Advantages of 99mTc-CNDG SPECT/CT over Enhanced CT in the Staging of Non-Small Cell Lung Cancer

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Research Article

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**Abstract**

**Objective** To explore the value of $^{99m}$Tc-isonitrile deoxyglucosamine (CNDG) SPECT/CT in the staging and resectability diagnosis of non-small cell lung cancer (NSCLC) compared with enhanced CT.

**Methods** This research was approved by the hospital ethics review committee. Sixty-three patients with NSCLC received $^{99m}$Tc-CNDG SPECT/CT, enhanced CT and initial TNM staging before treatment. Thirty-three patients who underwent radical surgery took postoperative pathological TNM staging as the reference standard. Another thirty patients who underwent radiochemotherapy, among them the reference standard of 7 patients of N staging and 5 patients of M staging was based on biopsy pathology and the diagnosis of the remaining lesions was confirmed by at least one different image or clinical imaging follow-up for more than 3 months. The McNemar test and receiver operating characteristic (ROC) curve analysis were used to compare the diagnostic accuracy of staging and resectability of $^{99m}$Tc-CNDG SPECT/CT and enhanced CT in NSCLC respectively.

**Results** For all patients and surgical patients, the accuracies of $^{99m}$Tc-CNDG SPECT/CT in diagnosing the T stage and N stage were higher than those of enhanced CT (all patients: 90.5%, 88.9% vs. 79.4%, 60.3%; surgical patients: 81.8%, 78.8% vs. 60.6%, 51.5%), and the differences were statistically significant (all patients: T stage, $P=0.016$; N stage, $P=0.000$; surgical patients: T stage, $P=0.016$; N stage, $P=0.004$). For all patients the accuracy of $^{99m}$Tc-CNDG SPECT/CT in diagnosing the M stage was higher than that of enhanced CT (96.8% vs. 90.5%), but the difference was not statistically significant ($P=0.289$). ROC curve analysis showed that the accuracy of $^{99m}$Tc-CNDG SPECT/CT in diagnosing the potential resectability of NSCLC was significantly better than that of enhanced CT ($P=0.046$).

**Conclusion** This preliminary clinical study shows that $^{99m}$Tc-CNDG SPECT/CT is of great value for accurate clinical staging of NSCLC compared with enhanced CT, and can significantly improve the accuracy of resectability diagnosis.

**Introduction**

Malignant tumors are characterized by uncontrolled proliferation, invasion and metastasis, during malignant tumors evolution, glucose transporters (Gluts) which are the main carriers of cell glucose transmembrane transport and hexokinase (HK) which is an important rate-limiting enzyme in the glycolytic pathway are overexpressed, which significantly increases the glucose uptake and glycolysis rate of malignant tumor cells. The abnormal increase in glucose metabolism in malignant tumor cells is more than 200 times greater than that in normal cells, which is called the Warburg effect. Based on this, PET/CT and SPECT/CT of nuclear medicine tumor molecular imaging modalities are used for tumor glucose metabolism imaging, and $^{18}$F-2-deoxy-D-fluoro-glucose ($^{18}$F-FDG) has become a widely used glucose metabolism imaging agent in tumor diagnosis, staging and treatment decision. However, $^{18}$F-FDG PET/CT has some shortcomings, such as false-positives in benign proliferative inflammatory lesions, false-negatives in some types of malignant tumors or well-differentiated malignant
tumors, complex preparation of $^{18}$F-FDG, expensive equipment and poor accessibility to primary hospitals.5

