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DIAGNOSTIC PERFORMANCE OF SPECTRAL IMAGING IN THE DIFFERENTIATION OF LUNG CANCER FROM INFLAMMATORY MASS

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Abstract: Objectives: To collect and analyze the studies regarding the diagnostic value of spectral computed tomography (CT) for the differentiation between lung cancer and inflammatory mass. Material and Methods: English and Chinese studies regarding the differentiation of lung cancer from inflammatory mass with spectral CT were systematically searched in Medline, Pubmed, China National Knowledge Infrastructure database (CNKI), Wanfang database, Cochrane Library and Embase from January 2006 to December 2017. Review Manager 5.3 was used to calculate the standardized mean difference (SMD) and 95% confidence intervals (CI) of iodine concentration (IC), water concentration (WC), normalized iodine concentration (NIC) and slope of energy spectrum curve. Stata12.0 was used to evaluate the diagnostic efficacy and publication bias. Results After a detailed search, 14 studies including 638 cases of lung cancer and 308 cases of inflammatory mass were admitted eventually. SMD and 95%CI of IC, WC, NIC and slope between lung cancer and inflammatory mass were -1.48 (-2.49, -0.48), 0.01 (-0.20, 0.23), -0.85 (-1.45, -0.25) and -0.82 (-1.52, -0.11). All the results showed statistical difference except WC. The sensitivity and specificity of NIC were 0.82 (0.75, 0.87), 0.93 (0.73, 0.98), respectively. Conclusion The energy spectrum CT is adequate to differentiate lung cancer from inflammatory mass with the iodine-related indicators of IC, NIC, and slope of spectrum curve. Besides, NIC is regarded as the most valuable indicator for better reflection of blood supply of the lesions.
Keywords Spectral CT; lung cancer; inflammatory mass; standardized mean difference; Meta-analysis.

1. INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide. Sporadic pulmonary nodules are common and occur in 15% to 31% of asymptomatic individuals [1]. Screening on suspicious people using low-dose computed tomography (CT) are common in recent year, and the detection rate of lung nodules is as high as 51%. Plain and enhanced CT examination are adequate to show the location, morphological characteristics, and degree of enhancement of the lesions [2]. However, the coincidence rate for the diagnosis of malignant nodules accounted for only 1% -12%, and up to 30% of benign nodules underwent surgical resection eventually, as a result of lack of functional information such as evaluations on tumor perfusion or microvascular permeability [3]. Consideration on the risk of biopsy, the issue on how to non-invasively and accurately diagnose the pulmonary malignant nodules has increasingly become a focus of clinical concern. With the development of dual-source CT and gemstone CT, spectral imaging has become a hot topic and provides more information on the diagnosis of pulmonary nodules in recent years. It can calculate the concentration of different substances including iodine concentration (IC), water concentration (WC), normalized iodine concentration (NIC), and the slope of the energy spectrum curve among different energy intervals, which can be used to evaluate the blood supply and enhancement characteristics of the tumor quantitatively [4, 5]. It can also analyze the

composition of lesions through different energy spectrum curves and provide comprehensive information for tracking the tissue origins, which helps the differentiation of benign and malignant tumors [6]. Nowadays, there are a wide range of relevant studies supporting the diagnostic values of spectral imaging in the field of pulmonary nodules [4, 7, 8]. However, there are still some controversies on the differential diagnosis of lung cancer and inflammatory masses among these studies. For example, in the study of Jiang et al.[9], no significant differences could be found in NIC and slope of the energy spectrum curve between lung cancer and inflammatory mass, no matter in arterial or venous phase. In contrast, Zhang et al.[6] found that the NIC and slope of malignant nodules were significantly higher than those of inflammatory nodules. When the diagnostic threshold of venous NIC was set at 3.0, the sensitivity and specificity for distinguishing benign and malignant nodules were 93.8% and 85.7%, respectively. However, most studies considered that the IC, NIC, and slope of energy spectrum curve of malignant nodules were lower than those of inflammatory lesions [10-12]. Besides, though inflammatory masses belong to benign lesions, they are different from general benign tumors and chronic granulomas, due to their abundant blood supply. Whether there are still differences among inflammatory masses and lung cancer which is also abundant in blood supply, is worth exploring. To resolve the above-mentioned controversy about the ability of spectral imaging in the diagnosis of pulmonary lesions, we now collect published literatures with higher quality and larger sample sizes for meta analysis, the results of which may provide more reliable evidences and promote the diagnostic accuracy of pulmonary diseases using spectral CT.

