

行政院原子能委員會 委託研究計畫研究報告

鎇-99m-MIBI 學術研究用臨床試驗

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中文摘要：

Technetium-99m methoxyisobutylisonitrile (Tc-99m MIBI) 是一種親脂性陽離子複合物，它被認為是對偵測腫瘤有助益的放射性製劑，有報告指出，其攝取程度與腫瘤血流灌注、細胞內粒腺體量有關，而它的排出則與細胞之 P-醣蛋白有關，並可被細胞之多藥物抗性-1 基因所強化。Tc-99m 標化 MIBI 擁有單光子造影要求的理想能量 (140 KeV)，因此可以獲得較好腫瘤偵測品質，這也是吾人對其在頭頸部腫瘤偵測尚寄予厚望的原因。

本研究乃針對此一製劑在口腔癌病人，治療前後之影像評估癌病殘留或復發病灶的應用價值。按口腔上皮癌佔所有癌症約 5%，為國人男性第四大癌症。值得一提的是，口腔癌經治療後，其解剖位置和所產生的非特異性炎症反映常導致傳統影像檢查包括電腦斷層攝影及磁振影像對殘留或復發病灶的判定造成困擾，這也是我們選擇這類癌病作為研究標的的原因。病人收集對象則以臨床類似口腔癌患者接受 Tc-99m MIBI 檢查，並在 2 周內接受電腦斷層攝影或磁振檢查。癌病診斷最後以組織病理學檢查為準，以求其術後對殘留復發偵測能力，並比較傳統影像檢查的優劣性。研究發現，Tc-99m MIBI 對於解剖影像無法確認病灶範圍病例可提供癌病侵犯位置及範圍，減少急、慢性發炎病灶之假陽性反應；同時，單光子造影比平面造影有較高偵出率；合併電腦斷層攝影及單光子造影之核醫儀器則可進一步對病灶作同步定位。研究同時，發現接受 Tc-99m MIBI 單光子造影檢查病人檢查時與檢查後兩日內並無明顯不適及副作用產生。

英文摘要

Technetium-99m methoxyisobutylisonitrile (Tc-99m MIBI) has been designed as a radiotracer for oncological studies, which is a lipophilic cation complex. The tumor uptake of Tc-99m MIBI correlates with perfusion and intracellular mitochondria levels. Cancer of the oral cavity composed of about 5% of all malignancies and has been ranked as the fourth most common cancer of men in Taiwan. Conventional imaging modalities are limited in monitoring the possible residual or recurrent tumor due to anatomical derangement and scar formation resulting from operation and radiotherapy. This study was sought to compare the effectiveness of Tc-99m MIBI single photon emission computed tomography (SPECT) and conventional imaging, comprising computed tomography (CT) and magnetic resonance imaging (MRI), in the detection of residual or recurrent oral cavity cancer (SCC) before and after treatment. All patients underwent Tc-99m MIBI SPECT and CT or MRI within 2 weeks. The final diagnoses were based on the histology of biopsy specimen or clinical follow-up. The detect ability of Tc-99m MIBI SPECT for cancer recurrence or residual and its comparison with conventional imaging (CT or MRI) for the detection of residual or recurrent oral SCC was being calculated. We found that Tc-99m MIBI SPECT might be useful to delineate location and extension of the oral cavity SCC when the anatomic images are equivocal. It is especially true when the bulk tumor can not be completely removed by surgical operation and receives alternative radiotherapy. Tc-99m MIBI provided less uptake in inflammatory lesions, either acute or chronic. This enabled us to discriminate benign natures such as wound infection, effects of operation or radiotherapy from tumor residual or recurrent. In addition, it appeared that SPECT provided more information regarding location and extension of residual or recurrent tumor. Our preliminary observation indicates that Tc-99m MIBI SPECT may play a role in the detection of residual/recurrent oral cavity cancer. No obvious side effects were found in patients immediately and 2 days after administration of Tc-99m MIBI.

