行政院原子能委員會

委託研究計畫研究報告

鎝99標記HL-91應用於腫瘤診斷之第二階段臨床研究

計畫編號：932001 INER 018

受委託機關（構）：臺中榮民總醫院

計畫主持人：放射腫瘤科　翁益強醫師

聯絡電話：04-23592525 分機 5618

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一、中文摘要

前言與背景： HL-91 經過多次試驗，證明對缺氧細胞的標記效果良好。由於腫瘤組織生長速度很快，由血液供應至組織的氧氣濃度因為腫瘤細胞快速分裂成長，造成腫瘤組織內氧氣濃度因大量消耗而降低，時常會出現局部缺氧現象，因此可利用 HL-91 偵測腫瘤細胞的位置或復發。試驗目的是可以安全地使用的 HL-91 可選擇性的附著在頭頸部癌症中缺氧的組織之上，再藉由一般核子醫學常用的 ^{99m}Tc(鎝)進行標記，就可以用造影的方式偵測腫瘤組織以及其分布情形。而此次試驗所得之數據將可用於評估以 ^{99m}Tc(鎝)標記 HL-91 於人體內標記腫瘤缺氧細胞的有效性，進而偵測腫瘤的復發情形。最後此項檢查結果會與目前臨床常用來偵測腫瘤復發情形的電腦斷層報告與正子攝影報告一起比較。

樣本與方法： 樣本取樣是從臨床挑選頭頸部癌症病人，曾經治療過，目前懷疑局部復發，且尚未治療者。此類病人需配合臨床例行檢查，包括電腦斷層與正子攝影，並盡可能安排被懷疑之腫瘤切片檢查，而最終診斷是否腫瘤復發是以腫瘤切片報告或臨床追蹤至少六個月。受試者須全程嚴密監控，定期檢查與記錄可能發生的不良反應。此試驗偵測腫瘤復發結果之精確性，會與電腦斷層與正子攝影檢查結果之精確性一起做比較。

結果： 至十一月截止，因申請衛生署人體實驗延後與臨床條件嚴格，從今年六月中旬才開始收案，最後只收集七個個案。其中六個個案最終被診斷腫瘤復發，另一個案雖然起初治療後傷口久久無法癒合，但追蹤至五個月尚無復發跡象。臨床例行檢檢查中，電腦斷層與正子攝影檢查陽性報告符合腫瘤確認復發個案有六個，而 ^{99m}Tc(鎝) HL-91 檢查中，六個腫瘤確認復發中五個個案報告是陽性。兩個個案報告陰性中一位臨床腫瘤切片是腫瘤復發陽性。電腦斷層與 ^{99m}Tc(鎝) HL-91 檢查都無假陽性，但正子攝影有一個案報告是假陽性。^{99m}Tc(鎝) HL-91、電腦斷層與正子攝影此三項檢查之精確性分別是 85.7%、100% and 85.7%。七個個案做 ^{99m}Tc(鎝) HL-91 無任何副作用與異常事件。

結論： ^{99m}Tc(鎝) HL-91 檢查並無副作用且應可以用來偵測頭頸部腫瘤復發

二、英文摘要

Backgroud: ^{99m}Tc-HL-91 has been proven useful in the evaluation of hypoxic condition in a tumor. Recently, ^{99m}Tc-HL-91 has also been shown to has the ability to localize primary or recurrent cancer. The purpose of this study was to evaluate the safety of ^{99m}Tc-HL-91 produced by INER in patients with head and neck cancers. We also evaluated the efficiency of the ^{99m}Tc-HL-91 imaging in the detection of recurrent head and neck cancer. The results were compared to spiral computed tomography (CT) scan and FDG-PET scan.

Materials and Methods: The patient who was suspected to have recurrent head and neck cancer underwent Tc-99m HL-91 imaging, CT scan, FDG-PET scan and biopsy, if possible. Final diagnosis was made based on pathologic report or clinical follow-up. Detailed record was made if there was any adverse effect after the injection of ^{99m}Tc-HL-91. Diagnostic accuracy was calculated for all the three diagnostic modalities including Tc-99m HL-91 imaging, CT scan and FDG-PET scan.

Results: At the end of this study, only 7 cases were collected. Of the 7 patients, 6 patients were diagnosed to have tumor recurrence. Only one patient was diagnosed to have no recurrence after 5-month follow-up. CT scan and FDG-PET scan detected all positive cases, however, the Tc-99m HL-91 imaging detected 5 patients but missed one. Both CT scan and Tc-99m HL-91 imaging showed no false positive result but FDG-PET scan showed one false positive result. The diagnostic accuracies of detecting recurrence in head and neck cancer were 85.7%, 100% and 85.7% for the Tc-99m HL-91 scan, CT scan and FDG-PET scan, respectively. No any discomfort or adverse event was found in the patients after injection of Tc-99m HL-91.

Conclusion: Our preliminary results suggest that Tc-99m HL-91 produced by INER is quite safe for clinical use and may have potential on the

detection of cancer recurrence in patients with head and neck cancer.

