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Evaluation of suspected local recurrence in lung cancer and head & neck cancer: A comparison between ^{99m}Tc-HL91 SPECT and CT for biopsy proven lesions

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Abstract CT has rather low accuracy for the follow-up of tumors after therapy. This study was to determine whether the diagnostic accuracy can be improved with ^{99m}Tc-HL91 SPECT in comparison with parallel results of CT imaging. Thirty patients of lung cancer or head & neck cancer, suspected of recurrences on clinical symptoms and CT during clinical follow-up after therapy, underwent ^{99m}Tc-HL91 SPECT. The radioactivity ratios of tumor to normal tissues (T/NT) were calculated using the region of interest technique. Results of ^{99m}Tc-HL91 SPECT were verified by histopathology. The ^{99m}Tc-HL91 average uptake ratios of T/NT in the group of recurrent lesions and non-recurrent lesions were 1.58±0.16 and 1.18±0.14, respectively. A significant difference was found between T/NT data of the two phases (t=4.87, P<0.001). The ^{99m}Tc-HL91 SPECT shows sensitivity of 72.73%, specificity of 89.47% and accuracy of 83.83% for differentiating recurrent lesion, while the CT shows sensitivity of 63.63%, specificity of 84.21% and accuracy of 76.67%. A combination of ^{99m}Tc-HL91 SPECT and CT for 21 patients with lung cancers or head & neck cancers with congruent results shows sensitivity of 100%, specificity of 94.12% and accuracy of 95.23%. It is concluded that ^{99m}Tc-HL91 SPECT may play a role in differentiating recurrent lesions in patients with lung cancer and head & neck cancer. Furthermore, the combination of CT and ^{99m}Tc-HL91 SPECT is a more effective method for diagnosing recurrence of lung cancer and head & neck cancer.

Key words Tumor recurrence, SPECT, ^{99m}Tc-HL91, CT

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1 Introduction

Failure of cancer therapy is mainly due to tumor recurrence. It is certain that early detection of tumor recurrence has a significant impact on patient survival. Then, it has an important role in the prognosis to allow early initiation of appropriate treatment of local recurrent small-volume disease, for which more treatment options can be selected than for advanced disease. Early detection of tumor recurrence may be important for optimal patient management. The current surveillance strategy, consisting of physical examinations and conventional imaging modalities, such as ultrasound, CT and/or MRI, has limited sensitivity and cannot detect early tumor recurrences, especially in asymptomatic patients, because sensitivity of these anatomical imaging techniques is dependent on lesion size. Also, post-treatment alterations, such as scar, necrosis or inflammation, often result in anatomical asymmetries and frustrate tumor recurrence detection with the anatomical imaging techniques alone, especially in patients who have undergone surgery and/or radiation therapy[1,2].

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Many malignant tumors are characterized by perfusion heterogeneity, which results in tumor regions that are acutely or chronically hypoxic[3,4]. The tension of tumor oxygen is 3~6 mm Hg and that of the normal tissue is 30~40 mm Hg[5]. So, tumor hypoxia is an important biologic feature of malignancies, which affects their response to radiotherapy and chemotherapy[6]. A strong correlation between hypoxia and recurrence rate was reported in advanced cancer[7]. Experimental evidence also showed that hypoxic tumors may predict a more aggressive and metastatic phenotype[8,9]. For this reason, there has been growing interest in developing techniques to assess the oxygenation status of individual tumors. A routine measurement of tumor hypoxia shall be a useful diagnostic tool, as it allows doctors to choose patients who could benefit from adjuvant therapies to treat these resistant tumors. Among the techniques available to assess tumor hypoxia is the use of bioreductive agents with or without nitroimidazole group, which are selectively metabolized and retained in hypoxic cells. When labeled with radioisotopes, these compounds may allow the non-invasive assessment of tumor hypoxia using nuclear imaging techniques [10, 11]. The recently developed ^{99m}Tc-HL91 (99mTc labeled 4, 9-diaza-3,3,10,10-tetramethyldodecan-2,11-dione dioxime, HL91), which lacks the nitroimidazole group, showed even greater hypoxia selectivity[12]. ^{99m}Tc-HL91 is a new hypoxia imaging agent that demonstrates increased uptake and retention in tumor hypoxic tissues in vitro and visualized malignant tumors in clinical studies[13,14]. But fewer clinical studies on tumor recurrence have been reported. In this study, in comparison with CT, we evaluate the diagnostic value of ^{99m}Tc-HL91 SPECT for local recurrence of lung cancer and head & neck cancer. We have correlated the results with histopathological ones as a gold standard method of tumor recurrence.