$^{99m}$Tc-labeled glucose SPECT/CT is a widely available, inexpensive and convenient molecular imaging technique of nuclear medicine.$^{99m}$Tc has excellent nuclide properties ($E_\gamma=140$ keV, $T_{1/2}=6.02$ h), and its various oxidation states can be coordinated with different ligands to prepare various new radiopharmaceuticals. $^{99m}$Tc is supplied internally by a molybdenum technetium generator at a low price, additionally the number of SPECT/CT scanners worldwide far exceeds that of PET/CT scanners, which confers $^{99m}$Tc labeled glucose SPECT/CT with broad clinical application prospects.6,7 Recently, Zhang JB et al.8 of Beijing Normal University drew on the fact that the single ligand isonitrile (CN-R) can form a stable $^{99m}$Tc complex ($[^{99m}$Tc(CN-R)$_6$]+) with a $^{99m}$Tc( ) nucleus in high yield innovatively synthesize isonitrile deoxyglucosamine (CNDG), and obtained a new glucosamine imaging agent $^{99m}$Tc-CNDG. In this study, surgical operation pathology, biopsy pathology and clinical imaging follow-up after treatment were used as reference standards for staging of non-small cell lung cancer (NSCLC), and the accuracies of $^{99m}$Tc-CNDG SPECT/CT in the diagnosis of TNM staging and resectability of NSCLC were prospectively evaluated compared with conventional enhanced CT.

**Patients and Methods**

**Patients**

This prospective study was approved by the hospital ethics review committee (LLKY191007). From January 2019 to August 2021, sixty-three patients (27 women, 36 men) with NSCLC diagnosed pathologically in our hospital were enrolled in this study. The mean age of the patients was 60.5±8.8 years (range, 43-83 years). In addition to routine laboratory examination, neck and abdomen ultrasound, chest radiology, brain CT, brain MRI, $^{99m}$Tc-methylene diphosphate (MDP) bone imaging and other standard staging inspections, all patients underwent $^{99m}$Tc-CNDG SPECT/CT and enhanced CT within 2 weeks. The inclusion criteria were as follows: (1) patients who underwent radical surgery or radiochemotherapy within 2 weeks after imaging evaluation; and (2) patients who underwent pathology staging of radical surgery, pathology staging of puncture biopsy and clinical imaging follow-up staging for more than 3 months. The exclusion criteria were as follows: (1) patients with insulin-dependent diabetes mellitus or patients with a fasting blood glucose concentration exceeding 11.1 mmol/L before injection of $^{99m}$Tc-CNDG; (2) patients who received radiochemotherapy before examination; and (3) patients with hepatic and renal insufficiency. All patients were included in this study after informed consent was obtained.

**$^{99m}$Tc-CNDG SPECT/CT**

Fresh sodium pertechnetium solution was obtained by washing with a molybdenum technetium generator provided by Beijing Institute of Atomic Energy (Beijing, China), CNDG was provided
by Beijing Shihong Pharmaceutical Center of Beijing Normal University (Beijing, China) with a freeze-dried kit. 2220-4400 MBq/1-5 ml sodium pertechnetium solution was added to a freeze-dried bottle of CNDG (1 mgCNDG, 0.06 mg SnCl\textsubscript{2}•H\textsubscript{2}O, 1 mg sodium citrate, 1 mg L- cysteine), it was placed in a water bath at 100°C for 20 min, and then cooled to room temperature for later use. Radiochemical purity was determined by chromatography with a γ counter, and only when the labeling rate was greater than 95% could it be used.

Patients needed to fast for more than 6 hours before injecting $^{99m}$Tc-CNDG, and only a high-protein and low-sugar diet were allowed before imaging. After intravenous injection of $^{99m}$Tc-CNDG (14.8-22.2 MBq/kg), patients rested in a supine position and 800-1000 ml of sugar-free water was used for hydration before imaging. SPECT/CT was performed from the clavicular area to the upper abdomen after 3 hours. The Symbia T16 SPECT/CT system from Siemens company was used, and it was equipped with a low-energy high-resolution collimator. The acquisition parameters were as follows: 5.6°/frame, 25 s/frame, 180° noncircular orbit rotation and 256×256 matrix. The images were reconstructed by an iterative method. Chest spiral CT was used for attenuation correction, anatomical localization and structural imaging diagnosis. SPECT/CT fusion images were obtained by using the Syngo workstation of Siemens company. Any related side effects of the intravenous injection and imaging of $^{99m}$Tc-CNDG were recorded.

**Enhanced CT**

The Discovery 750HD CT system from GE company was used. One hundred milliliters of the contrast agent Ultravist (300 mg/ml) was injected intravenously, and the injection rate was 2 ml/second. After 30 seconds, continuous scanning was performed from the clavicular area to the upper abdomen. The acquisition parameters were as follows: voltage 120 kV, current 230 mA and pitch 1. The images were reconstructed with a 3.0 mm slice thickness.