計畫目的與緣起

Cancers of the oral cavity account for approximately 5% of all malignancies and have been ranked as the fourth most common cancer of males in Taiwan (1). Despite progress in surgical skill and adjuvant chemoradiotherapy, the overall 5-year survival rate of patients with oral squamous cell carcinoma (SCC) is still low (2). Early detection of tumor recurrence is essential to reduce morbidity and mortality. Computed tomography (CT) and magnetic resonance imaging (MRI) are the imaging modalities of choice for the initial staging of oral SCC because of their superiority in outlining the full extent of the primary tumor and evaluating regional lymph node metastasis. However, the anatomical imaging modalities are of limited value for the detection of recurrent or residual disease because of anatomical distortions and scarring resulting from surgery and radiotherapy. Fluorine-18fluorodeoxyglucose positron emission tomography (FDG PET) has been reported to be more accurate than CT or MRI for the identification of tumor recurrence in head and neck cancers (3-5). However, appropriate timing of FDG PET (at least 4 months after radiotherapy) is necessary in order to distinguish residual/recurrent disease versus post-therapy changes by FDG PET (6). Furthermore, cost and limited availability of PET may also restrict its applicability. Thallium-201 has been widely used in the diagnosis of various tumors with or without single photon emission tomography (SPECT) (7-11).

^{99m}Tc MIBI is a lipophilic cationic complex and which was originally introduced for myocardial perfusion imaging (12). ^{99m}Tc MIBI nonspecifically localizes in mitochondria and

the cytoplasm. It is retained by membrane potentials across the membrane of the cell and mitochondria (13). Early detection of tumor recurrence after primary therapy for oral SCC is essential to reduce morbidity and mortality, but, as already mentioned, the value of anatomical imaging modalities for this purpose is limited owing to anatomical distortions and scarring resulting from surgery and radiotherapy. Available data indicated that Tc-99m MIBI SPECT has been reported to be a valuable tool for the diagnosis of head and neck cancer, particularly in the post-treatment setting (14-18). However, the value of Tc-99m MIBI SPECT in the detection of recurrent oral SCC, the most common head and neck cancer in Taiwan, has yet to be clarified. In view of the literatures, little Tc-99m MIBI SPECT data was reported in this regards. Valdes-Olmos et al. have reported a higher accuracy for ^{201}Tl SPET compared with CT/MRI in the detection of recurrent head and neck cancer. In 30 patients (including four with oral SCC), they found the sensitivity, specificity, and accuracy of ^{201}Tl SPET versus CT/MRI for the detection of recurrence to be 93% versus 76%, 78% versus 30%, and 87% versus 64%, respectively (17). Mukherji et al. also reported ^{201}Tl SPET was superior to CT for differentiating recurrent tumor from non-neoplastic post-treatment changes in 33 patients (including 7 oral cancers) with treated SCC of the extra cranial Head and neck. In their study, the sensitivity and specificity of ^{201}Tl SPET was 88% and 94%, respectively. Although the negative predictive value of CT was very high (100%), its positive predictive value was only 55% (18). The mechanisms for tumor uptake of Tl-201 and Tc-99m MIBI are somewhat different, Tl-201 is mainly

dependent on activity of Atlases while Tc-99m MIBI is on activity of mitochondria. The emission energy of Tc-99m is also better than Tl-201 for patients imaging. It is plausible to expect that Tc-99m MIBI SPECT would be better or at least not worse than Tl-201 SPECT. In a comparative study between FDG PET and Tc-99m MIBI SPECT, the sensitivity, specificity, and accuracy for Tc-99m MIBI SPECT, based on biopsy results, were 73%, 96%, and 89% respectively. If combined with CT interpretation, the sensitivity, specificity, and accuracy became 100%, 96%, and 96% respectively. However, if CT interpretation only, the sensitivity, specificity, and accuracy became 73%, 88%, and 83% respectively [19].

Biopsy of previously irradiated tissues carries a significant risk of complications, such as bleeding and superimposed infection. If our results showed a high accuracy for Tc-99m MIBI SPECT at the primary sites for detecting residual/recurrent disease in patients with oral SCC, Then, a negative Tc-99m MIBI SPECT result may help obviate unnecessary biopsy in patients with a low clinical suspicion but a positive CT or MRI result.