2 Materials and methods

2.1 Patients

From September 2004 to March 2007, 30 patients with lung cancers and head & neck cancers were prospectively enrolled in the study. They included those who were suspected of a recurrence of disease, based on clinical symptoms, conventional CT images etc. This subject group, 21 men and 9 women, in an average age of 47.2, consisted of three patients with lung adenocarcinoma, five with lung squamous cell carcinoma, four with the buccal mucosa squamous cell carcinoma, two with brain gliomas, and 16 patients with nasopharyngeal squamous cell carcinoma (12 low-grade carcinoma and four undifferentiated carcinoma). All the patients had undergone surgery or radiotherapy. The ethical committee of the No.1 Hospital of Xiamen Affiliated to Fujian Medical University approved the study protocol and informed the consent form. All patients gave their written consent before entering the study.

^{99m}Tc-HL91 SPET scanning was performed at an interval of at least six months after the first operation or radiotherapy. Histopathological verification of imaging findings was obtained from complete mass resection with or without radical lymph node dissection in four patients, direct endoscopic lesion biopsy in 16 patients and CT-guided biopsy in 10 patients. Tumor resections and/or biopsy were performed within two weeks of the ^{99m}Tc-HL91 scan. None of the patients underwent treatment between ^{99m}Tc-HL91 and surgery or biopsy.

2.2 Preparation of ^{99m}Tc-HL91

HL91 was provided by Syncor Star Medicinal Technology Co. Ltd., Beijing, China. One milligram HL91was dissolved in 2 mL saline containing 110 MBq (30 mCi) ^{99m}Tc-pertechnetate. After 15 min at room temperature, the radiochemical purity of each prepared ^{99m}Tc-HL91 was determined before use by paper and thin layer chromatography, and exceeded 95% in all cases.

2.3 Imaging studies

2.3.1 SPECT

After intravenous injection of 110 MBq ^{99m}Tc-HL91, anterior, posterior and lateral planar images were performed at 4 h using a twin-headed gamma camera (FORTA, Philips) equipped with low-energy high-resolution collimators. Localized SPECT acquisitions were made for known tumor regions at 4 h with a 64×30 sec acquisition over 360° with high-resolution collimation. A symmetrical 15%

window was set at 140 keV and the data were stored in a 128×128 matrix. Images were reconstructed using a Butterworth filter and presented as transaxial, coronal and sagittal slices. All patients underwent a ^{99m}Tc-HL91 scan within two weeks of the CT scan.

2.3.2 CT

The CT examinations were performed on a spiral CT scanner (16-slice CT, Aquilion Toshiba), in fast scan technique in the plane parallel to the palatine with intravenous application of 80~120 mL of nonionic iodine contrast agent. The slices, in 3 mm thick, were taken without any gap between two consecutive slices. The CT images were interpreted independently by at least two experienced radiologists.

2.4 Image analysis

Evaluation of the images of ^{99m}Tc-HL91 was done by two independent, experienced nuclear medical physicians. Regions of interest (ROIs) of tumor were drawn manually on images within the anterior, posterior or transaxial slice recording the highest tumor uptake. The same size ROI on opposite normal tissue was used as the reference, and radioactivity ratios of tumor to normal (T/N) were calculated.

2.5 Statistical analysis

The data were analysed with SPSS 13.0 code. The results were expressed as means ± SD. The T/N ratios were analyzed by *t* test. $P < 0.05$ was considered as statistically significant.

3 Results

From histopathology analysis of 30 anatomical sites of the patients, 11 sites (36.67%) were positive for tumor recurrence, and 19 sites were negative (63.33%).

In the tumor recurrence group, tumor could be identified 4 h after injection with a significantly higher radioactivity as compared with that in opposite normal tissue. The T/NT, tumor-to-normal tissue radioactivity ratios, was 1.58±0.16 (Table 1). In the non-recurrence group, the radioactivity in primary lesion 4 h after injection was similar to that in opposite normal tissue, with T/NT ratio of 1.18±0.14. The difference between T/NT data of the two group was significant (P<0.001).

Table 1 Tumor to normal tissue ratios (T/NT) of ^{99m}Tc-HL91 SPECT versus biopsy results ($\bar{x}$ ±SD)

Biopsy results	Cases	T/N
Metastases	11	1.58±0.16
Benign	19	1.18±0.14
t	—	4.87

From histopathologic confirmation, 19 patients had benign lesions and 11 had malignant lesions of recurrent lung cancer and head & neck cancer. The sensitivity, specificity and accuracy of CT were 63.63%, 84.21%, and 76.67%, respectively. Seven CT findings were true positive, 3 were false positive, 16 were true negative and 4 were false negative (Table 2). The smallest recurrent tumor detected by CT was 6.0 mm. However, the sensitivity, specificity and accuracy of ^{99m}Tc-HL91 SPECT were 72.73%, 89.47%, and 83.83%, respectively. Eight ^{99m}Tc-HL91 SPECT findings were true positive, 17 were true negative, two were false positive, and three were false negative (Table 2). The smallest recurrent tumor detected by ^{99m}Tc-HL91 was 10.0 mm.

