a potential tool for the individualization of treatment.*

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The world has seen a dramatic rise in the incidence of lung cancer in the past century. This, once rare, disease has become a serious socio-economic problem; it is currently the most common cancer and the leading cause of cancer death worldwide. Adenocarcinoma is the most widespread type of pulmonary cancer (1). Advances in radiological imaging techniques, as well as research into the various aspects that affect the tumour's proliferation, have prompted novel approaches to adenocarcinoma's diagnosis and treatment, resulting in a new classification in 2011, which was then incorporated into the latest revision of the WHO lung cancer classification. Among other changes, the adenocarcinoma originally named bronchioloalveolar carcinoma was reclassified (2).

Stage 1 and sometimes stage 2 lung adenocarcinoma (atypical adenomatous hyperplasia, in situ adenocarcinoma, and minimally invasive adenocarcinoma) have a very good prognosis as a result of their slow growth rate (3). Radical removal of these tumours results in up to 100% survival rates. According to some studies, partial resection can be successfully used as a therapeutic method instead of lobectomy, where appropriate (4). A computed tomography (CT) image usually shows a subsolid nodule, *i.e.*, growth of abnormal tissue with ground glass opacity exhibiting a solid

component that is either absent or minimal. Ground glass opacity corresponds to the parts of the tumour showing the lepidic pattern of growth (5). Lepidic growth is defined as a pattern of cell proliferation along the lining of the alveolar structures and bronchioles of the lung; the stroma and blood vessels remain unaffected. The invasive component correlates with a solid tumour component.

A histological examination should show that the invasive component is not present in non-invasive forms and does not exceed 5 mm in minimally invasive forms. Invasive variants that have a worse prognosis, are diagnosed on the basis of histological examinations that reveal an invasive component that is larger than 5 mm. These lesions can sometimes produce images of consolidation resembling pneumonia, pulmonary infarction, or diffuse involvement similar to interstitial lung disease (6).

Our retrospective study set out to assess the extent to which CT imaging is useful in making a distinction between non-invasive and minimally invasive types of pulmonary adenocarcinoma, using the size of the solid component as the determining factor. An accurate diagnosis using CT imaging can lead to more precise prognoses and individually-tailored therapy. All imaging and surgical procedures were performed after an informed consent was obtained; the study was conducted in concordance with Helsinki declaration.

Patients and Methods

A total of 64 patients (38 men, 26 women, mean age 64 years) who were treated at our institution between January 2015 and August 2019 were enrolled in the study. All had been diagnosed with adenocarcinoma based on a histological examination and undergone surgery for peripheral lung cancer following a preoperative finding of a subsolid nodule using CT. The CT scans were performed no longer than a month before surgery using Somatom Definition AS and Somatom Definition Flash multidetector devices (Siemens Healthineers, Erlangen, Germany). An edge enhancement algorithm was applied to the images of the lung nodules and they were then examined on thin sections with a collimation of 0.6 mm. The stage was determined after the application of Iomeron 350 (Bracco, Milan, Italy), a contrast solution. The volume of the contrast solution was 80 ml and the application rate was 3 ml/s.

The radiologist examining the images was blinded to the results of the histological examination. All nodules were subjected to a three-dimensional analysis; the dimensions of the entire nodule and the solid component were automatically taken using the Syngo.via oncology software (Siemens Healthineers, Erlangen, Germany) (Figure 1).

The nodule size was calculated as the average of the largest and perpendicular dimensions. Nodule size was then assessed in view of the histopathological findings: a nodule no larger than 3 cm with a solid component no larger than 5 mm was defined as a non-invasive or minimally invasive tumour variant. Volume doubling time was calculated for the nodules that were followed-up.

Results

The assessment performed using CT imaging was successful in identifying 14 out of 18 histologically-assessed minimally invasive or non-invasive tumours. False positivity occurred in 4 cases. Out of 46 histologically-assessed invasive cases 45 were identified correctly using CT imaging alone. False negativity occurred in one case.

The use of CT for distinguishing non-invasive and minimally invasive variants of peripheral pulmonary adenocarcinoma, succeeded with 77.8% sensitivity, 97.8% specificity, a positive predictive value of 93.3%, and a negative predictive value of 91.8%. The doubling time was determined in 28 patients, who had multiple subsequent check-ups: 677 days for non-invasive and minimally invasive variants and 588 days for invasive variants on average.

Discussion

The results of our study demonstrate that CT imaging is a tool capable of aiding health practitioners in making a distinction between invasive, minimally invasive, and non-invasive tumour variants (as defined by the current WHO classification). Prognosis, as well as the individualization of treatment, can be affected by this distinction; namely, the timing of surgical treatment, the extent of resection and the decision to commence systemic treatment. The extent of the solid tumour component can be used as a predictor of invasiveness (7).