2. MATERIALS AND METHODS

Data sources and search methods

Studies regarding the differential diagnosis between lung cancer and inflammatory mass using spectral imaging were systematically searched in Pubmed, Medline, Embase, Cochrane Library, Web of Science and China National Knowledge Infrastructure database from January 2006 to December 2017. The languages were limited in English or Chinese. Two of the authors completed the search independently. The keywords used in the search in either the title or abstract of the article were listed as follow: lung cancer, pulmonary inflammatory nodule or mass, spectral imaging, dual energy CT and gemstone CT. We also performed manual retrieval and scrutinized relevant references in the included studies to avoid missing some valuable studies.

Study selection

Two reviewers who were blind to the institutions, countries, and journals reviewed the potential studies independently. The inclusion criteria were as follows: (a) spectral CT was used to differentiate lung cancer from inflammatory mass; (b) at least one of the spectral parameters (i.e. IC, WC, NIC and slope of energy spectrum curve) was provided by the original study; (c) tumors must be confirmed by pathology, and inflammatory mass, or lesions can be diagnosed by clinical treatment or follow-up; (d) neither medication nor surgery was applied before CT examination; and (e) the scores of quality assessment related to the quality of study design were at least 9. Evaluation criteria were stated in the quality assessment section. The exclusion criteria were as follows: (a) case report, review, letter, meeting record, graduation thesis or studies that have not yet published; (b) duplications which originated from the same authors; (c) animal experiment; and (d) data were incomplete or unsuccessfully obtained from the authors.

Data abstraction and quality assessment

The following items were extracted in this analysis: first author, publication year, study types, number of patients, age, nodule size, nodule number, flow rate, and dose of contrast agent, as well as mean value and standard deviation (SD) of spectral parameters. True positive, false positive, false negative, and true negative values of venous NIC were also needed to calculate the sensitivity and specificity. We assessed the quality of each study with 14 criteria in terms of the risk of bias using the Revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist [13]. The criteria were judged as “Yes (low risk of bias),” “No (high risk of bias),” or “Unclear.” We discussed or invited a senior clinician to reach a consensus opinion when the results were discrepant.

Data synthesis

The pooled effect sizes and 95% confidence

intervals (CI) were calculated by Review Manager software version 5.3 (Cochrane Collaboration, Oxford, UK). Publication bias was evaluated by calculating the P value using Stata version 12.0 (StataCorp LP, College Station, TX). P>0.05 of Egger's test denoted no significant publication bias. Inconsistency index (I^2) and Cochran's Q test were used to estimate inter-study heterogeneity which may originate from age, gender, tumor subtype, flow velocity, dose and influence the accuracy of the pooled results; I^2>50% or P<0.05 was considered potential heterogeneity, and a random-effect model was applied for calculating the pooled results. Otherwise, a fixed-effect model was appropriate. As the parameters from different studies varied to some extent, we used the standardized mean difference (SMD) as the pooled results, which suggested less heterogeneity compared to weighted mean difference. Stata.12.0 was used to calculate the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, area under the curve (AUC), and their 95% CIs with a bivariate mixed-effects binary regression model. The receiver operating characteristic (ROC) curve was used to determine the diagnostic value of NIC in distinguishing between Lung cancer and inflammatory mass.

3. RESULTS

Literature search and selection of studies

Seventy-two studies were acquired after a primary search on study titles and abstracts. Eleven studies were excluded including animal experiments (n=4), duplications of studies by the same authors (n=4), and reviews (n=3). After downloading and reading full texts of the remaining 61 studies, we excluded an additional 33 studies because of data irrelevant to this analysis or lack of quantifiable parameters in the related studies. Eight studies were excluded for the assessment quality scores lower than 9, four studies for the diagnosis had not been confirmed by pathology. Eventually, a total of 14 studies (5 studies in English and 9 studies in Chinese) with totally 946 cases, including 638 cases of lung cancer and 308 cases of inflammatory mass were included for the analysis. A flowchart detailing the selection process based on inclusion and exclusion criteria is shown in Figure 1. Patient characteristics and imaging protocols of the included studies are summarized in Table 1. The diagnostic data of venous NIC for the differential diagnosis of pulmonary lesions are listed in Table 2.