三、計劃目的

1. To determine the efficacy of ^{99m}Tc-HL-91 in detection of recurrence (confirmed by pathologic biopsy) in head and neck cancer, comparison with computed tomography (CT scan).
2. Monitor the safety and distribution of the ^{99m}Tc-HL-91 in human body.

四、計劃緣起

Cancer has become the first leading cause of death in many countries including Taiwan. Imaging modality is one of the most important tools for the currently clinical oncology.

Radionuclide imaging with radiopharmaceuticals like gallium-67-gallium citrate (^{67}Ga), thallium-201-thallous chloride (^{201}Tl), technetium-99m-sestamibi (^{99m}Tc-MIBI), and the novel fluorine-18-fluorodeoxy-glucose (FDG) play useful roles in differentiating benign and malignant primary tumors, staging, detecting recurrent disease, and post-therapy evaluation. ^{67}Ga and ^{201}Tl have been used for tumor imaging for decades, but poor emission characteristics, problems in respect of relatively long half-life and cyclotron production are significant disadvantages of these two agents. ^{99m}Tc-MIBI has been shown with good results in some tumors, however, the high hepatic and intestinal activity make it not suitable for abdominal and pelvic imaging. FDG-PET is both sensitive and specific for this purpose, but it is still expensive and not widely available for routine purposes in clinical oncology.

Many malignant tumors are characterized by perfusion heterogeneity due to its proliferation more rapid than the vascularity, which results in tumor regions that are acutely or chronically hypoxia. Approximately 80% of squamous cell carcinomas of the head and neck are poorly perfused when compared to the surrounding normal tissue and contain regions of hypoxic cells.

Over the past several years there has been a significant amount of work on the development of radiopharmaceuticals capable of defining hypoxic tissue in brain, heart, and tumors. ^{99m}Tc-HL-91 is an amine oxime core radioligand with hydrophilic property and has shown

oxygen-dependent passive in vivo and in vitro binding with higher binding under hypoxic conditions than under non-hypoxic conditions. The precise mechanism of selectively increased ^{99m}Tc-HL-91 uptake in hypoxic tissue is not fully understood. In summary, when ^{99m}Tc-HL-91 enters a viable cell, there are unknown reductive reactions in hypoxic region. In the present of normal oxygen levels, ^{99m}Tc-HL-91 is immediately re-oxidized and diffuse out of cells. Therefore, retention is not prolonged in normal tissue. In hypoxic tumor tissue, however, the low oxygen concentration able to effectively compete to reoxidize the molecule and further reduction appears to take place to form reductive products. The net effort of the reductive products retain in hypoxic tumor cell, after all.

The latest research shows that new nuclear medicine imaging procedures detect the recurrence of head and neck cancer earlier than other conventional imaging methods. Earlier detection leads to earlier therapies and likely higher survival rates among those patients suffering from this deadly disease. A study reported by Elma Abella Columna, M.D. and her colleagues in 1998 found that whole-body Positron Emission Tomography (PET) imaging with fluorine-18 fluorodeoxyglucose (FDG) was more accurate than CT scans and MRIs for detecting and staging local and regional tumor recurrence among 51 patients with known or suspected recurring head and neck cancer. PET was able to detect 90 percent of the recurrences of cancer that were local, or in the same area as the original tumor, compared to CT scans and MRIs, which correctly identified disease in 74 percent of the cases. PET also correctly predicted whether or not tumors were cancerous in 87 percent of patients with local tumor recurrences, compared to 63 percent of cases when CT scans and MRIs were used. Similar results were found with regional recurrences of cancer.

Using a cut-off value of median intratumoral PO_2 of 10 mmHg, Brizel et al. found a significantly higher disease free survival at 12 months in squamous cell carcinoma of head and neck (SCCHN) patients with PO_2 values above 10 mmHg (78% vs. 42%, P = 0.009). In their series, the average tumoral median PO_2 for relapsing patients was 4.1 mmHg and 17.1 mmHg in non-relapsing patients (P = 0.007). Due to the hypoxic characteristics of SCCHN, HL-91 has the potential of early detection of recurrent lesions. In the series of Technetium-99m-labeled HL-91 to identify tumor hypoxia and correlation with fluorine-18-FDG by Cook et al, ^{99m}Tc-HL-91 showed visible uptake into the tumor area in all seven studies where the tumor was clearly identified by ^{18}F-FDG PET; ^{99m}Tc-HL-91 uptake was not detected in one study (carcinoid) in which ^{18}F-FDG was weakly positive. ^{99m}Tc-HL-91 exhibits good imaging characteristics, with imaging at 4 hr providing good lesion-to-normal tissue background ratios, that are further enhanced by SPECT. However, another series of ^{99m}Tc-HL-91 versus computed tomography (CT scan) and biopsy for the visualization of tumor recurrence of squamous head and neck carcinoma by C. Van de Wiele et al, the result showed ^{99m}Tc-HL-91 is a safe radioligand and that metabolic binding in a large fraction but not all of local SCCHN recurrences may be expected. It may due to high background activity of head and neck region.