The goal of this study was thus to investigate the usefulness of Tc-99m MIBI SPECT in the detection of recurrent SCC of the oral cavity, compared to CT/MRI and histopathological findings.

執行方法與進度說明

Patients.

Eleven consecutive patients (4 women and 7 men, ages 45 to 68 years) that clinically suspected to have recurrence of oral SCC were prospectively enrolled in this study. All patients underwent Tc-99m MIBI SPECT/CT and diagnostic CT or MRI examinations within 2 weeks. The Final diagnoses were based on the histology of the biopsy specimen or aspiration cytology. Primary tumors were staged according to the tumor-node-metastasis (TNM) system of the American Joint Committee on Cancer (AJCC cancer staging manual, 5th ed. Philadelphia, 1997, Lippincott-Raven.). Patients were treated initially with either surgery, chemotherapy, and/or radiotherapy.

SPECT Image.

An INER-made (Institute of Nuclear Energy Research) MIBI preparation (maximal 150 mCi or 5.56 GBq, in about 1-3 ml) was obtained. Labeling and quality control procedures were carried out according the manufacturer's instruction. The labeling efficiencies were always higher than 95%.

Tc-99m MIBI SPECT was performed 15 minutes and 2 hours after the intravenous injection of 740 MBq Tc-99m MIBI. SPECT scans of the head were performed in all patients using a dual-detector gamma camera (Hawke eye; VariCam, Elscint) equipped with low-energy high-resolution collimators. The acquisition parameters included a 360°rotation with 60 stops at 30

seconds each to obtain data in a 128 x 128 matrix with a slice thickness of 0.65 mm. Images were reconstructed using a Butterworth filter with a cut-off frequency of 0.35 and an order of 9. These were re-oriented parallel to the base of the brain, and sagittal and coronal reconstructions were then obtained. Except for physiological uptake of Tc-99m MIBI, such as pituitary glands, nasal and oral cavity, bilateral pharyngeal recesses, maxillary sinuses, parotid, palatine, sub-mandibular and sublingual salivary glands), asymmetrically increased focal uptake of tracer in the oral cavity or neck region was interpreted as positive for recurrent tumor in consensus by two experienced nuclear physicians who had knowledge of the primary sites.

CT or MRI examination.

CT scans were obtained using a multi-slice helical CT multi-slice helical CT (Aquiline, Toshiba, Otawara, Japan) to include the area from the skull base to the thoracic inlet at 3 mm intervals and with 2-mm collimation. Contrast material (100ml of Optiray 320; Mallinckrodt Canada Inc., Pointe-Claire, Quebec, Canada) was intravenously administered in all patients.

MRI was performed with a 1.5-T Philips Gyroscan S-15 in all patients. Axial T1- (TR/TE= 531/15 msec) and T2-weighted (TR/TE=2791/70 msec) fast spin-echo sequences were obtained before and after intravenous injection of gadolinium-diethylenetriamine penta-acetic acid. The slice thickness was 8mm and the inter-slice gap 0.8 mm. The field of view was 16 cm, and the matrix was 256 x 256 pixels.

Statistical analysis.

Statistical calculations were performed using SPSS for Windows (V 10.0, SPSS, Inc., Chicago, IL). The sensitivity, specificity, accuracy, and positive and negative predictive values for identification of recurrent oral cavity SCC were calculated for Tc-99m MIBI SPECT and CT/MRI in the usual manner.

