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Progress in the Application of Energy-spectrum CT Imaging and Radiomics for the Diagnosis of Lung Cancer and Subtype Differentiation

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Abstract. Lung cancer is the most prevalent malignancy and a serious threat to human health, and the early non-invasive diagnosis of lung cancer has been a hot topic of research in recent years. Lung cancer is subtyped into small cell lung cancer and non-small cell lung cancer, which is closely related to long-term smoking exposure history and chronic lung diseases, and its subtypes are inseparable from the diagnosis and prognosis of lung cancer. With the iterative development of CT technology, energy spectrum CT has been applied. Energy spectral CT of lung cancer can reduce artifacts, improve signal-to-noise ratio and clarity of images, and provide more information for CT diagnosis of lung cancer by combining multi-parameter energy spectral data at the same time. Radiomics refers to the acquisition of a large number of imaging histological features from other imaging images such as CT, ultrasound and MR, and the selection of valuable imaging histological clinical data for analysis. The exploration of disease by energy-spectrum CT combined with radiomics is a hot spot and trend in current research, and this paper will review the research progress of both on lung cancer subtypes.

Keywords: Lung Cancer；Spectral CT；Radiomics；Pathological type

1. Overview of Lung Cancer

1.1 Prevalence of Lung Cancer

In the latest GLOBOCAN analysis report[1], the lung cancer has become the most common malignant tumor worldwide. Among the incidence of malignant tumors, lung cancer is the most common cause of cancer death in men and the second most common cause of cancer death in women after breast cancer, accounting for 18.4 % of the total cancer mortality. According to the data from the National Cancer Center of China, lung cancer currently ranks as the top malignant tumor in China, and the mortality rate remains high. With the improvement of lung cancer screening technology[2], the death rate of lung cancer has decreased by 20 % from the peak of 2021.

Socioeconomically, the burden of lung cancer treatment in our country remains high and represents a great challenge to public health[3]. The development and etiology of lung cancer are complex, and it is important to explore the risk factors and etiology of lung cancer to stop its progression and reduce its sociological impact.

1.2 Etiology and Risk Factors of Lung Cancer

Lung cancer is a group of tumors with molecular genetic and morphological heterogeneity, and the molecular phenotypes of different subtypes of lung cancer are still being studied. Lung cancer is a group of tumors with molecular genetic and morphological heterogeneity[4]. The prevalence of NSCLC is higher, accounting for about 85 %, and NSCLS consists of four main subtypes: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Related studies have shown[5] that mutations in chromosomal karyotype P53 and epidermal growth factor EGFR are closely related to the incidence of NSCLC, with EGFR mutations accounting for approximately 85 % of

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NSCLC. It is currently believed that the etiology associated with the development of lung cancer includes lung cancer-related risk factors in addition to growth gene mutations.

With the industrialization of the country, air pollution in the living environment and the increase of the aging population, more and more people are exposed to lung cancer-related risk factors. According to the results of a Meta-analysis on the influencing factors of lung cancer in the Chinese population[6], smoking and secondhand smoke exposure, pre-existing chronic lung diseases, air and air pollution, previous family history of related tumors, occupational exposure to special populations, unhealthy diet and other sub-healthy psychological factors are all risk factors for the occurrence of lung cancer in China. Studies have shown [7] that approximately 10-20% of patients who smoke will be diagnosed with lung cancer, compared to 1-2% of non-smokers. Hwag found that patients with tuberculosis combined with lung cancer had a significantly higher rate of EGFR gene mutations in the lung cancer epidermal growth factor receptor than patients with non-tuberculosis combined with lung cancer. Canada[8]. A study evaluated the close relationship between radon released from indoor decoration and lung carcinogenesis, in which the incidence of radon-related lung cancer was about 13% in men and 14% in women. The results of a tumor-related family history mete analysis showed that the incidence rate of family-related lung cancer was 2.87 times higher than that of no tumor-related family history[9]. All of the above epidemiological history data indicate that risk factors are closely related to the development of lung cancer.

Lung cancer-related etiology and risk factors have attracted widespread attention from scholars at home and abroad. Some scholars have found that the subtypes of smoking-related lung cancer and non-smoking-related lung cancer are complex and variable[1]. The subtypes of lung cancer are closely related to the later treatment choices of patients, and the discussion of these lung cancer subtypes is a hot topic of research nowadays. Therefore, finding the cause of the problem, improving the efficiency of lung cancer diagnosis, and improving tertiary prevention of lung cancer are the keys to early diagnosis and treatment of lung cancer.