This study focused on the feasibility and safety of ^{99m}Tc-HL-91 imaging and its usefulness for the visualization of local tumor recurrence of head and neck carcinoma as compared to spiral computed tomography (CT) scan or pathohistologic reports.

五、執行方法及進度說明

Subject:

Inclusion Criteria

Subjects must meet **all** of the inclusion criteria for the entry of this study:

1. Victims of head and neck cancer, status post treatment for at least three months;
2. Clinically suspected but not yet proven recurrence of head and neck carcinoma. One of following symptoms and signs:

- neck mass;
- intense edema or fibrosis;
- increasing pain;
- delayed mucosal healing;
- persistent wound;
- fistula or chronic inflammation;
- neurological signs.

3. Normal liver and renal function (BUN ≦ 30, creatinine ≦ 1.8 mg, bilirubin ≦ 2 mg, SGPT or SGOT ≦ twice normal range);
4. Serum hemoglobulin ≧ 8 mg/dL;
5. Karnofsky performance scores ≧ 70.

Exclusion Criteria

Subjects were excluded from this study for **any** of the following reasons:

1. Chronic respiratory disease;

2. Medical history of serious allergy, asthma or sensitivity to analogous drug;
3. Pregnant and lactating.

Methods:

This was a pilot study to determine the feasibility of ^{99m}Tc-HL-91 in detection of recurrence in head and neck cancer, comparison with CT scan. Subjects received ^{99m}Tc-HL-91 injections as well as accept Single Photon Emission Computerized Tomography (SPECT) imaging for 240 minutes. The HL-91 SPECT were undergone qualitative on-site assessments which were performed by experienced blinded nuclear medicine physicians (with regards to any information on the patient identification and their medical history). All suspected lesion underwent pathologic biopsy as possible.

Detailed Plan

This pilot study detected and compared the recurrence (confirmed by pathologic biopsy) in head and neck cancer with computed tomography (CT scan).

- Investigator evaluated the eligibility of the patient who was potential to enter this study and arrange series of examination including interview, medical history, clinical examination, laboratory tests and tumor work-up.
- The investigator attempted to complete all procedures at the time any subject was removed from the treatment.

^{99m}Tc-HL-91 SPECT imaging

1. HL-91, 0.2 mg and ^{99m}Tc-HL-91 were prepared by reconstitution of a HL-91 kit with 4.5 ml, 740 MBq of ^{99m}Tc-sodium pertechnetate solution and standing at room temperature for 15 min;
2. After HL-91 injections were done, SPECT were done for 240 minutes;
3. Data were acquired in step and shoot mode (60 stops/head, 30 s frame time) in a 128 x 128 matrix and transferred to a computer system for processing. Raw data were reconstructed using a commercially available computer system and post-filtered using a Gaussian smooth (7.5 mm full width at half maximum);
4. Transaxial, coronal and sagittal slices were visually assessed for the presence of foci of increased tracer accumulation by two experienced radiologists;
5. Lesion(s) suspected of recurrence by either radiologist were confirmed by biopsy as described in *Section 5.5*.

Spiral CT scan

1. After HL-91 SPECT has been done and not more than 4 weeks, patient will undergo CT scan to detect the recurrence of head and heck cancer;
2. Spiral CT scan is recommended. Imaging was visually assessed for the presence of foci of increased tracer accumulation by two experienced radiologists;
3. Lesion(s) suspected of recurrence by either radiologist were confirmed by biopsy as described in *Section 5.5*.

Pathologic Biopsy

1. Patients were arranged to have blood clotting tests performed within 1 week of the biopsy to ensure that they do not have any bleeding

tendency. It is necessary to ensure that these tests are performed or else there were a delay on the day of the biopsy.

2. Tumor specimen should be obtained by surgery, excision biopsy, punch biopsy or fine needle aspiration. Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report;
3. Pathology report documenting that submitted block or slides contain tumor. The result should be confirmed by at least one certified pathologist clinically with above five-year experience;
4. Hematology test and biochemistry assessment were performed for follow-up evaluation.

STUDY CALENDAR

Event and time schedule was shown in *Table1*.

Efficacy Assessments

Recurrence in head and neck cancer was detected by HL-91 (SPECT) and spiral CT scan then followed by pathological confirmation and laboratory follow-up. The accuracy (recurrence predictive value) of ^{99m}Tc-HL-91 and CT scan in detection of recurrence was compared. Lesions of suspicious of recurrence should be confirmed by pathologic biopsy.

$$\text{Accuracy} = \frac{\text{True Recurrence}}{\text{True Recurrence} + \text{Negative Recurrence}}$$

Safety Assessments

Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, regular monitoring of hematology and serum chemistry, and regular measurement of vital signs, and the performance of physical examination. The following tests were performed as indicated in visit schedule.