**Image Analysis**

Image interpretation was performed by two independent review boards of trained nuclear medicine physicians/radiologists. Readers were blinded to all patient dates other than the suspicion of NSCLC. If the diagnosis was inconsistent, consensus was reached through discussion. The interpretation of $^{99m}$Tc-CNDG SPECT/CT was as follows: positive radioactive uptake was based on a visual method combined with a semiquantitative parameter method, and visual assessment was based on whether the lesion had abnormal radioactive local uptake higher than the surrounding background. The parameter used in the semiquantitative method was the target to nontarget tissue uptake ratio (T/NT), and it was judged as positive when \( T/NT \geq 1.2 \). According to the fused image, the lesion site with abnormally high positive radioactivity was located, and the nature of the lesion was determined by lesion radioactive uptake combined with the structural image characteristics. The interpretation of enhanced CT was as follows: positive lesions were interpreted based on the imaging structure and blood supply characteristics,
and the nature of the lesions was determined according to lesion size, anatomical shape, enhancement degree and structural infiltration (including chest wall, mediastinum, esophagus, spine, etc.).

**Treatment Methods and Reference Standards**

Radical resection of lung cancer and lymph node dissection were performed for those patients who were clinically evaluated as resectable. With reference to $^{99m}$Tc-CNDG SPECT/CT and enhanced CT before the operation, the surgeon removed all accessible abnormal tumor tissues and abnormal lymph nodes in the hilum and mediastinum, and then numbered the localized tumors and lymph nodes. The pathologist performed hematoxylin-eosin staining and immunohistochemistry to obtain histopathological results and pathological TNM staging. Radiochemotherapy was performed for those patients who were clinically evaluated as unresectable, and the TNM staging of these unresectable patients was determined by the biopsy pathology of the lesion and at least one different imaging method or clinical imaging follow-up for more than 3 months. The diagnosis of lesions by $^{99m}$Tc-CNDG SPECT/CT and enhanced CT was assessed in relation to the results of postoperative pathology, biopsy pathology and follow-up imaging.

The international multidisciplinary classification standard of lung cancer jointly introduced by the International Society for Lung Cancer Research IASLC and the American Thoracic Society ATS in 2011 was adopted for the pathological classification of lung cancer.⁹ The eighth edition Union for International Cancer Control UICC TNM staging standard was adopted for lung cancer staging.¹⁰ Regional lymph node stations of lung cancer were divided into 14 groups according to the international lymph node map recommended by IASLC.¹¹ Potential resectability was characterized as the prevalence of 3 conditions: a T stage of less than 4, an N stage of less than 3, and an M stage of 0.¹²

**Statistical Analysis**

Statistical analysis was conducted using SPSS software (IBM SPSS Statistics 19, USA). Quantitative variables were expressed as the mean±standard deviation, and qualitative variables were expressed as percentages. An Independent sample t test was used to compare the mean of the two samples, McNemar’s test was used to compare the classified variables, and receiver operating characteristic (ROC) curve analysis was used to compare the diagnostic accuracy of resectability between the two methods. $P < 0.05$ was considered statistically significant.

**Results**

**Biological Distribution and Safety of $^{99m}$Tc-CNDG in the Human Body**

The imaging quality of $^{99m}$Tc-CNDG SPECT/CT in the sixty-three patients with NSCLC was good. Three-hour whole-body imaging showed that there was no obvious uptake of $^{99m}$Tc-CNDG in the normal brain, myocardium, lung, bone and muscle. A small amount of $^{99m}$Tc-CNDG was found in the liver, spleen, nasopharynx, synovium of joints and peripheral blood, and a large amount of $^{99m}$Tc-CNDG was found in
the kidney, bladder, gallbladder and intestine. The low background of the lung, brain, myocardium, bone and muscle made it easy to display lung lesions and metastatic lesions of brain, bone and mediastinal lymph node, while the metastatic lesions of liver, adrenal gland and abdominal lymph node were relatively difficult to display because of the high background of surrounding tissues. No adverse reactions were reported during the injection and imaging of $^{99m}$Tc-CNDG.