CT sensitivity was reduced mainly in the case of false positives, caused by an overestimation of the size of the solid tumour component. One reason for this decreased sensitivity is that ground glass opacities and the solid component of a tumour are separated by a gradual transition, making the boundary separating them difficult to identify. Furthermore, the collapsed lung, fibrous tissue, or mucin accumulation may all imitate solid tumorous tissue.

Two possible solutions to this problem exist: firstly, the use of a mediastinal window that filters out lower densities could be used to assess the solid component (8). Secondly, mathematical and statistical methods used for texture analysis have been shown to hold promise (9).

It is important to note that the finding of a subsolid pulmonary nodule does not necessarily indicate the presence of an adenocarcinoma. According to the literature, 37% to 70 % of these nodules may be benign, of inflammatory or infectious origin (10). It is therefore common practice to monitor subsolid, as well as solid, nodules that are smaller than 8 mm.

It is generally accepted that a doubling time between 30-400 days indicates the potential malignancy of a nodule. It is nevertheless evident from our analysis, as well as from other sources, that the doubling time of a subsolid nodule may be

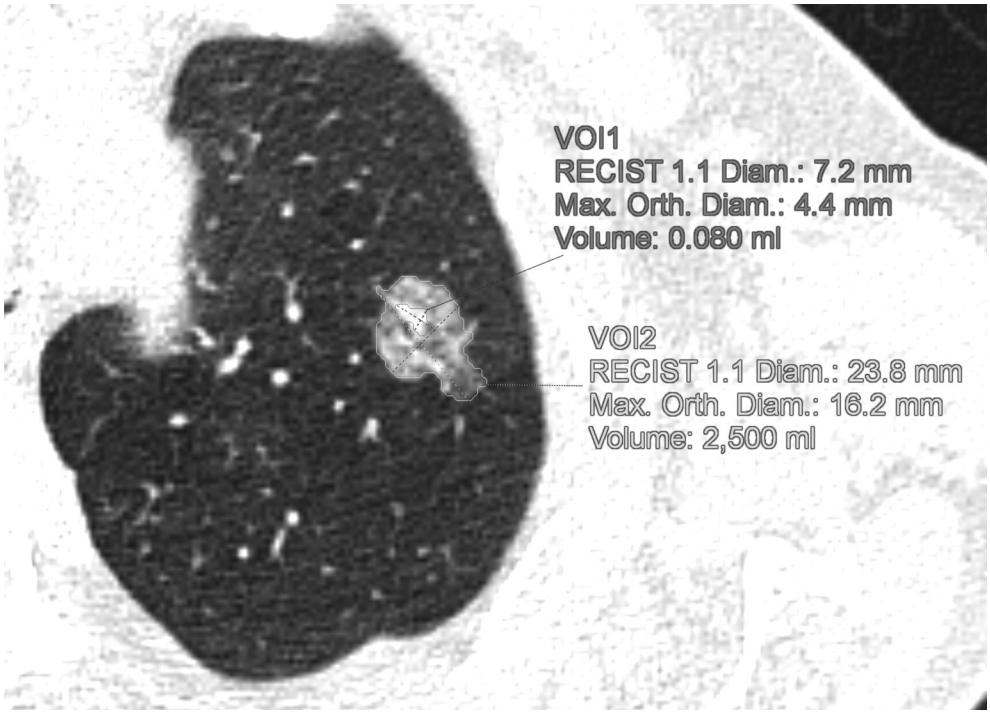

Figure 1. *Three-dimensional analysis of the semisolid nodule in the upper right lobe: the whole node and the solid component were measured separately.*

longer. Longer monitoring intervals are therefore recommended for subsolid nodules. According to the recommendations of the Fleischner Society, subsolid nodules should be monitored for up to 5 years following the diagnosis, as opposed to the two-year follow-up recommended for solid nodules (11).

The performance of PET/CT with fluorine-18 labelled fluorodeoxyglucose (18F-FDG) presents an alternative method for the evaluation of subsolid pulmonary nodules. 18F-FDG has been shown to accumulate in the invasive component, but not in the non-invasive component. Unfortunately, mucinous tumour variants present a hurdle in the use of this method, as they may not show increased 18F-FDG uptake despite the presence of the invasive component. It should also be noted, that nodules smaller than 5-8 mm may give rise to false negatives due to their small size and that inflammatory consolidations, such as FDG tumours, may accumulate and be a source of false positives. The use of CT imaging in such cases can help and compensate for the above-mentioned problems (12).

Our study was limited by a relatively small cohort, its retrospective nature and the fact that we assessed the maximum dimensions of the nodules and their solid components, but not their volumes. This was due to the correlation made with histological examination, where volumes cannot be measured.