- Hematology: hemoglobin, hematocrit, complete blood count, differential and platelets.
- Biochemistry: SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, albumin, glucose, BUN, creatinine, uric acid, total cholesterol and triglycerides.
- Blood Clotting Tests: prothrombin time (PT) and activated partial thromboplastin time (APTT).

For hematology and blood chemistry parameters, the analysis were performed directly on the laboratory values reported in the CRF.

WITHDRAWAL OF SUBJECTS

Withdrawal of Subjects

Subjects were withdrawn from the study (i.e. from any further study medication or study procedure) for the following reasons:

A. At their own request;
B. If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being;
C. At the specific request of the sponsor

In all cases, the reason for and date of withdrawal must be recorded in the case report form (CRF) and in the subject's medical records. The

subject must be followed up to establish whether the reason is an adverse event.

As far as possible, all examinations scheduled for the final study day must be performed on all subjects who receive the investigational product but do not complete the study according to protocol. The investigator must make every effort to contact subjects lost to follow-up. Attempts to contact such subjects must be documented in the subject's records (e.g., times and dates of attempted telephone contact).

Replacement of Subjects

Subjects will not be replaced.

Adverse Events And The Reporting Requirements

All adverse events (AEs) should be recorded on the CRF.

Adverse Event Definition

An adverse event is defined as:

1) any unintended, unfavorable clinical sign or symptom;
2) any new illness or disease or deterioration of an existing illness or disease;
3) any clinically relevant deterioration in a laboratory variable or other clinical tests (e.g. X-ray) whether or not considered treatment related.

Note that the definition could include accidents as well as the events listed below:

1) changes in medication (drug and/or dose);
2) medical, nursing and/or pharmacy consultation;

3) admission to hospital;
4) surgical operations.

Planned hospital admission and/or surgical operation for an existing disease before the patient is enrolled in a clinical trial are not to be considered adverse events.

Furthermore, the intensity of the event were classified according to the following terms:

mild - the AE causes minimal discomfort and does not interfere in a significant manner with the patient's normal activities.

moderate - the AE is sufficiently uncomfortable, which causes some impairment to the patient's normal activities.

severe - the AE is incapacitating, preventing the patient from participating in his/her normal activities.

Adverse events were recorded as safety endpoint. Any adverse event spontaneously reported or observed by the research team during the treatment were recorded. Adverse events were recorded in response to an open question asked at each visit. In case of serious adverse events, the investigator may decide to discontinue the treatment.

Severe Adverse Event Definition

A serious adverse event (SAE) is an untoward medical occurrence that at any dose:

1) results in death;
2) is life-threatening;

("Life-threatening" means that the patient was at immediate risk of death at the time of the event. "Life-threatening" does not mean an event that

hypothetically might have caused death if it were more severe, or resulted in permanent or significant disability/incapacity.)

3) requires inpatient hospitalization or prolongation of existing hospitalization;

(Outpatient treatment in an emergency room is not in itself a serious adverse event, although the reasons for it may be, e.g. bronchospasm, laryngeal edema.)

4) results in persistent or significant disability/incapacity;

5) leads to a congenital anomaly or birth defect; or

6) leads to events that require medical or surgical intervention to prevent permanent impairment of function or permanent damage to a body structure.

(Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Medical and scientific judgment may be required.)

An adverse event fulfilling any one or more of these criteria should be reported as a serious adverse event, irrespective of the dose of drug given, and even if it is the result of an interaction or drug abuse.

A distinction should be drawn between serious and severe adverse events. The term of ‘severe’ is often used to describe the intensity (severity) of a specific even (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as ‘serious,’ which is based on patient’s event outcome or action criteria usually associated with events

that pose a threat to a patient's life or functioning. The seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Procedures for Adverse Event Reporting

Adverse events should be collected by means of a standard question i.e. "Have you had any health problems since the previous visit?" Spontaneously reported and/or observed adverse events and the responses to this question should be recorded on the Adverse Event Form with information about the degree of seriousness and any action taken.

Expressions judged to be synonymous to the symptoms might also be considered as symptoms of disease under this clinical trial.

All changes in the patient's ordinary medication, e.g. newly added medication should be reported in the concomitant medication page in the CRFs. Reasons for changes in medication that reflect an adverse event should be recorded on the Adverse Event Form.

Procedures for Serious Adverse Event Reporting

During the clinical trial, if any serious adverse event occurs, the investigator should inform the *Clinical Project Manager* or other representatives of sponsor within 3 calendar days by fax and/or telephone. Sponsor should file the initial report of serious adverse event (SAE) to the Department of Health (DOH) and *Adverse Event Reporting System* within 15 calendar days (7 calendar days for death or life-threatening events) after being aware of the event. Completed follow-up report of death or life-threatening events must be filed within 15 calendar days. All serious events, whether or not considered causally related to the study drug, should be reported.

The investigator were asked to assess serious adverse events regarding

their casual relationship to the study drug according to the following classifications:

1) Highly probable

Time relationship exists. No other possible causative factor(s) exists. Improvement on dechallenges or dose reduction (if performed) has occurred. Recurrence of symptoms on rechallenge (if performed) has occurred. A specific laboratory investigation (if performed) has confirmed the relationship.