Pathology and Follow-Up

Of the sixty-three patients with NSCLC, 33 patients (52.4%) were clinically evaluated as operable and underwent radical resection of lung cancer plus lymph node dissection, and another 30 patients (47.6%) were clinically evaluated as inoperable and underwent radiochemotherapy. Among the 33 surgical patients, 30 patients underwent endoscopic radical resection of lung cancer plus lymph node dissection, and 3 patients underwent thoracotomy radical resection of lung cancer plus lymph node dissection. Among the 30 nonsurgical patients, 7 patients and 5 patients obtained histopathological N staging by lymph node biopsy and M staging by bone or pleural biopsy, respectively. The diagnoses of the remaining lesions were confirmed by at least one different image or follow-up imaging for more than 3 months.

For the 33 surgical patients with postoperative pathology, TNM staging was classified as stage IA in 19 patients, IB in 4, IIA in 1, IIB in 2, IIIA in 4, and IIIB in 3. For the 30 nonsurgical patients with biopsy pathology and clinical imaging follow-up, TNM staging was classified as stage IIIA in 2 patients, IIIB in 5, IIIC in 3, IVA in 14, and IVB in 6. The histopathological results of the 63 patients are presented in Table 1.

TNM Staging Accuracy

The uptake of $^{99m}$Tc-CNDG was abnormally increased in the primary tumor of all sixty-three patients. The mean primary tumor size was $34.11 \pm 20.58$ mm (range, 9-90 mm) and the mean primary tumor T/NT was $3.55 \pm 1.78$ (range, 1.2-9.0). 1 patient with suspected ipsilateral different lung lobe metastasis by enhanced CT showed negative $^{99m}$Tc-CNDG SPECT/CT, and no metastasis was confirmed by postoperative pathology. There were 2 patients with nodular pericardial invasion, 1 patient was positive on both enhanced CT and $^{99m}$Tc-CNDG SPECT/CT, and 1 patient with only $^{99m}$Tc-CNDG SPECT/CT showed abnormally increased tumor activity. 1 patient suspected of pericardial invasion by enhanced CT showed no abnormal tumor activity by $^{99m}$Tc-CNDG SPECT/CT, and was confirmed as having a benign lesion after 10 months of enhanced CT follow-up after radical resection of lung cancer. Among the 13 patients with incorrect T staging on enhanced CT, 7 patients were overestimated (11.11%) and 6 patients were underestimated (9.52%). Among the 6 patients with incorrect T staging on $^{99m}$Tc-CNDG SPECT/CT, 4 patients were overestimated (6.35%) and 2 patients were underestimated (3.17%).

Of the 33 surgery patients with regional lymph node pathological diagnosis conducted by surgical mediastinal lymph node dissection 8 patients had lymph node metastasis and 25 patients had no lymph node metastasis. In 22 metastatic lymph node stations, the mean lymph node size was $9.23 \pm 2.29$ mm (range, 4-14 mm), and the mean lymph node T/NT was $2.70 \pm 1.76$ (range, 1.1-8.3). In 124
nonmetastatic lymph node stations, the mean lymph node size was 6.78±3.08 mm (range, 3-18 mm), and the mean lymph node T/NT was 1.11±0.29 (range, 1.0-2.8). The differences in lymph node size and T/NT between the two groups were statistically significant (all \( P < 0.001 \)). Of the 22 metastatic lymph node stations, 17 stations were not enlarged by enhanced CT, of which 13 stations were found to have increased abnormal radioactive uptake by \(^{99m}\text{Tc-CNDG SPECT/CT}\), and 4 stations were found to have no increased abnormal radioactive uptake by \(^{99m}\text{Tc-CNDG SPECT/CT}\). 5 stations were enlarged by enhanced CT, all of which were found to have increased abnormal radioactive uptake by \(^{99m}\text{Tc-CNDG SPECT/CT}\). Of the 124 nonmetastatic lymph node stations, 109 stations were not enlarged by enhanced CT, of which 2 stations were found to have increased abnormal radioactive uptake by \(^{99m}\text{Tc-CNDG SPECT/CT}\). 15 stations were enlarged by enhanced CT, of which 8 stations were found to have no increased abnormal radioactive uptake by \(^{99m}\text{Tc-CNDG SPECT/CT}\). The pathological manifestations of those patients with abnormal radioactive uptake increase in nonmetastatic lymph nodes were inflammatory proliferation reactions. Of the 30 nonsurgery patients with regional lymph node metastasis diagnosis based on lymph node biopsy pathology and follow-up imaging, all these nonsurgery patients had lymph node metastasis.