1.3 Clinical Manifestations of Lung Cancer

With the continuous improvement of tertiary prevention of lung cancer, it is crucial to diagnose lung cancer from clinical symptoms as early as possible. The clinical manifestations of lung cancer are mainly respiratory symptoms such as coughing, coughing, and blood in the sputum. However, patients with lung cancer basically do not have typical symptoms in the early stage, and when typical symptoms appear, distant metastases often have already occurred, and patients with distant metastases also have lung cancer syndromes, such as dyspnea caused by compression of the trachea, varicose veins caused by invasion of superior vena cava, pestle finger, and other chronic manifestations. Display the gold standard for lung cancer diagnosis is histopathological biopsy[10]. At present, the main invasive methods for tissue biopsy are bronchoscopy, puncture, thoracoscopic biopsy, etc. These operations may have problems such as the sample size of early-stage lung cancer being too small and it is difficult to make an accurate diagnosis. In contrast, middle and late-stage lung cancer often has distant metastasis and a poor prognosis, with a long-term survival rate of 14-16%[11]. The long-term survival rate is only 14-16%. Early diagnosis of lung cancer and resection of early-stage lung cancer tissues can effectively improve the prognosis of patients. With the development of imaging technology and fiberoptic bronchoscopy, whether lung cancer can be diagnosed as early as possible by non-invasive means is a hot topic of current research. At this time, seeking convenient imaging diagnostic techniques is the key to diagnose early lung cancer.

1.4 Diagnostic Imaging History of Lung Cancer

1.4.1 Diagnostic history of lung cancer

Early screening for lung cancer is selected by chest X-ray. It was later found that chest X-ray does not reduce the morbidity and mortality of lung cancer and early lung cancer less than 1 cm in size cannot be detected, and chest X-ray is not currently recommended as the first choice for screening for lung cancer.

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The International Early Lung Cancer Program (I-ELCAP) has proposed the use of low-dose CT technology for lung cancer screening. CT screening technology has a higher resolution than x-ray, and low-dose CT reduces the radiation dose from x-ray, allowing CT to screen for more and smaller masses than chest radiographs. With the management and screening of clinical lung nodules (LU-RADS)[12] which is widely promoted and applied, low-dose CT is now the most common screening tool. Subsequently, it was found that conventional low-dose CT, although effective in screening for early-stage lung cancer and precancerous lesions, showed 81 % of false positive results[10]. Furthermore, studies have shown that the detection rate of early central lung cancer by CT technology is significantly lower than that of peripheral lung cancer. Since invasive bronchoscopy is required for the screening of central lung cancer, finding a non-invasive and relatively economical screening technique is the key to lung cancer screening[10]. Therefore, finding non-invasive and relatively economical techniques is the key to lung cancer screening.

Other imaging methods currently used by clinicians to examine and screen for lung cancer include enhanced CT scan, positron emission tomography (PET) scan, magnetic resonance imaging, and ultrasound. Enhanced CT scan of the lung helps to determine its benignity and malignancy at the same time, and can detect other diseases besides lung cancer, such as chronic obstructive pulmonary disease, cardiovascular disease, and tumors of the esophagus, which does have good clinical application. PET examination, on the other hand, has many inconveniences such as high price and site limitation, so it has its limitations when used for routine screening of lung cancer, and is currently more commonly used to determine distant metastases in patients with confirmed lung cancer. Magnetic resonance imaging of lung masses is mainly used to detect brain and adrenal metastases and shows the better invasion of pericardium, nerves, and muscles. Ultrasound, on the other hand, is used as a complementary tool to be able to evaluate whether pleural effusion and pleural hypertrophy are related to tumors in the lung and to perform ultrasound-guided biopsy puncture examination of suspected metastatic lymph nodes to confirm the diagnosis.

1.4.2 Imaging manifestations of lung cancer

Lung cancer is broadly classified into central, peripheral and diffuse types, of which the most common is peripheral lung cancer. Early stage peripheral lung cancer is characterized by mixed ground glass shadow or partially solid nodules[13]. The five-year survival rate is as high as 100%, which is quite critical for early interventional treatment of lung cancer patients. Progressive peripheral lung cancer presents on imaging as isolated pulmonary nodules or pulmonary masses (SPNs), but there are many benign inflammatory masses that also present as SPNs, and there are homozygous and heterozygous cases judging from CT morphology. It has been shown that malignant tumors have distinctive features such as irregular borders (burrs and deep lobes), typical internal signs (liquefied necrosis, cavities and vacuoles, etc.), and faster growth rate, so it is specific to determine the benignity and malignancy of tumors based on their 3D morphology and growth rate from CT morphological features. Different tumor markers are more sensitive indicators for lung cancer subtypes. Recently, the combination of tumor markers with higher specificity and CT examination with high sensitivity is often used to diagnose lung cancer.