2) Probable

Time relationship exists. Adverse event is more likely explained by the study drug than another cause. Improvement on dechallenges or dose reduction (if performed) has occurred.

3) Possible

Time relationship exists but other possible causative factor(s) may exist. Improvement on dechallenges or dose reduction (if performed) may or may not have been seen.

4) Unlikely

Time relationship is non-existent or doubtful and/or other factor(s) certain or probable have been causative. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as unlikely.

Not related

Time relationship is non-existent or the cause of the event had been identified or the drug cannot be implicated.

STATISTICAL CONSIDERATIONS

Sample Size

The required sample size: 70 lesions, about 40 patients.

Definition of Populations to Be Analyzed

Per-protocol (PP) Population – patients who complete the study (SPECT and CT scan), and complete the scheduled follow-up examinations (pathologic biopsy), without major protocol violations (e.g., ineligible enrollment)

Standard analysis were performed in the PP population. This were the only subject population used for the efficacy analysis.

Safety analyzable population – all subjects who were randomized to study, who received at least one dose in the study:

All safety evaluations and analyses were performed on the safety analyzable subject population.

Statistical Analysis

All untreated subjects were described separately and the reasons why they did not receive the treatment were given.

All analysis were descriptive. Categorical data were displayed in contingency tables.

Continuous data such as disease control were summarized with at least the following: median, minimum and maximum values. For censored data, life-tables were provided.

Statistical tests may be used on some parameters but emphasis were on consistency of results, robustness and clinical plausibility rather than pure statistical significance.

Analysis of Efficacy and Safety

i Efficacy analysis

The accuracy (clinically confirmed recurrence by pathologic biopsy) of ^{99m}Tc-HL-91 and CT scan in detection of recurrence were attained and examined by McNemar Test to test the difference. Baseline comparability for demographics and other patient characteristics were made using appropriate chi-square test for categorical variables and analysis of variance for continuous variables

ii Safety analysis

Adverse events were summarized the number and percentage of subjects having any adverse event, having an adverse event in each body system and having each individual adverse event. Any other information collected (i.e. severity or relatedness to study medication and vital signs) were listed as appropriate.

Laboratory data were summarized presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, and ranges).

ETHICAL REQUIREMENTS

Declaration of Helsinki and Ethical Review

The study were performed in accordance with the principles stated in the Declaration of Helsinki. Meanwhile, the study protocol, including the final version of the subject's information and informed consent form to be

used, must be approved by an ethics committee before enrollment of any subject into the study. The opinion of the ethics committee should be dated and given in writing. A list of those present at the committee meeting (names and positions) should be attached whenever possible. It is the responsibility of the investigator to forward this information to sponsor before the start of the study i.e. a copy of the approval from the ethics committee clearly identifying the protocol submitted for review.

The investigator is responsible for informing the ethics committees of any serious adverse events and/or major amendments to the protocol as per local requirements. The investigator should file all correspondence with the committee.

Subject Information and Consent

The investigator will ensure that the subject is given full and adequate verbal and written information about the nature, purpose and possible risks and benefit of the study. Subjects must also be notified that they are free to discontinue their participation in the study at any time. The investigator is responsible for seeing that signed informed consent is obtained from each subject before enrollment.

The subject's information and the ICF are enclosed. If modifications are made according to local requirements, sponsor must approve the new versions. A copy of the subject's information and a copy of the Informed Consent Form should be retained by the subjects.

Subject Data Protection

Number, initials, date of birth and sex will identify all subjects in the CRFs. The principal investigator is responsible for keeping a list of all

subjects (who have been allocated subjects numbers) including subjects' numbers, full names and last known address.

The subjects should also be informed in writing about the possibility of audits by authorized representatives of the company and/or regulatory authorities in which case a review of those parts of the hospital records relevant to the study may be required. The subjects should be informed in writing that the results would be stored and analyzed in a computer, maintaining confidentiality in accordance with local data laws.

Insurance

The sponsor has subscribed to an insurance policy covering, in its terms and provisions its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

六、 結論與建議

At the end of this study, only 7 cases were collected. We spent lots of time in applying the agreement of this trial in accordance with the scientific protocol as well as with applicable law and professional standards, it postponed to do case finding. The final protocol also limits the scope of case finding in clinic course. Finally, we collected 7 cases from late June to Nov. 2005.

The patient characteristics are shown in Table 2. Of the seven patients, 6 were males and one was female. The age range was from 50 years old to 71 years old. There were 3 tongue cancers, 2 buccal cancers, one hypopharyngeal cancer, and one laryngeal cancer. Clinical symptoms and signs included 4 neck masses, two oral masses, and one poor healing of oral wound. Pre-study screen including renal function, hepatic function, hemoglobulin, and Karnofsky scale were all within normal limits except two with slight renal impairment (patient E and G) and one with slight impairment of hemoglobulin (patient C, hemoglobulin 10.8 gm%).