In 118 metastatic lymph node stations, the mean lymph node size was 14.65±5.91 mm (range, 7-52 mm), and the mean lymph node T/NT was 2.10±0.82 (range, 1.2-5.8). All 118 metastatic lymph node stations were found to have increased abnormal radioactive uptake by \(^{99m}\text{Tc-CNDG SPECT/CT}\), of which 101 stations were enlarged by enhanced CT. Among 25 patients with incorrect N staging on enhanced CT, 10 patients were overestimated (15.87%) and 15 patients were underestimated (23.81%). Among 7 patients with incorrect N staging on \(^{99m}\text{Tc-CNDG SPECT/CT}\), 6 patients were overestimated (9.52%) and 1 patient was underestimated (1.59%).

No distant metastasis was found in the clinicopathological diagnosis of the 33 surgical patients, while 20 of the 30 nonsurgical patients were diagnosed as distant metastasis based on biopsy pathology and follow-up imaging. There were 6 patients with pleural metastasis, and both enhanced CT and \(^{99m}\text{Tc-CNDG SPECT/CT}\) were positive. There were 5 patients with contralateral lung metastasis, who were positive on enhanced CT, and 4 patients were positive on \(^{99m}\text{Tc-CNDG SPECT/CT}\). There were 9 patients with bone metastasis, who were positive on \(^{99m}\text{Tc-CNDG SPECT/CT}\), only 4 patients showed abnormal bone density by enhanced CT, in 1 patient with osteoclastic bone metastasis in the rib detected by CT, \(^{99m}\text{Tc-CNDG SPECT/CT}\) showed an abnormal radioactive uptake increase, while \(^{99m}\text{Tc-MDP bone imaging}\) showed no abnormal radioactive uptake. There were 2 patients with benign bone lesions with abnormal bone density on CT that was suspected to be bone metastases, and \(^{99m}\text{Tc-CNDG SPECT/CT}\) and \(^{99m}\text{Tc-MDP bone imaging}\) confirmed that there were no abnormalities. There were 3 patients with adrenal metastasis, all of whom were positive on enhanced CT, 1 patient was positive on \(^{99m}\text{Tc-CNDG SPECT/CT}\), and 2 patients did not show any adrenal metastasis on \(^{99m}\text{Tc-CNDG SPECT/CT}\) due to the high radioactive distribution near the kidney. There were 1 patient with liver metastasis and 1 patient with subcutaneous metastasis, and both enhanced CT and \(^{99m}\text{Tc-CNDG SPECT/CT}\) were positive. Among 6 patients with incorrect M staging on enhanced CT, 1 patient was overestimated (1.59%) and 5 patients...
were underestimated (7.94%). Both of 2 patients with incorrect M staging on $^{99m}$Tc-CNDG SPECT/CT were underestimated (3.17%).

For all patients and surgical patients who underwent postoperative pathology the accuracies of $^{99m}$Tc-CNDG SPECT/CT in diagnosing T stage and N stage were higher than those of enhanced CT, and the differences were statistically significant. For all patients the accuracy of $^{99m}$Tc-CNDG SPECT/CT in diagnosing M staging was higher than that of enhanced CT, but the difference was not statistically significant. The comparison of the diagnostic accuracy of TNM stage between the two methods is presented in Table 2. The staging diagnoses of $^{99m}$Tc-CNDG SPECT/CT and enhanced CT in surgical patient and in nonsurgical patient are shown in Figure 1 and Figure 2, respectively.

**Potential Respectability**

To compare the accuracies of $^{99m}$Tc-CNDG SPECT/CT and enhanced CT in evaluating the potential resectability of NSCLC, the areas under the ROC curve of the two methods were calculated, as shown in Figure 3. The accuracy of $^{99m}$Tc-CNDG SPECT/CT in evaluating the potential resectability of NSCLC was significantly higher than that of enhanced CT ($P=0.046$).