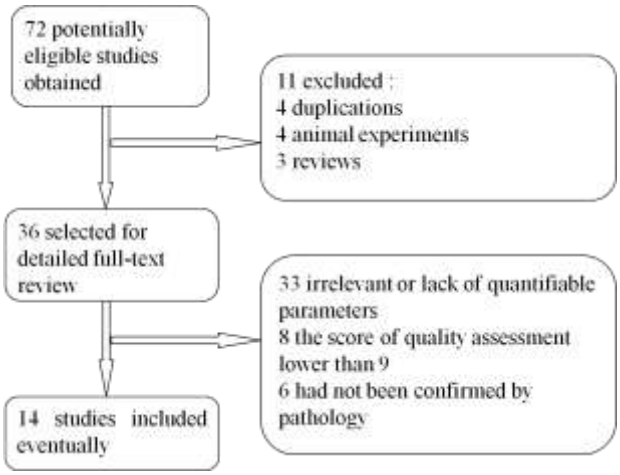

Fig. 1. Flowchart plots the selection process of included studies based on inclusion and exclusion criteria. Fourteen studies that met the inclusion criteria are included.

Table 2 The diagnostic data of venous NIC for the differential diagnosis of pulmonary lesions

Author	TP	FP	FN	TN
Wang SY et al.[14]	51	9	12	23
Guan et al.[15]	16	0	8	24
Wang LJ et al.[17]	30	6	8	14
Zhang et al.[6]	35	4	2	22
Hou et al.[10]	30	0	5	25

TP, true positive; FP, false positive; FN, false negative; TN, true negative.

Quantitative analysis

IC for differentiation between lung cancer and inflammatory mass

The IC values of lung cancer and inflammatory masses from eight included studies were pooled. A total of 390 cases of lung cancer and 191 cases of inflammatory lesions were analyzed. The mean value and SD of IC for each study are shown in Figure 2. Heterogeneity tests indicated significant heterogeneity between studies (I^2=96%, P<0.001). Therefore, we pooled IC using a random-effect model. The results showed that IC value of lung cancer was lower than that of inflammatory lesions. The difference was statistically significant. The pooled SMD of IC was -1.48 (-2.49, -0.48), P=0.004. The Egger's test showed no potential publication bias effect in IC (P=0.057).

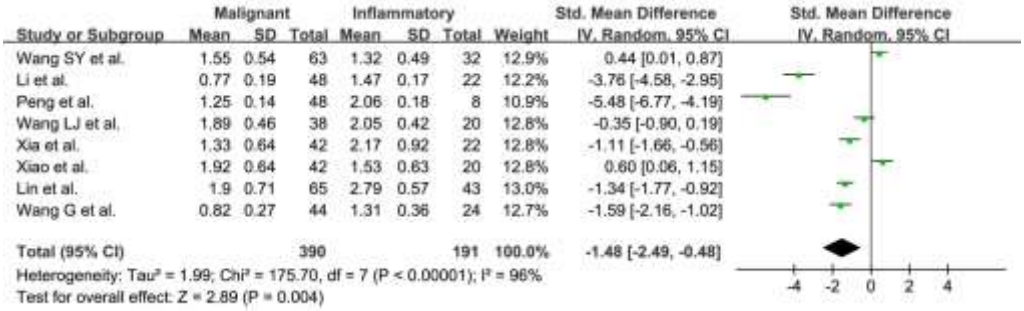

Fig. 2.Forest plot of the mean value of IC between lung cancer and inflammatory mass using a random-effects model.