The result of scintigraphic imaging, CT scan and biopsy were shown in Table 3. Of the 7 patients, 6 patients were finally diagnosed to have tumor recurrence (4 patients were based on the pathologic results and 2 patients were based on both CT scans, FDG-PET scans and clinical follow-up). One patient was diagnosed to have no recurrence after 5-month follow-up. In the 6 patients with tumor growth, all positive lesions were detected by CT scan and FDG-PET scan. However, the Tc-99m HL-91 imaging detected 5 patients missed one (Fig. 1&2). The only one negative case was correctly diagnosed by Tc-99m HL-91 image and CT scan but FDG-PET scan showed false positive result in this case (Fig. 3). The false positive result of FDG-PET scan in this case may be due to inflammation or tissue healing.

The diagnostic accuracies of these diagnostic modalities are shown in

Table 4. The diagnostic accuracies of detecting recurrence in head and neck cancer were 85.7%, 100% and 85.7% for the Tc-99m HL-91 scan, CT scan and FDG-PET scan, respectively. The ratio of Tc-99m HL-91 uptake between tumor and normal tissue (T/N) is calculated in positive finding in ^{99m}Tc-HL91 studies and the ratios of 5 patients are 1.4, 2.0, 2.0, 2.0, and 1.1 respectively.

After the examinations of Tc-99m HL-91, all patients were followed up at our outpatient department based on the study schedule. No any discomfort or adverse event was found during the follow-up. The results suggest that the Tc-99m HL-91 produced by INER is a safe radiopharmaceutical.

CONCULSION

The pilot study of ^{99m}Tc-HL91 study has an encouraged result although the sample size is small. The diagnostic accuracy of Tc-99m HL-91 scan was 85.7% in the detection of recurrent head and neck tumor. In addition, no adverse event is recorded in this study. Our preliminary results suggest that Tc-99m HL-91 produced by INER is safe for clinical use and may have potential on the detection of cancer recurrence in patients with head and neck cancer.

七、參考文獻

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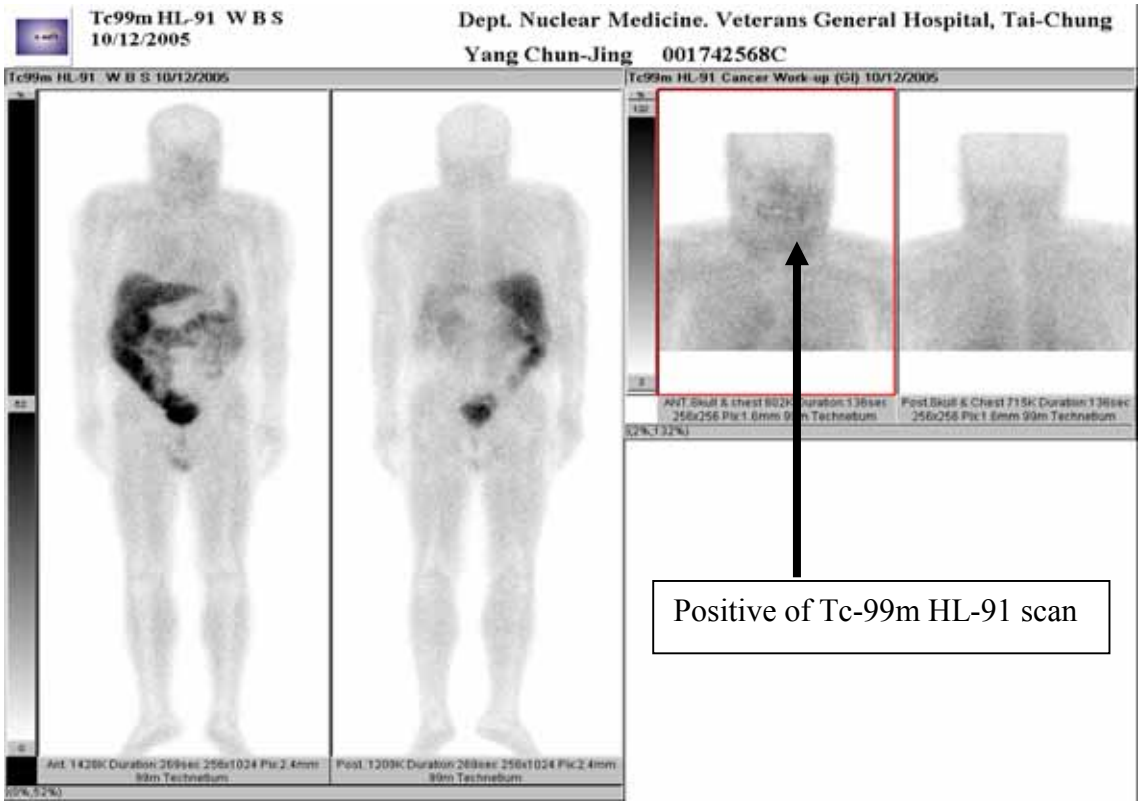
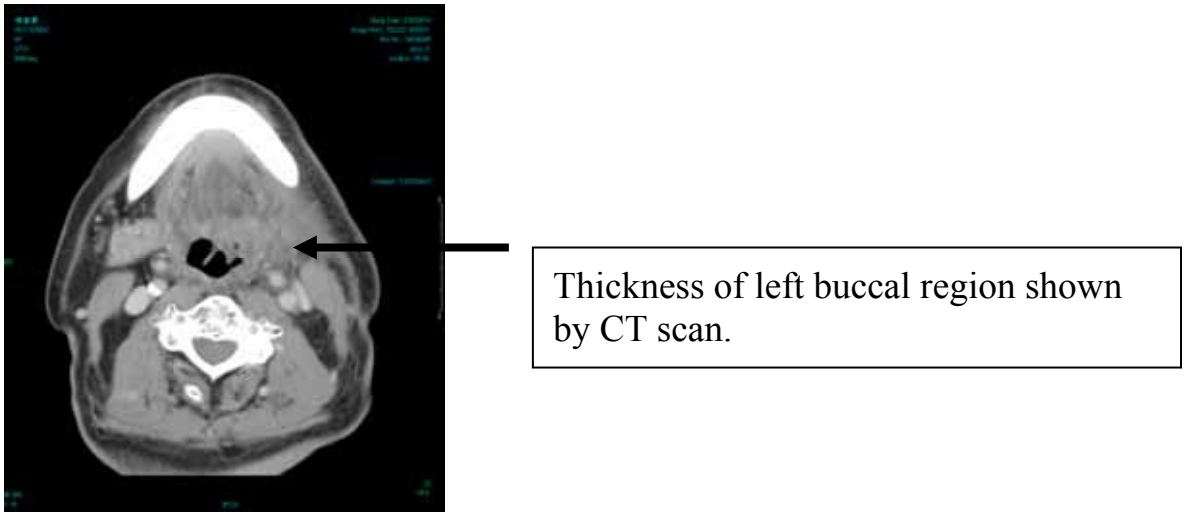
八、附表