**Discussion**

TNM staging of NSCLC is a standard method to determine the tumor range based on the characteristics of the primary tumor, regional lymph node and distant metastasis which is the pillar of clinical treatment decision and prognosis evaluation of NSCLC and the resectability of NSCLC patients can be accurately evaluated according to TNM staging.\(^{13}\) Enhanced CT of structural image can be used to diagnose obvious local mediastinal and distant invasion by showing tumor size morphology, pulmonary nodules, pleural nodules, pericardial nodules, lymphadenopathy, adrenal nodules and abnormal bone density, but the diagnostic accuracy is poor for slightly atypical invasion and metastasis. Thus enhanced CT is unreliable for accurate staging of NSCLC.\(^{14}\) Molecular imaging of nuclear medicine with functional metabolism can be used to accurately diagnose malignant tumors at an early stage. In recent years, $^{18}$F-FDG PET/CT has become a widely and frequently used imaging method in the diagnosis and staging of NSCLC.\(^{5,15,16}\) A meta-analysis showed that $^{18}$F-FDG PET/CT changed 25.3%-62.0% of the TNM stages of NSCLC, which led to changes in the clinical decision-making of 19.0%-52.0% of patients. At present, $^{18}$F-FDG PET/CT has been recommended in many international guidelines for clinical TNM staging of NSCLC.\(^{14}\)

Similar to $^{18}$F-FDG, the hydroxyl group of glucosamine C\(_2\) is replaced by an amino group. Glucosamine and glucose share a common metabolic pathway, and their amino groups play a dual role as coordination sites and functional targets.\(^{1,8,17}\) Studies have shown that glucosamine retains the metabolic activities of Gluts and HK even in the case of large coordination groups, and $^{99m}$Tc-labeled glucosamine is also located in the nucleus through the biosynthesis path of hexosamine.\(^{18}\) To date, $^{99m}$Tc-ethylenedicystine
deoxyglucosamine (ECDG) and $^{99m}$Tc-CNDG are the most representative, and $^{99m}$Tc-ECDG has entered a Phase clinical study.\(^8\) A preliminary clinical study of $^{99m}$Tc-ECDG SPECT/CT in early evaluation of the response of nine patients with locally advanced head and neck squamous cell carcinoma after radiochemotherapy showed that $^{99m}$Tc-ECDG SPECT/CT accurately predicted the treatment response of 7 patients (77.8%).\(^{19}\) Recently Dai D et al.\(^{20}\) reported a clinical study of 17 patients with NSCLC confirmed by biopsy, in which $^{99m}$Tc-ECDG SPECT/CT was used to detect and stage the tumor. The results showed that although the tumor uptake of $^{99m}$Tc-ECDG was low and the blood background was high compared with $^{18}$F-FDG, the coincidence rate of $^{99m}$Tc-ECDG in detecting the primary tumor and metastatic lesion reached 100% and 70% respectively, and the diagnostic efficiencies of $^{99m}$Tc-ECDG SPECT/CT for primary tumor and metastatic lesions of lung cancer were not inferior to those of $^{18}$F-FDG PET/CT.

Studies have confirmed that unlike $^{18}$F-FDG and other $^{99m}$Tc-labeled glucose derivatives, the uptake of $^{99m}$Tc-CNDG by malignant tumor cells is related not only to Gluts, but also to the hydrophilic cation characteristics of CNDG, which increase its uptake by malignant tumor cells through its transmembrane negative potential.\(^8,21\) Preclinical animal experiments showed that the tumor uptake rate and T/NT of $^{99m}$Tc-CNDG were significantly higher than those of previous various glucose derivatives labeled with $^{99m}$Tc, which can clearly display malignant tumors with a diameter of 3 mm.\(^8\) Recently, Wang QF et al.\(^{22}\) prospectively studied the diagnostic efficiencies of $^{99m}$Tc-CNDG SPECT/CT and enhanced CT in 95 patients with lung cancer. The results showed that the sensitivity, specificity and accuracy of $^{99m}$Tc-CNDG SPECT/CT in diagnosing lung cancer were higher than those of enhanced CT (97.5%, 76.5%, 93.8% vs. 87.5%, 41.2%, 79.4% respectively) and the differences in sensitivity and accuracy were statistically significant (all $P<0.05$).