WC for differentiation between lung cancer and inflammatory mass

The WC values of lung cancer and inflammatory masses from six included studies were pooled. A total of 249 cases of lung cancer and 129 cases of inflammatory lesions were analyzed. The mean value and SD of WC for each study are shown in Figure 3. Heterogeneity tests showed no heterogeneity between studies (I^2=13%, P=0.33). Therefore, we pooled WC using a fixed-effect model. Results showed no statistical difference of WC between lung cancer and inflammatory mass. The pooled SMD of WC was 0.01 (-0.20, 0.23), P=0.91. The Egger's test showed no potential publication bias effect in IC (P=0.085).

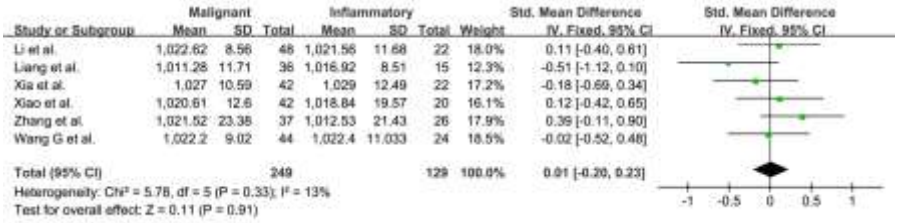

Fig.3.Forest plot of the mean value of WC between lung cancer and inflammatory mass using a random-effects model.

NIC for differentiation between lung cancer and inflammatory mass

The NIC values of lung cancer and inflammatory masses from six included studies were pooled. A total of 296 cases of lung cancer and 135 cases of inflammatory lesions were analyzed. The mean value and SD of NIC for each study are shown in Figure 4. Heterogeneity tests showed significant heterogeneity between studies (I^2=86%, P<0.001). Therefore, we pooled WC using a random -effect model. The results showed that NIC value of lung cancer was lower than that of inflammatory lesions. The difference was statistically significant. The pooled SMD of WC was -0.85 (-1.45, -0.25), P=0.006. The Egger's test showed no potential publication bias effect in IC (P=0.553).

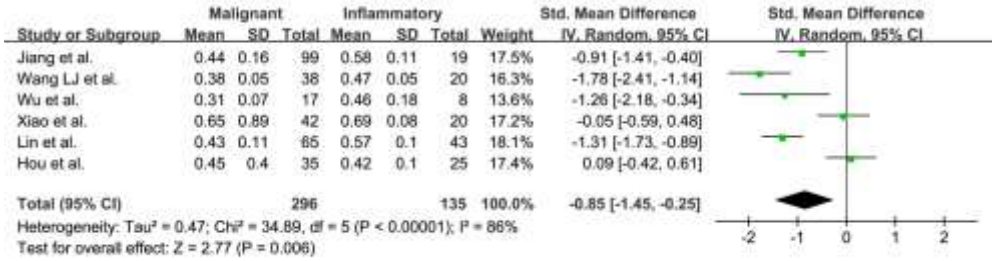

Fig. 4.Forest plot of the mean value of NIC between lung cancer and inflammatory mass using a random-effects model.

The slope of energy spectrum curve for differentiation between lung cancer and inflammatory mass

The slope values of lung cancer and inflammatory masses from 12 included studies were pooled. A total of 572 cases of lung cancer and 262 cases of inflammatory lesions were analyzed. The mean value and SD of slope for each study are shown in Figure 5. Heterogeneity tests showed significant heterogeneity between studies (I^2=95%, P<0.001). Therefore, we pooled slope using a random -effect model. The results showed that slope value of lung cancer was lower than that of inflammatory lesions. The difference was statistically significant. The pooled SMD of slope was -0.82 (-1.53, -0.11), P=0.02. The Egger's test showed no potential publication bias effect in slope (P=0.933).