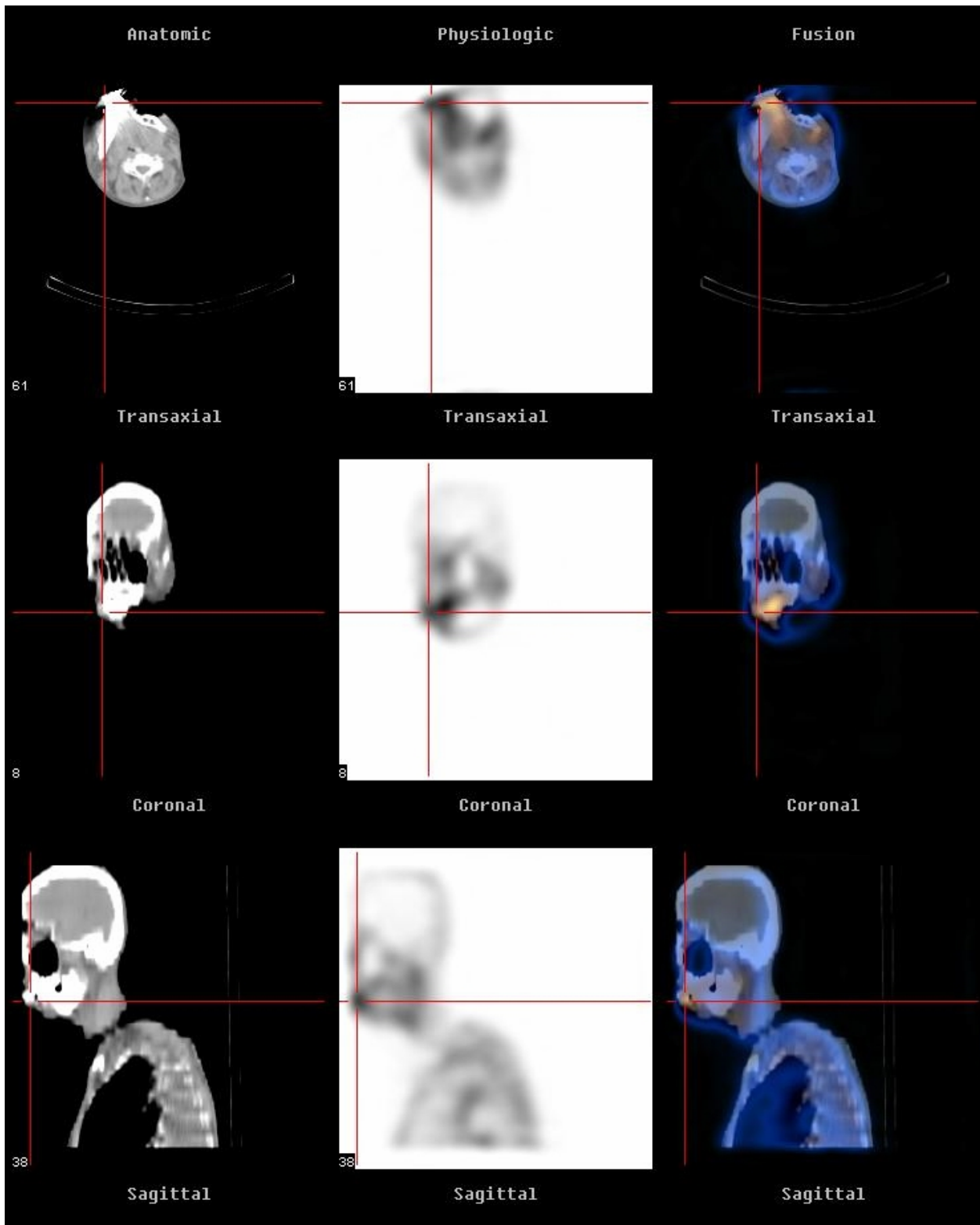
In the current study, the purchase of radiopharmaceutical was a little delayed for the time table, it was thus the studied number is still limited for powerful statistical analysis. However, there were trend seen in the study and will disclose in the next section. The representative case was demonstrated as figure.