In this study, the sodium pertechnetium solution used in $^{99m}$Tc-CNDG SPECT/CT was supplied from the inside of a molybdenum technetium generator, meanwhile CNDG allowed for the supplyment to be available in kit form. The preparation of $^{99m}$Tc-CNDG was simple and effective. This research proved that $^{99m}$Tc-CNDG SPECT/CT imaging had the advantages of good quality, low price, convenient method and technically wide accessibility. In this study, the efficacy of $^{99m}$Tc-CNDG SPECT/CT and enhanced CT in TNM staging of NSCLC was compared for the first time. The study showed that $^{99m}$Tc-CNDG SPECT/CT could accurately distinguish the boundary between atelectasis, obstructive pneumonia and malignant lung tumor, and accurately diagnose abnormal nodular radioactivity increases in lung metastases and tumor invasion to the pleura and pericardium. The study showed that $^{99m}$Tc-CNDG SPECT/CT could be used to accurately diagnose metastatic and nonmetastatic lymph nodes in NSCLC, especially normal size metastatic lymph nodes and enlarged nonmetastatic lymph nodes. The study also showed that $^{99m}$Tc-CNDG SPECT/CT could diagnose bone metastases early without pathological bone density abnormalities and osteoclastic bone metastases without abnormal radioactivity increases by $^{99m}$Tc-MDP bone imaging, and correct the diagnosis of patients who were misdiagnosed with bone metastases by CT bone density abnormalities. The accurate diagnosis of $^{99m}$Tc-CNDG SPECT/CT on the invasion range of the primary tumor, regional lymph node metastasis and
distant metastasis made it better than enhanced CT in accurately evaluating the potential resectability of NSCLC. However, there were some problems in $^{99m}$Tc-CNDG SPECT/CT, including the inherent limitation of image resolution and the detection sensitivity of SPECT/CT, higher peripheral blood background, higher bone joint uptake and higher distribution of liver and kidney which would be expected to be solved in the future with the development of cadmium zinc telluride digital detection technology, image postprocessing technology and further research of CNDG.

The limitations of this study include the following. (1) This study was a single-center study with a small sample size and had selection bias in patient collection. (2) There was no $^{18}$F-FDG PET/CT in our hospital, so there was no comparative study with $^{18}$F-FDG PET/CT in the same period. (3) The research reference standard was not the pathological TNM staging in all lesions, and there was a deviation in the evaluation of imaging diagnostic performance. (4) The imaging range of this study was limited to the clavicular area to the upper abdomen, and the potential value of $^{99m}$Tc-CNDG SPECT/CT in diagnosing brain metastasis was not evaluated.

**Conclusion**

This preliminary clinical study shows that $^{99m}$Tc-CNDG SPECT/CT is of great value for accurate clinical staging of NSCLC compared with conventional enhanced CT, and that $^{99m}$Tc-CNDG SPECT/CT can significantly improve the accuracy of resectability diagnosis of NSCLC. $^{99m}$Tc-CNDG SPECT/CT not only has the advantages of low price, convenient methodology and popular technology but also has the features of broad-spectrum for tumor imaging and unique mechanism for tumor uptake. Further confirmation of clinical research on $^{99m}$Tc-CNDG SPECT/CT is expected to bring new prospects for tumor glucose metabolism imaging in nuclear medicine.

**Declarations**

**Authorship Contribution:**

Author1: Ideas, Methodology, Management;

Author2: Patient enrollment, Surgical treatment;

Author3: Program, Patient follow-up;

Author4: Radiochemotherapy, Validation;

Author5: Image analysis, Oversight and consult;

Author6: Data/Evidence collection, Image acquisition, Quality control.