Therefore, early detection and diagnosis of lung cancer is a hot spot for domestic and foreign research and has a broad research application prospect. Chest X-ray and low-dose CT examination methods have certain limitations in terms of their results and examination methods and diagnostic efficacy. And the current imaging workload is large and cannot avoid interference by human subjective factors, thus producing leakage and misdiagnosis. With the continuous development of CT examination technology, energy-spectrum CT technology has a special role in the diagnosis of some diseases, and the determination of benign and malignant lung cancer has a special role, and the study of energy-spectrum CT on lung cancer subtypes is also a new hot spot. With the rapid development of radiomics and artificial intelligence, which reduces the interference of human factors, the three roles are complementary to each other[14].

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2. Overview of Energy Spectrum CT

Ultrasound, magnetic resonance imaging, DSA and positron emission computed tomography (PET-CT) all have their own advantages and disadvantages in diagnosing and screening diseases, but the diagnosis of diseases still needs to be confirmed by pathological biopsy, and the upgrading of non-invasive imaging technology is one of the hot issues to be solved in clinical practice. Short-time rapid switching of dual Kvp, joint application of statistical iterative techniques, avoiding the problems of motion artifacts and many scattered rays, and theoretically realizing the separation of substances to achieve the detection and quantification of substances, have been developing in clinical research and diagnosis.

2.1 Principle of Energy Spectrum CT

The principle of energy spectrum CT is based on CT technology imaging. The CT principle is based on the application of the X-ray beam through a certain thickness of the body will produce attenuation, the detector received X-ray through the photoelectric converter and digital converter output digital signal. Energy spectrum CT is based on this, according to the two atomic number difference is obvious material to the absorption of x-ray different, can be quantified x-ray attenuation curve, according to its x-ray attenuation curve can achieve a quantitative analysis of substances. Physicists provide many absorption curves of pure substances and mixed substances and the formula of absorption coefficients associated with CT values, and the density of substances is measured indirectly from CT values with the formula CT (x,y,Z,E) = Dwater (x y ,z)μwater(E) + Diodine (x,y,z) μiodine (E), where μ water (E) and μ iodine(E) are the absorption coefficients of water and iodine, respectively. The most commonly used differential apparent substance pair is the iodine-water substance pair, i.e., iodine in contrast media and water in human large blood vessels, and the quantitative analysis of the substance is achieved by indirect measurement of the atomic number of the substance pair.

Another imaging principle and advantage of Energy Spectrum CT is a short time (<5 ms) rapid switching dual energy technology of the energy spectrum, switching from 80 kVp to 140 kVp high and low energy in less than 5 ms[15]. This technique eliminates the motion artifacts of the organ and reduces the impact of volumetric effects on the CT values by combining the TG technology. The Energy Spectrum CT post-processing workstation, GSI Viewer, provides several parameters for analysis, including single-energy imaging to improve image clarity, spectral absorption curves to reflect material absorption data, material separation and quantification techniques, and several post-processing tools, such as histograms, optimal signal-to-noise ratios, and scatter plots. The quantitative parameters of spectral CT include iodine concentration (IC), normalized iodine concentration (NIC), the slope of spectral HU curve (λHU), effective atomic number (EFN), and the number of atoms in the spectrum. (effective atomic number, Eff- Z). The above parameter analysis and post-processing techniques can reduce the image artifacts and improve the signal-to-noise ratio while showing the characteristics of lesions, components, and blood supply by multi-parameter energy spectrum analysis, which provides more information for the diagnosis of diseases and improves the accuracy of diagnosis.

2.2 Brief Description of the Progress of Clinical Application of Energy Spectrum CT Imaging

2.2.1 Pre-diagnosis of tumors

Energy spectrum CT imaging technology is capable of demonstrating fine structures with low definition. Energy-spectrum CT imaging technology has unique advantages for the diagnosis of microscopic lesions through its single-energy imaging characteristics, combined with material separation techniques. Peijie Lu et al.[16] showed that mono-energy 65 keV can maximize the contrast between small lesions without blood supply and normal tissues, significantly improving the detection rate of small liver cancer lesions. Energy-spectrum CT shows low-contrast structures such as tendons and ligaments comparable to anatomical height[17]. In order to provide more diagnostic

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information for the clinic, Sun found that Spectrum CT can clearly demonstrate the anatomical height of the knee joint and its accessory ligaments.

