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Use of computed tomography to define invasive lung cancer presented by ground-glass opacity (literature review)

Relevance. *Lung cancer (LC) for several decades occupies a leading position in the structure of cancer mortality in the Republic of Kazakhstan. There are difficulties in differential diagnosis of peripheral cancer and other lung lesions. Ground-glass opacity often accompanies oncological pathology of lungs. Assessment of ground-glass opacity using computed tomography is controversial in detecting early LC.*

Materials and methods. *The conducted literature review of PubMed database covered the period of 2012- 2018. The keyword search included "Ground glass, CT features, lung cancer, adenocarcinoma." Out of 69 sources, only 20 scientific publications corresponded to the established selection criteria.*

Results. *Ground-glass opacity is a good prognostic indicator for LC regardless of the tumour pathomorphological characteristics. High-resolution computer tomograms allow detecting the minimal invasive component of LC. The size of the lug lesion manifested by ground-glass opacity may be a specific determinant for pre-invasive LC.*

Conclusion. *Interpretation of ground-glass opacity as an early sign of LC requires further study.*

Keywords: *ground-glass opacity, lung cancer, CT.*

Relevance. Lung cancer (LC) is one of the most common malignant neoplasms in the world. For several decades, LC occupies a leading position in the structure of cancer mortality in the Republic of Kazakhstan: in 2015, its share amounted to 16.5% [1]. Ground-glass opacity often accompanies oncological pathology of lung. On computer tomograms, the ground glass is visualized as a weakly expressed, "matte" airspace disease with a differentiated pattern of blood vessels and bronchi on this background. This symptom arises as a result of averaging the plane air parameters in the changed anatomical structures of lung tissue, the magnitude of which is beyond resolution of computed tomography (CT) [2]. Currently, detection of ground glass opacity is increasing due to the widespread use of CT (multi-slice computer tomography and low-dose computed tomography) to detect LC. There are difficulties in differential diagnosis of peripheral cancer and other lung lesions [3]. CT allows identifying the morphological characteristics of LC [4]. Assessment of ground-glass opacity using computed tomography is controversial in detecting early LC.

Materials and methods. The literature review was based on the data of scientific research available for 2012-2018 in PubMed by keywords "Ground glass, CT features, lung cancer, adenocarcinoma." A total of 69 literature sources were found, 49 publications of them were excluded not meeting the selection criteria. The literature review included 20 literature sources meeting the selection criteria.

Results and discussion. In the study of CT features of invasive lung adenocarcinoma and pre-invasive tumours showing as ground glass opacity, Lee S.M. et al. noted that the size of formations less than 10 mm could be a specific determinant for pre-invasiveness and excluded the possibility of cancer invasiveness in the lung tissue. According to the authors, at "mixed ground glass" opacity the pre-invasive adenocarcinoma clearly differed from the invasive one by smaller tumour size, non-lobed shape, as well as by spicule-shaped contours absence [5].

According to Lim H.J. et al., a detailed analysis of the ground glass opacity showed that the size of formation on CT scans less than 10 mm served as a clear determinant for exclusion of invasive adenocarcinoma and was a prognostically favourable symptom [6]. Moreover, Liu L.H. et al. have found that the threshold value of the ground glass site diameter for prediction of invasion was 12.50 mm. [7]. According to other authors, the optimal size of the "ground glass" node for distinguishing the pre-invasive state and the minimal invasive adenocarcinoma was 13.0 mm (sensitivity 83.0%, specificity 80.0%), and the solid component size was 2 mm (sensitivity 88.0%, specificity 97.0%) [8].

Symptoms such as spicules presence and vessels dilatation showed a significant difference between the pre-invasive and invasive carcinoma ($p<0.05$), while the bosselated contours, pleura retraction, air bronchogram symptom and the bulls presence did not show a statistically significant difference between invasiveness and pre-invasiveness of the lung tumour ($p>0.05$) [7]. However, Wu F. et al. believed that flat contours were the most characteristic for ground glass of less than 1 cm in

size with pre-invasive pathology (atypical adenomatous hyperplasia, adenocarcinoma in situ), and bosselated and spicule-shaped contours were characteristic in case of invasive tumour (minimal invasive adenocarcinoma and invasive adenocarcinoma) [9,10,11].