In 21 patients with congruently results of ^{99m}Tc-HL91 SPECT and CT, there were four cases with congruently true positive findings of CT and ^{99m}Tc-HL91 SPECT, 16 cases with congruently true negative findings, and one case with congruently false positive. The sensitivity, specificity and accuracy of combined CT and ^{99m}Tc-HL91 SPECT were 100%, 94.12%, and 95.23%, respectively in these 21 patients with lung cancer and head & neck cancer (Table 2).

Table 2 Comparison between CT and ^{99m}Tc-HL91 SPECT findings for detecting tumor recurrence

Imaging	Cases	TP	TN	FP	FN	Sensitivity	Specificity	Accuracy
HL91	30	8	17	2	3	72.73%	89.47%	83.33%
CT	30	7	16	3	4	63.63%	84.21%	76.67%
HL91+CT	21	4	16	1	0	100%	94.12%	95.23%

Note: HL91: ^{99m}Tc-HL91 SPECT; CT: computed tomography; TP: true positive; TN: true negative; FP: false positive; FN: false negative.

4 Discussion

Anatomical imaging such as CT and MRI is the first line imaging modality and used to outline the tumor involved anatomical planes. However, anatomical imaging has high false positive ratio in the detection of recurrent tumor. Following radiotherapy and surgery, a variety of changes, such as edema, loss of tissue planes, fibrosis, and scarring, may interfere with the detection of recurrent tumors. CT cannot differentiate between inflammatory tissue, post- surgical or post-radiotherapy fibrosis, and recurrent tumors, consequently falling short of providing reliable indices of the presence or absence of recurrent tumors [1,2]. In this study, three cases had false positive CT findings and four cases had false negative CT findings (Table 2).

Abnormal perfusion in malignant neoplasms leads to decrease of oxygen delivery relative to normal tissue. Furthermore, a relatively high rate of tumor cell proliferation increases oxygen consumption by tumor tissue. The result of decreased oxygen supply and increased demand is regional hypoxia. Because of the latter, malignant tumors have higher retention of the hypoxia agent ^{99m}Tc-HL91 than other tissues, and ^{99m}Tc-HL91 image can be a successful positive tumor image [15]. Moreover, hypoxia and ischemia in the tumor may lead to a lower clearance of ^{99m}Tc-HL91 from tumor tissues than that from normal tissues. So, the radioactivity ratios of tumor to normal organs and tissues (T/N) increase significantly after injection of ^{99m}Tc-HL91. With this characteristic, delaying imaging can increase the relevant ratio of malignant tumor by ^{99m}Tc-HL91 imaging. In this study, ^{99m}Tc-HL91 has shown specific localization in the majority of malignant tumors identified by histopathology. Tumor-to-normal tissue background activity ratios (T/N) are sufficient for tumors to be readily identified by planar imaging and in most cases also by SPECT imaging. Tumor activity is more easily identified at 4 h rather than at 1 h post injection, mainly due to a reduction in background activity[15].

For the above reasons, ^{99m}Tc-HL91 imaging is regarded as a metabolic imaging technique, and can detect tumor hypoxia. The results indicate that ^{99m}Tc-HL91 SPECT is advantageous over CT in terms of sensitivity, specificity and accuracy for detecting tumor recurrence of head & neck cancer and lung cancer. The false negative results of ^{99m}Tc-HL91 SPECT in three patients with recurrent nasopharyngeal carcinoma can be attributed to small diameters (< 9 mm) of the lesions in relation to the resolution of the camera and partial volume effects. Also, significant scatter effects from physiologic but intense ^{99m}Tc-HL91 uptake of the salivary glands may reduce the sensitivity of ^{99m}Tc-HL91 SPECT for detecting recurrent head & neck cancer. In this study, the sole case of a false positive ^{99m}Tc-HL91 SPECT finding was probably due to the accumulation of ^{99m}Tc-HL91 in an inflammatory lesion. In addition, using ^{99m}Tc-HL91 SPECT alone, it is difficult to determine the precise location and relationship between recurrent tumor and surrounding structures (Figs.1~6). Therefore, a combination of anatomic imaging, such as CT with ^{99m}Tc-HL91 SPECT, is necessary to ascertain the local recurrence in head & neck cancer and lung cancer.