2.2.2 Graded diagnosis of tumors

Multi-parametric analysis of energy-spectrum CT imaging technology enables diagnosis, TMN typing and homology analysis of tumors[18]. It has been shown that energy-spectrum CT is a useful tool for identifying benign and malignant thyroid nodules and for pathological staging. It has been shown that energy-spectrum CT has unique clinical applications in identifying benign and malignant thyroid nodules and in pathological staging and that the mean CT values and iodine content of benign and malignant thyroid nodules differ significantly at single energy of 140 keV. There are also results showing that[19]. The slope of the energy spectrum curve can reflect the extent of gastric cancer infiltration into the fatty interstitial space around the gastric wall, and the change of iodine concentration in the gastric wall correlates with the extent of its infiltration. The TNM analysis of a tumor is important for the clinical decision of treatment plan, and the energy spectrum CT imaging can provide more energy spectrum information on the malignancy degree, infiltration depth, and surrounding lymph node metastasis. Lijun Chen[20] et al. showed that the histogram, scatter plot and energy spectrum curve of primary breast cancer lesions correlated with their anterior lymph nodes.

In summary, the parameter analysis of energy-spectrum CT has demonstrated good diagnostic prospects in several systems, which helps to improve the diagnostic efficacy of tumors. However, energy-spectrum CT has not yet formed a unified parameter diagnostic standard among the energy-spectrum parameters of different systems, which will be discussed next in the research progress of energy-spectrum CT in lung cancer.

2.3 Research Progress of Energy Spectrum CT for Lung Cancer Evaluation

2.3.1 Assessment of benign and malignant pulmonary nodules by energy-spectrum CT

Early-stage lung cancer appears as isolated lung nodules on CT, and demonstration of lung nodule morphology can help determine the benignity or malignancy of lung nodules. Several studies have demonstrated that energy-spectrum CT can improve the clarity and detection rate of lung nodules. Related studies have shown that high-energy imaging in mono-energy imaging can eliminate the effects of sclerotic artifacts from ribs and enhance contrast agents, while low-energy imaging can better visualize microcalcifications in the lung[15]. 40-70 keV proved to be the best mono-energy imaging for lung nodules, as there are variations between patients and devices, and energy-spectrum CT can automatically match the best mono-energy imaging interval based on the mono-energy curve. Studies have demonstrated the advantage of energy-spectrum CT in the detection of small, irregularly shaped pulmonary nodules, facilitating early detection of nodules with malignant signs such as irregular margins, burr-like, and with vascular clustering signs.

Isolated pulmonary nodules (SPNs) are diverse, and there are cases of heterogeneous diseases with the same image. Currently, the most common application for characterizing the benignity and malignancy of pulmonary nodules is with enhanced CT, and studies have shown that energy-spectrum CT has greater clinical application in place of conventional enhanced scans[21]. The studies have shown that energy-spectral CT has a greater clinical application in replacing conventional enhancement scans. In a single energy-spectral CT scan of lung nodules, enhanced images can be obtained along with iodine base maps and energy spectral curves, which are useful for material analysis of iodine concentration in iodine-intake tissue[22]. It has been found that the iodine concentration NIC in the iodine base map of benign lung nodules is significantly higher than that of malignant lung nodules. The energy spectrum curve and the effective atomic number reflect the degree of absorption of the substance into the CT value, which is useful for identifying its benign and malignant nature. Some studies have demonstrated that[23]. Statistical differences in energy spectrum CT parameters between SPNs of inflammatory, malignant and tuberculous nodules were demonstrated, confirming that the slope of the energy spectrum curve λHU, effective atomic

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number NIC and iodine concentration IC were significantly higher in inflammatory SPNs than in malignant SPNs, and in malignant SPNs than in tuberculous SPNs. providing new diagnostic methods and more diagnostic information for benign and malignant nodules in the lung.