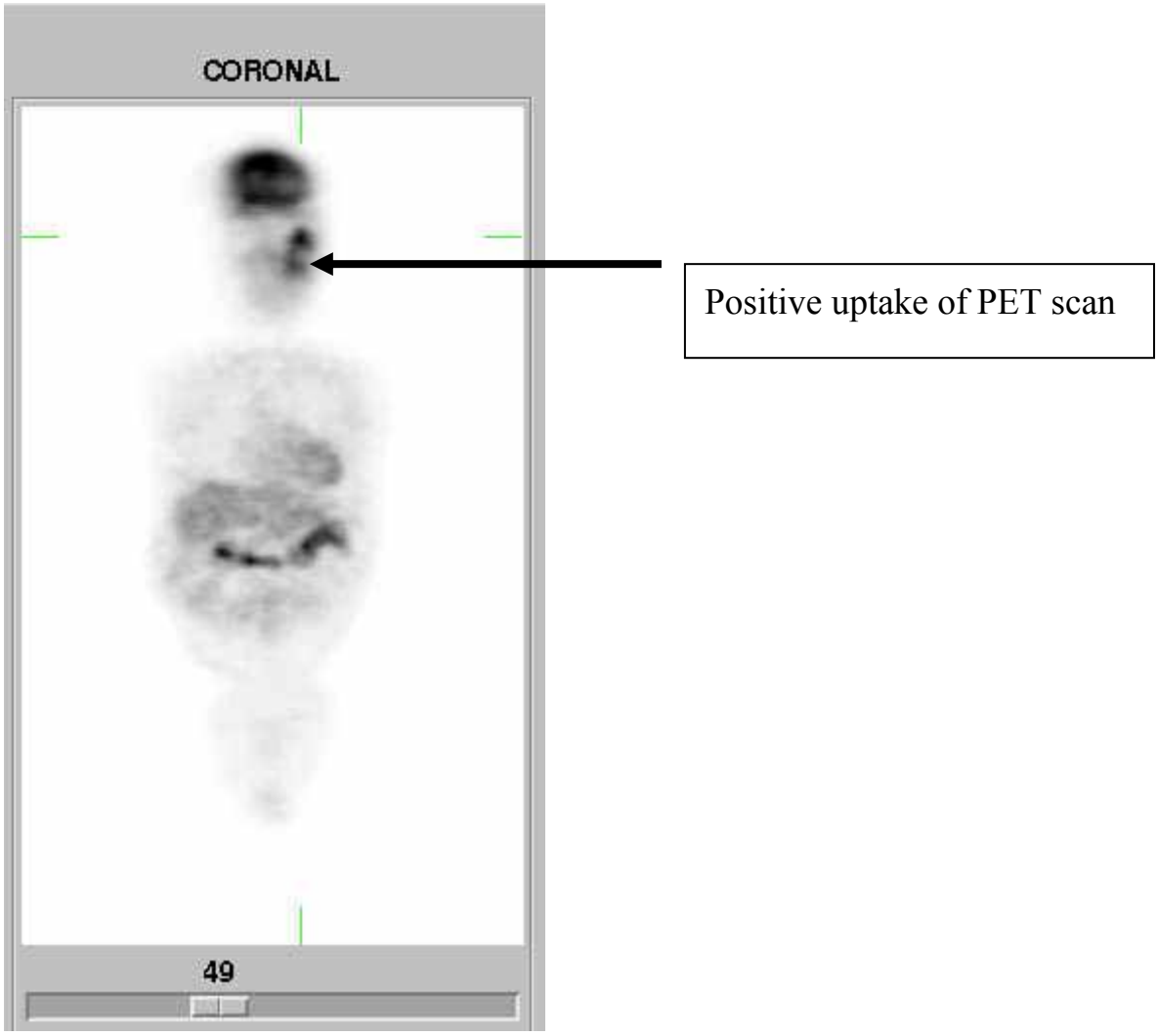
Figure 1. A 71 y/o male with buccal cancer. Recurrence of cancer in the oral cavity was diagnosed.