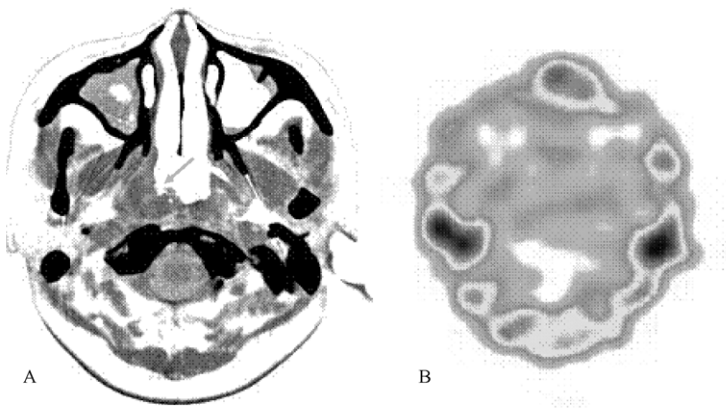

Fig.1 Scans from a 57-year-old female patient with nasopharyngeal carcinoma after radiotherapy. (A) False-positive CT finding: a mass and asymmetry in the right nasopharynx (arrow). (B) True-negative ^{99m}Tc-HL91 SPECT finding. The histopathologic findings revealed a benign lesion.

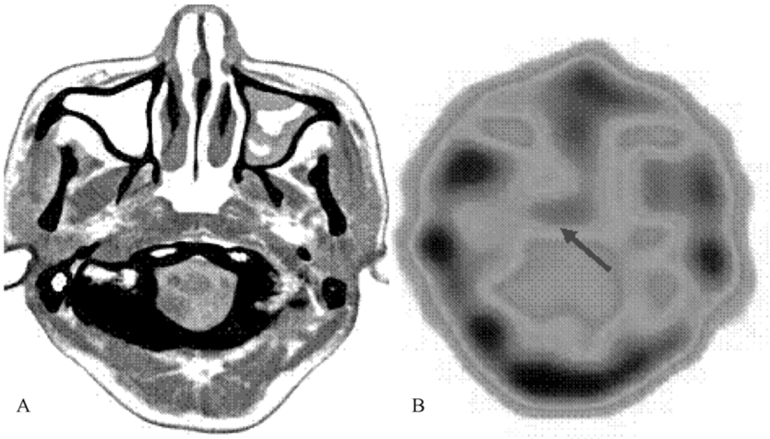

Fig.2 Scans from a 40-year-old male patient with nasopharyngeal carcinoma after radiotherapy. (A) False negative CT finding. (B) ^{99m}Tc-HL91 SPECT finding: abnormal ^{99m}Tc-HL91 uptake in the right nasopharynx (arrows). The histopathologic findings revealed recurrent nasopharyngeal carcinoma.

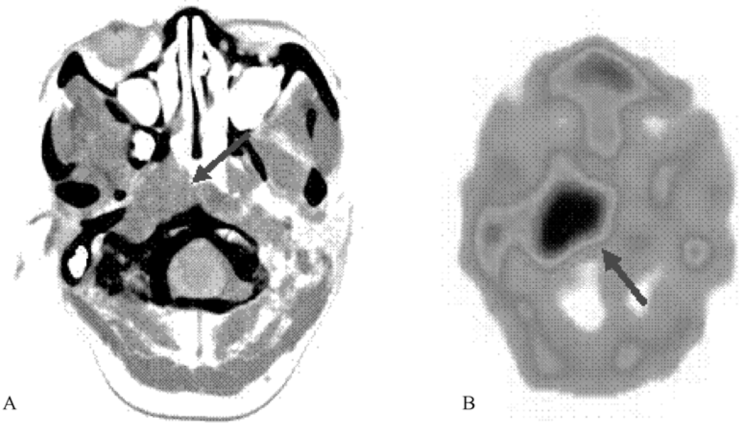

Fig. 3 Scans from a 45-year-old male patient with nasopharyngeal carcinoma after radiotherapy. (A) CT finding: a mass and asymmetry in the right nasopharynx (arrow). (B) ^{99m}Tc-HL91 SPECT finding: abnormal ^{99m}Tc-HL91 uptake in the right nasopharynx (arrow). The histopathologic findings revealed recurrent nasopharyngeal carcinoma.