In conclusion, the CT pattern of pulmonary adenocarcinoma can be used as a biomarker of tumour invasiveness. Information on the degree of tumour invasiveness is useful not only in making a prognosis, but also for the purpose of individualizing treatment. Its correct identification plays a role in the timing of surgical treatment, the extent of resection and the decision to commence systemic treatment.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Hynek Mirka – Designed the study, performed the analysis, wrote the paper; Jiri Ferda – contributed to design the study, collected data; Gabriela Krakorova – collected data, contributed to analysis; Josef Vodicka – collected data, contributed to analysis; Petr Mukensnabl – collected data, contributed to analysis; Ondrej Topolcan – contributed to analysis and writing the article; Radek Kuceera – contributed to analysis and writing the article.

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References

1 de Groot PM, Wu CC, Carter BW and Munden RF: The epidemiology of lung cancer. Transl Lung Cancer Res *7(3)*: 220-233, 2018. PMID: 30050761. DOI: 10.21037/tlcr.2018.05.06

2 Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, Chirieac LR, Dacic S, Duhig E, Flieder DB, Geisinger K, Hirsch FR, Ishikawa Y, Kerr KM, Noguchi M, Pelosi G, Powell CA, Tsao MS, Wistuba I and WHO Panel: The 2015 World Health Organization classification of lung tumors: Impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol *10(9)*: 1243-1260, 2015. PMID: 26291008. DOI: 10.1097/JTO.0000000000000630

3 Russell PA, Wainer Z, Wright GM, Daniels M, Conron M and Williams RA: Does lung adenocarcinoma subtype predict patient survival?: A clinicopathologic study based on the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary lung adenocarcinoma classification. J Thorac Oncol *6(9)*: 1496-1504, 2011. PMID: 21642859. DOI: 10.1097/JTO.0b013e318221f701

4 Tsutani Y, Miyata Y, Nakayama H, Okumura S, Adachi S, Yoshimura M and Okada M: Appropriate sublobar resection choice for ground glass opacity-dominant clinical stage IA lung adenocarcinoma: wedge resection or segmentectomy. Chest *145(1)*: 66-71, 2014. PMID: 24551879. DOI: 10.1378/chest.13-1094

5 Weichert W and Warth A: Early lung cancer with lepidic pattern: adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic predominant adenocarcinoma. Curr Opin Pulm Med *20(4)*: 309-316, 2014. PMID: 24811831. DOI: 10.1097/MCP.0000000000000065

6 Aherne EA, Plodkowski AJ, Montecalvo J, Hayan S, Zheng J, Capanu M, Adusumilli PS, Travis WD and Ginsberg MS: What CT characteristics of lepidic predominant pattern lung adenocarcinomas correlate with invasiveness on pathology? Lung Cancer *118*: 83-89, 2018. PMID: 29572008. DOI: 10.1016/j.lungcan.2018.01.013

7 Ichinose J, Kohno T, Fujimori S, Harano T, Suzuki S and Fujii T: Invasiveness and malignant potential of pulmonary lesions presenting as pure ground-glass opacities. Ann Thorac Cardiovasc Surg *20(5)*: 347-352, 2014. PMID: 24088912. DOI: 10.5761/atcs.oa.13-00005

8 Saito H, Kameda Y, Masui K, Murakami S, Kondo T, Ito H, Oshita F, Tsuboi M, Yokose T, Noda K, Nakayama H and Yamada K: Correlations between thin-section CT findings, histopathological and clinical findings of small pulmonary adenocarcinomas. Lung Cancer *71(2)*: 137-143, 2011. PMID: 20566399. DOI: 10.1016/j.lungcan.2010.04.018

9 Liu Y, Liu S, Qu F, Li Q, Cheng R and Ye Z: Tumor heterogeneity assessed by texture analysis on contrast-enhanced CT in lung adenocarcinoma: association with pathologic grade. Oncotarget *8(32)*: 53664-53674, 2017. PMID: 28881840. DOI: 10.18632/oncotarget.15399

10 Kim H, Park CM, Koh JM, Lee SM and Goo JM: Pulmonary subsolid nodules: what radiologists need to know about the imaging features and management strategy. Diagn Interv Radiol *20(1)*: 47-57, 2014. PMID: 24100062. DOI: 10.5152/dir.2013.13223

11 MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, Mehta AC, Ohno Y, Powell CA, Prokop M, Rubin GD, Schaefer-Prokop CM, Travis WD, Van Schil PE and Bankier AA: Guidelines for management of incidental pulmonary nodules detected on CT images: From the Fleischner society 2017. Radiology *284(1)*: 228-243, 2017. PMID: 28240562. DOI: 10.1148/radiol.2017161659

12 Wu HB, Wang L, Wang QS, Han YJ, Li HS, Zhou WL and Tian Y: Adenocarcinoma with BAC features presented as the nonsolid nodule is prone to be false-negative on 18F-FDG PET/CT. Biomed Res Int *2015*: 243681, 2015. PMID: 25879020. DOI: 10.1155/2015/243681

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