2.3.2 Progress in the study of lung cancer subtypes by energy-spectrum CT

Parametric analysis of energy-spectrum CT likewise differed significantly according to the histological subtype and pathological grade of lung cancer. One study confirmed significant differences in energy-spectrum CT parameters combined with tumor markers between adenocarcinoma, neuroendocrine tumors, and squamous cell carcinoma, with adenocarcinoma having higher iodine values than squamous cell carcinoma. Other scholars[24]. The IC and λ HU at 40 keV were found to be significantly and positively correlated with the expression level of vascular endothelial growth factor (VEGF) in NSCLC, demonstrating the moderate predictive value of two important factors, NIC and VEGF mutation, in identifying EGFR mutations in adenocarcinoma. A further study[25] showed a significant difference in NIC between pure ground glass nodules (mGGN) and mixed ground glass nodules pGGN and suggested that the energy spectrum CT parameter could be used as an indicator of the blood supply status of GGN.

In conclusion, the technology of energy-spectral CT imaging has developed rapidly in recent years, and a lot of studies have been conducted on the application of energy-spectral CT in lung cancer, and the advantages of energy-spectral CT imaging technology have made significant progress in early diagnosis, assessment of lung cancer and judgment of prognosis. However, there is no unified consensus on the value of energy-spectral CT parameters in assessing the benignity and malignancy of lung cancer and the subtypes of lung cancer, and further research is still needed, which has good research prospects. With the development of radiomics, radiomics technology with high efficiency of excavation, data analysis of multidimensional information channels, and accurate calculation ability provides novel means for the analysis of lung cancer and its different subtypes.

3. Radiomics

3.1 Overview

The concept of Radiomics was first introduced by Dutch scholar Lambin in 2021[26]. It is a technical tool that has been developing rapidly in recent years. All types of imaging digital imaging modalities can be applied to the analysis of image histology, including MRI, CT, PET/CT, and ultrasound. Radiomics emphasizes the extraction of quantifiable information from images to transform medical images into data that can be analyzed. The process includes image collection of preferred lesions, image segmentation, extraction of feature information, and modeling of data for analysis. Radiomics can provide a personalized and non-invasive approach in the standardized clinical management of pulmonary nodules.

3.2 Progress in the Study of Radiomics and Lung Cancer and Its Differential Pathological Subtypes

Existing studies have shown high false-positive results for lung nodule screening and high psychological and socioeconomic impact on patients, and it is difficult to achieve consistency in the deployment of energy-spectrum CT parameters in different hospitals. The Chinese Medical Radiology Section made a consensus in 2018 to provide guidance on chest CT scan parameters, which reduces the impact of different devices on the analysis of lung nodule radiomics data.

Radiomics can characteristically reflect the size and morphology of the tissue and enable predictive models for the benignity and malignancy of lung nodules. Related studies have shown that[27] the pathological subtypes of lung cancer tissues are also crucial to patient prognosis, and domestic scholars Huang Zhicheng et al. used preoperative CT images of 1524 lung cancer patients (526 small cell lung cancer cases and 998 non-small cell lung cancer cases) based on The correlation correlation analysis with lasso dimensionality reduction finally retained 20 imaging

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histological features. The results showed that the radiomics model based on the neighborhood algorithm (KNN) model had the highest accuracy in discriminating SCLC from NSCLC, with 81.34% and 78.82% in the training and validation sets, respectively. This demonstrates that radiomics has great potential for the pathological staging of lung cancer[28-29].

Currently, radiomics is a non-invasive method in managing lung nodules and has improved the diagnostic efficiency of lung cancer in combination with energy-spectrum CT. However, radiomics still has its limitations, the characteristic extraction of lesions, and modeling methods are easily affected, and the current research data support is still in the primary stage. With the development of artificial intelligence and the standardization of radiomics by expert consensus, more reference information can be improved for accurate assessment of lung cancer and its subtypes.

4. Summary and Outlook

In the last decade or so, early non-invasive diagnosis of lung cancer has been a hot research topic due to its high incidence and high mortality rate. With the development of CT examination technology and computerized post-processing, the role of radiologists has changed to that of image analysts. Energy-spectrum CT multiparametric analysis has good prospects for clinical application in the study of lung cancer subtypes, but there are problems such as the lack of unified consensus on parameter indexes in current research. Secondly, radiomics is a retrospective and single-center study, the sample size of the study is too small, and there are few studies on different subtypes of lung cancer. With the inevitability of the combination of energy-spectrum CT diagnostic technology and radiomics, it is the trend to expand the sample size and standardize the scanning parameters, which will bring great help to the clinical diagnosis and treatment of lung cancer.

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