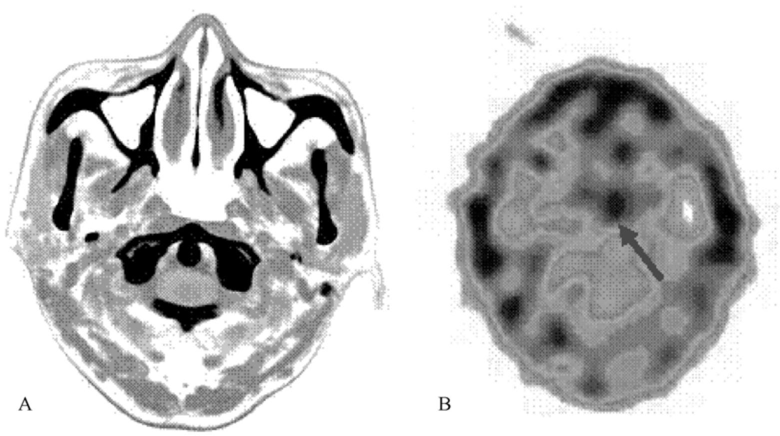

Fig.4 Scans from a 58-year-old female patient with nasopharyngeal carcinoma after radiotherapy. (A) True negative CT finding. (B) ^{99m}Tc-HL91 SPECT finding: abnormal ^{99m}Tc-HL91 uptake in the left nasopharynx (arrow). The histopathologic findings revealed nasopharyngeal inflammatory.

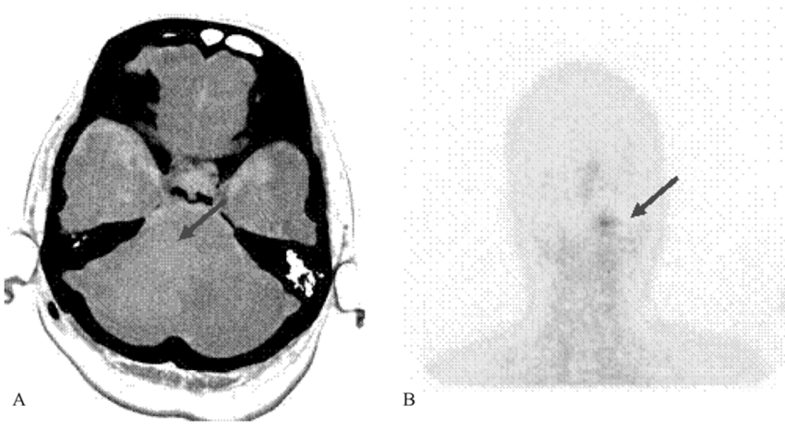

Fig.5 Scans from a 35-year-old male patient with cerebellum gliomas after radiotherapy. (A) CT finding: a mass and asymmetry in the right cerebellum (arrow). (B) ^{99m}Tc-HL91 SPECT finding: abnormal ^{99m}Tc-HL91 uptake in the right cerebellum (arrow). The histopathologic findings revealed recurrent cerebellum gliomas.

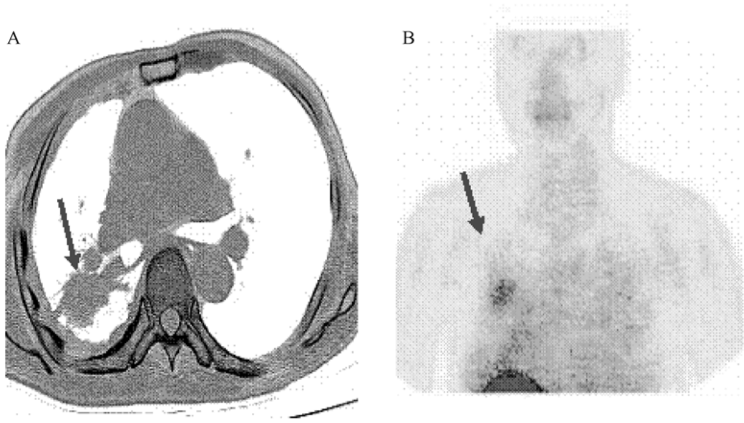

Fig.6 Scans from a 55-year-old male patient with lung cancer after surgery. (A) CT finding: a mass and asymmetry in the right chest (arrow). (B) ^{99m}Tc-HL91 SPECT finding: abnormal ^{99m}Tc-HL91 uptake in the right chest (arrow). The histopathologic findings revealed recurrent lung cancer.

5 Conclusion

It can be concluded that ^{99m}Tc-HL91 SPECT is capable of differentiating recurrent lesions in patients with lung cancer and head & neck cancer. However, combined use of CT and ^{99m}Tc-HL91 SPECT is a more effective method for diagnosing recurrence of lung cancer and head & neck cancer.

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