Studying the diameter of the tumour, its solid component and densitometric density using computed tomography, in presence of a ground glass site with underlying air bronchogram, the researchers found that such parameters as node size > 12.2 mm, size of solid component > 6.7 mm, and the largest density of the solid component within> -192 HU, were the significant symptoms of invasive adenocarcinoma [12, 13]. However, Si M.J. et al. in their work indicated that the size of ground glass node more than 7.5 mm increased the possibility of minimal invasive carcinoma [14].

Using CT data, Matsunaga T. et al. have found that in the presence of ground glass opacity in lung cancer was difficult to measure due to its multi-centric arrangement, and it was usually a prognostically favourable symptom. 71 (12.4%) of 572 patients were found to have difficulties in measuring the size of ground glass site, and the incidence of other pathological factors such as lymphatic invasion and vascular invasion in that cohort was significantly low ($p < 0.0001$) [15].

Such indicator as the size of ground glass site could serve as a differential sign between benign and malignant nature of the tumour. Wei S.Y. et al. have examined 663 patients with ground glass sites who later underwent surgery. After clinic pathological study, all cases with ground glass were divided into 2 groups: benign and malignant changes. The diameter of ground glass sites in the group of benign changes was 0.8±0.2 cm and was significantly less than in the group of malignant changes - 1.5 ± 0.8 cm, ($p <0.001$). The incidence of the symptom of uneven contours in the group with malignant changes (93.8%) was significantly higher than in the group with benign changes (20.4%), ($p<0.001$) whereas the "vacuole symptom", the local pleura retraction, the presence of spicules and the lobular structure of ground glass did not show significant differences in those two groups [16]. Nevertheless, according to other authors, the local ground glass opacity with clearly visualized bosselated contours and the presence of pleura retraction were more likely during a malignant process [17, 18].

Liang J. et al. have identified the main characteristics of invasive determination for "pure ground glass" opacity and "mixed ground glass" opacity using multivariate analysis. Thus, the number of vessels was an independent risk factor for "pure ground glass". That is, the number of vessels equal to "≥1" taken as a diagnostic criterion allowed predicting an invasive adenocarcinoma with a sensitivity of 100%. The number of vessels equal to "0" taken as a diagnostic criterion allowed predicting a pre-invasive state with a specificity of 100%. Volume of the solid component and the pleura retraction were the most important indicators for "mixed ground glass" [19]. At the same time, Xing Y. et al. and Moon Y. et al. indicated that the size and morphological changes in the vessels ($p<0.05$) were significant test of differences between atypical adenomatous hyperplasia and adenocarcinoma in situ in the group with the "mixed ground glass" opacity, while the bosselated and spicule-shaped contours, presence of bulls, air bronchogram and pleural retraction were not significant [20, 21].

Studying the association of ground glass opacity with metastasis to the lymph nodes, Ye B. et al. have concluded that in 94.4% of cases there was no metastasis to the lymph nodes in patients with "pure ground glass" opacity [22]. Hattori A. et al. argued that the presence of ground glass was a prognostically favourable symptom even in invasive non-small cell LC stage IA. Therefore, the authors recommended to clearly distinguish the "pure ground glass" opacity from "mixed ground glass" opacity on computer tomograms, as that was extremely important for the assessment of results of non-small cell LC [23]. Assessment of ground-glass opacity on CT-scans was controversial in detecting early LC. [24].

Conclusion. Ground-glass opacity is a good prognostic indicator for LC regardless of the tumour pathomorphological characteristics. The use of high-resolution computer tomograms allows detecting the minimal invasive component of LC. The size of the lung lesion manifested by ground-glass opacity may be a specific determinant for pre-invasive LC. Interpretation of ground-glass opacity as an early sign of LC requires further study.

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