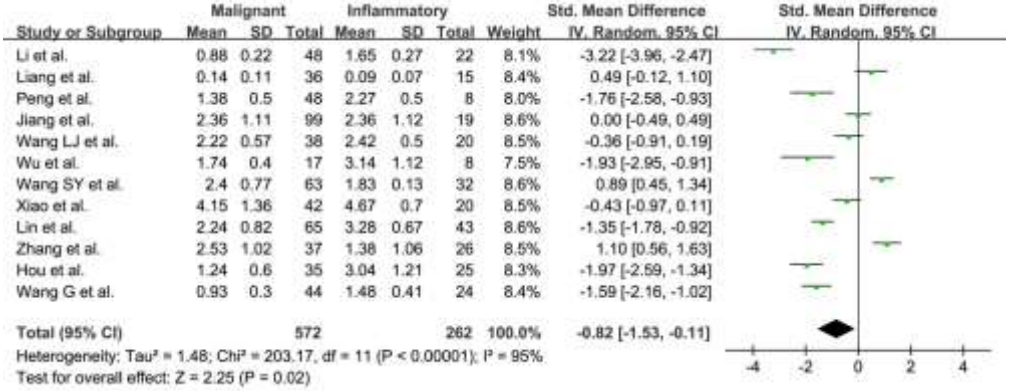

Fig. 5.Forest plot of the mean value of slope between lung cancer and inflammatory mass using a random-effects model.

The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, AUC of venous NIC were 0.82(0.75, 0.87), 0.93(0.73, 0.98), 11.2(2.7, 45.5), 0.2(0.14, 0.27), 57 (13, 254), and 0.87 (0.83, 0.89), respectively.

4. DISCUSSION

Because lung cancer is a kind of invasive tumor, morphological performance could be used to make a preliminary diagnosis of the pulmonary nodule nature in the past, and a series of radiomics studies based on the texture analysis of pulmonary nodules were derived, which illuminated the disorder arrangement of tumor cells and the morphologic heterogeneity in the cellular level [22]. However, these studies still lacks functional information. As the development of imaging technology, spectral CT imaging may resolve these problems, to a certain extent. It can not only evaluate the blood flow of the lesions through an iodine map, but also reflect the composition by energy spectrum curve, which provides richer information for the diagnosis of pulmonary lesions. The spectral parameters in the venous phase was selected for meta-analysis because the contrast agent had a greater uptake and more uniform distribution in this period than arterial phase. Numerous studies have shown the venous phase had a higher AUC and diagnostic efficiency than arterial phase in the diagnosis of pulmonary nodules [10, 14, 17]. This stage is more useful for the

differential diagnosis of lung cancer and inflammatory masses. Our study found that the IC, NIC, and slope of lung cancer were lower than those of inflammatory masses. The differences were all statistically significant. The inflammatory mass in this study mainly included inflammatory pseudotumor, organizing pneumonia, globular pneumonia, lung abscess (without formation of cavity), and inflammatory granuloma. These diseases are dominated by granulation hyperplasia. They are supplied by both bronchial artery and pulmonary artery. However, lung cancer is mainly supplied by the bronchial arteries. As a result, the different blood supplies led to a higher iodine concentration in the inflammatory masses than in lung cancer. Ding et al.[23] performed a perfusion study for the differential diagnosis of pulmonary nodules using a 64-slice spiral CT ,and found the blood volume and blood flow of inflammatory nodules were significantly higher than those of malignant nodules, further confirmed that the IC and NIC of the inflammatory mass were higher than lung cancer in this study due to abundant blood supplies in the inflammatory lesions. On the other hand, though lung cancer similarly showed a high iodine concentration in the venous phrase, it is mainly resulted from an increase in capillary volume due to a large number of microvascular hyperplasias. However, the newborn vessels are immature, disorganized, distorted, and non-uniform. The drainage of lymphatic vessels are absent in lung cancer, leading to a retention and delayed elimination of contrast agent in the capillaries. Therefore, the energy spectrum curve of lung cancer is flat, and the slope is lower. The study Zhang et al.[24] also confirmed that the average transit time of malignant nodules is longer than inflammatory masses using perfusion CT imaging. In contrast, the vessels of inflammatory masses expanded in the stimulation of inflammatory factors, resulting in a faster blood flow, and a larger iodine absorption. Besides, the elimination of contrast agent is faster with rich lymphatic vessels. Therefore, the curve is steeper and the slope is larger.

The blood flow of inflammatory masses increased during the congestive phase, and the cells occurred toxic edema, therefore, WC values are high both inside and outside the cells. Because lung cancer is also rich in blood supplies with a large blood volume, and its intracellular and extracellular WC are also high [20]. As a result, there is no statistical difference in WC between lung cancer and inflammatory mass.