**References**


**Table**

**Table 1** Characteristics of NSCLC Patients
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<tr>
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<tr>
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<tr>
<td>1c</td>
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</tr>
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<td>2viscpla</td>
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</tr>
<tr>
<td>2a</td>
<td>3 4.8%</td>
</tr>
<tr>
<td>2b</td>
<td>6 9.5%</td>
</tr>
<tr>
<td>3</td>
<td>10 15.9%</td>
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<tr>
<td>0</td>
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<td>43 68.3%</td>
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Note. All patients underwent histopathological diagnosis. Thirty-three patients (52.4%) underwent surgery including lymphadenectomy, all of whom underwent pathological T staging and N staging. Thirty patients (47.6%) underwent radiochemotherapy, of which 7 patients and 5 patients underwent biopsy pathological N staging and M staging, respectively. The remaining T, N and M staging were determined by clinical evaluation. NSCLC Non-small cell lung cancer, TNM Tumor–node-metastasis.

Figures

Figure 1

Representative case of surgery. A 50-year-old female with lung adenocarcinoma in the right upper lobe, postoperative pathological stage T3N2bM0. Enhanced CT image (A) showed that the lobulated primary tumor (arrow) and distal strip shadow (arrowhead) of the right upper lobe were abnormally enhanced which was suspected to be right upper lung cancer complicated with obstructive pneumonia. $^{99m}$Tc-CNDG fusion SPECT/CT image (B) confirmed that the primary tumor (arrow) and distal lesion (arrowhead) were a highly CNDG-avid, suggesting right upper lung cancer complicated with intrapulmonary metastasis. Enhanced CT image (C) showed that the lobulated primary tumor (arrow) of the right upper lobe and slightly larger lymph node station 4R (arrowhead) were abnormally enhanced. $^{99m}$Tc-CNDG fusion SPECT/CT images (D) confirmed that the primary tumor (arrow) and lymph node
station 4R(arrowhead) were a highly CNDG-avid, metastatic lymph node station 4R which was not confirmed by enhanced CT was definitely diagnosed by $^{99m}$Tc-CNDG SPECT/CT. Enhanced CT image (E) showed abnormal enhancement of obviously enlarged lymph node station 7(arrowhead). $^{99m}$Tc-CNDG fusion SPECT/CT images (F) showed that there was no abnormal increase in CNDG in lymph node station 7(arrowhead) and nonmetastatic lymph nodes station 7 which was misdiagnosed by enhanced CT was correctly diagnosed by $^{99m}$Tc-CNDG SPECT/CT. Postoperative pathology confirmed that the lesion far from the primary tumor of the right upper lobe was an intrapulmonary metastasis, lymph node station 4R was metastasis and lymph node station 7 was nonmetastasis. Compared with enhanced CT, $^{99m}$Tc-CNDG SPECT/CT accurately diagnosed intrapulmonary metastases and differentiated mediastinal lymph node metastasis.

Figure 2

Representative case of nonsurgery. A 60-year-old male with large cell carcinoma in the left lower lobe, clinicopathological staging T4N2aM1c. Enhanced CT image (A) showed that the nodular primary tumor (arrow) of the left lower lobe and pleural nodule (arrowhead) were abnormally enhanced. $^{99m}$Tc-CNDG fusion SPECT/CT image (B) showed that the primary tumor (arrow) and pleural nodule invading the left 6 anterior rib (arrowhead) were highly CNDG-avid, suggesting that the tumor had invaded the adjacent rib. Diagnostic bone window CT image (C) showed that the density of the left 6 anterior rib (arrow) near the pleural metastasis was normal. $^{99m}$Tc-MDP fusion SPECT/CT bone image (D) and anterior $^{99m}$Tc-MDP whole-body bone image (E) confirmed the left 6 anterior rib metastasis (arrow) and
additional the left 7 anterior rib metastasis (arrowhead). Compared with enhanced CT, \(^{99m}\text{Tc-CNDG}\) SPECT/CT accurately diagnosed the invasion of bone by pleural metastasis of lung cancer.

**Figure 3**

Graph illustrating receiver operating characteristic curves for potential resectability of tumors with \(^{99m}\text{Tc-CNDG}\) SPECT/CT and enhanced CT. Potential resectability of a tumor was defined as a T stage below 4, an N stage below 3, and an M stage of 0 \(^{99m}\text{Tc-CNDG}\) SPECT/CT area under the curve, 0.97; 95% confidence interval, 0.89-1.00 \([P=0.023]\). Enhanced CT area under the curve, 0.87; 95% confidence interval, 0.76-0.94 \([P=0.043]\).