(A) Tc-99m HL-91 scan showed an area of increased Tc-99m HL-91 uptake in the oral cavity (arrows),



(B) CT scan showed thickness of left buccal region (arrows),



(C) FDG-PET scan showed an area with increased FDG uptake in the oral cavity (arrows) correspondent to the lesion found in both Tc-99m HL-91 image and CT scan.

Figure 2. A 57 y/0 male with tongue cancer. Recurrence of tumor in the neck is diagnosed. (A) Tc-99m HL-91 scan showed no abnormal Tc-99m HL-91 uptake in the neck, (B) CT scan showed …….. (arrows), (C) FDG-PET scan showed an area with increased FDG uptake in the neck (arrows). This is a false negative result for Tc-99m HL-91 image.

Figure 3. A 56 y/0 female with tongue cancer. Poor healing of the surgical wound is noted. (A) Tc-99m HL-91 scan showed no abnormal Tc-99m HL-91 uptake in the neck, (B) CT scan also showed no evidence of tumor recurrence, (C) however, FDG-PET scan showed an area with increased FDG uptake in the oral cavity (arrows). No evidence of recurrence has been found in the more than 5-month clinical follow-up of this patient. This is a false positive case for FDG-PET imaging.

Table1. Events and Time Schedule

	Registration	Study Evaluation		
Periods	Screening	SPECT (HL-91)	CT scan	Pathologic Biopsy
Visits	Visit 1	Visit 2	Visit 3	Visit 4
Day	less than 2 weeks	Within 4 weeks		less than 2 weeks
Inform Consent	√			
Demographics	√			
Medical History	√			
Physical Examination	√	√	√	√
Vital signs	√	√	√	√
Hematology	√			√
Biochemistry	√			√
Pregnancy test	√			
Chest X-ray	√			
Inclusion/Exclusion Criteria	√			
^{99m}Tc-HL-91 SPECT		√		
Spiral CT scan			√	
Blood Clotting Tests				√*
Pathologic Biopsy				√
Adverse Events		√	√	√
Safety Evaluation and Follow up				√

* Follow up prothrombin time (PT), activated partial thromboplastin time (APTT) within 1 week before biopsy to ensure and be careful of any bleeding tendency.

Table 2. Patients' characteristics

case	Primary	Sex	Age	Clinic	Liver	Renal	Hemoglobulin	Karnofsky
A	Tongue	M	57	Neck mass	N	N	14.7	70
B	Tongue	F	56	Poor healing	N	N	13.8	80
C	Tongue	M	69	Neck mass	N	N	10.8	70
D	Hypopharynx	M	58	Neck mass	N	N	14.9	80
E	Buccal	M	71	Oral mass	N	Slight impairment	12.8	80
F	Larynx	M	50	Neck mass	N	N	15.7	70
G	Buccal	M	68	Oral mass	N	Slight impairment	11.9	70

Table 3. ^{99m}Tc-HL91 study and other studies findings

Case	HL91 SCAN	CT SCAN	PET	BIOPSY	Final result
A	Negative	Positive	Positive	Positive	Positive
B	Negative	Negative	positive	Non-done	Negative
C	Positive(T/N1.4)	Positive	Positive	Non-done	Positive
D	Positive(T/N2.0)	Positive	Positive	Positive	Positive
E	Positive(T/N2.0)	Positive	Positive	Positive	Positive
F	Positive(T/N2.0)	Positive	Positive	Non-done	Positive
G	Positive(T/N1.1)	Positive	Positive	Positive	Positive

Table 4. Diagnostic accuracy of different diagnostic modalities.

	Tc-99m HL-91	CT Scan	FDG-PET Scan
Sensitivity	83.3%	100%	100%
Specificity	100%	100%	0%
Accuracy	85.7%	100%	85.7%