Although this study only analyzed the diagnostic efficacy of NIC alone, most studies found that the AUC of NIC is the highest in the differential diagnosis of pulmonary nodules, and has high sensitivity and specificity [9, 17, 19]. IC is not only related to blood supply, but also related to the dose, viscosity and flow rate of contrast agent. Selecting the IC of aorta for calculating the NIC of the lesions helped to avoid the influence of individual differences between studies. Therefore, NIC is more suitable and recommended as the optimal parameter of energy spectral imaging in the differential diagnosis of pulmonary lesions.

Heterogeneity analysis is an important part of meta-analysis because the results may vary from study to study. The spectral parameters including IC, NIC, and slope showed significant heterogeneity (I^2>80%) except WC in this study. First, both lung cancer and inflammatory mass had rich and similar blood supply, and some results were completely opposite among the included studies. On the other hand, whether the conflicting or negative results from different studies were included in this meta-analysis, publication bias was significantly reduced in the meantime. Second, the types of inflammatory nodules or masses included in this study varied to a large extent, and some studies included chronic inflammatory granuloma such as pulmonary tuberculosis, resulting in a certain bias in the results. Third, the size of lung cancer and inflammatory masses were inconsistent between studies, and the blood supply of lesions may not be the same in different stages. For example, the rapid growth period of lung cancer and the acute congestive phase of inflammatory masses may cause unpredictable changes in the results. Fourth, the subtypes of lung cancer included were not consistent. Lung adenocarcinoma are more susceptible to occur cavity than squamous cell carcinoma due to the differences in blood supply. These were sources of heterogeneity and also limitations of this study. On the other hand, the majority of the scanners included in the study were GE Discovery 750HD CT, with more consistent spectral imaging parameters. The voltages were all switched instantaneously between 80 and 140kVp,

which ensured a good homogeneity between studies.

5. CONCLUSIONS

IC, NIC, and slope of spectrum curve are valuable parameters in the differential diagnosis of lung cancer and inflammatory nodules, especially venous NIC. Spectral imaging is of great significance because it can reflect both the blood supply and biological behavior of lesions.

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Table 1 Basic information and quality assessment of included studies

Author	Year	Study types	Patients(male/female)	Malignant	Inflammatory	Age(years)	Sizes(mm)	Contrast agent	Flow rate(ml/s)	Dose(ml)	Quality score
Wang SY et al.[14]	2016	Prospective	114（69/45）	63	32	57±11	≤30	iodixanol 270	3.5	80-100	9
Li et al.[11]	2013	Prospective	70（51/19）	48	22	62（48-82）	12-49	iohexol 300	3	1.2ml/kg	11
Guan et al.[15]	2013	Retrospective	48（33/15）	24	24	58（43-76）	NA	NA	NA	NA	13
Liang et al.[16]	2017	Retrospective	51（36/15）	36	15	56（14-80）	29±10	NA	NA	NA	12
Peng et al.[8]	2015	Prospective	67（41/26）	48	8	54（31-82）	32（12-51）	iohexol 300	3	100	11
Jiang et al.[9]	2017	Prospective	129（68/61）	99	19	51±8	10-50	ioversol 370	3	NA	10
Wang LJ et al.[17]	2017	Retrospective	58	38	20	20-80	NA	ioversol 320	3	85	9
Xia et al.[18]	2015	Prospective	64（47/17）	42	22	62		iohexol 300	3	NA	13
Wu et al.[19]	2014	Prospective	33（22/11）	17	8	53（36-76）	10-50	iopromide 370	3	1.1ml/kg	12
Xiao et al.[20]	2015	Prospective	62(40/22)	42	20	60(42-80)	NA	iodixanol 270	4	80-100	12
Lin et al.[12]	2016	Prospective	139(78/61)	65	43	59(23-78)	21.2±7.5	iopromide 300	3	90	10
Zhang et al.[6]	2016	Prospective	63(37/26)	37	26	55(30-87)	NA	iopamidol 370	4	80-100	9
Hou et al.[10]	2015	Prospective	60(35/25)	35	25	62(41-83)	33(23-66)	iopamidol 370	4	80-100	13
Wang G et al.[21]	2014	Prospective	68(50/18)	44	24	66.16±11.60	NA	iopamidol 300	3	1.2ml/kg	11