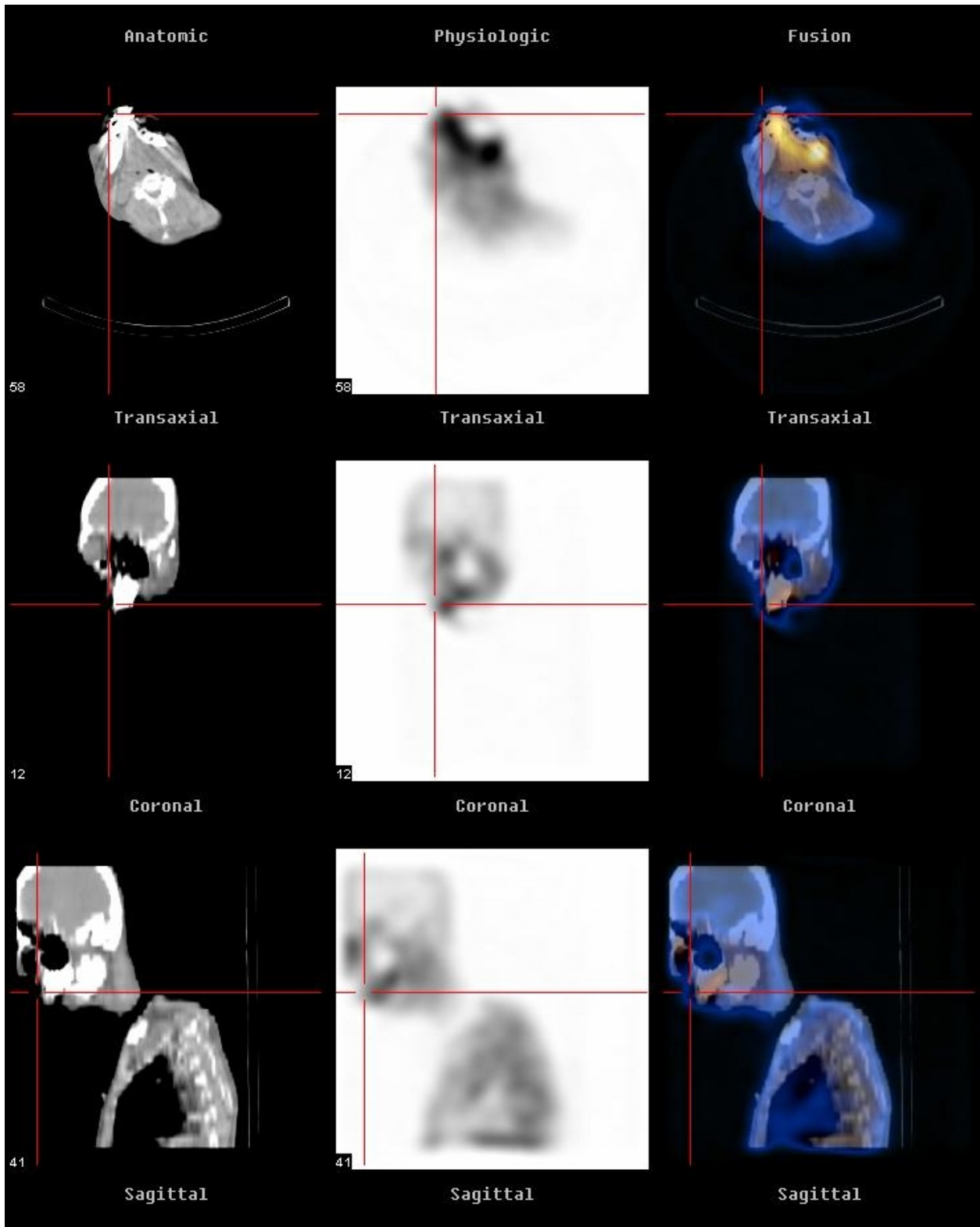
After drug administration, have the subjects assess tolerability of trial drug by using a 10-cm VAS after scan and perform investigator's global assessment for the tolerability of the test drug.

Figure. A 65 year-old male with squamous cell carcinoma who refused to receive surgical removal of the mass. Radiotherapy was performed with partial response. He visited to our radiotherapy department due to tumor recurrence involving left face and left submandible region.

A. Tl-201 SPECT revealed abnormal uptake in the same site seen on anatomic image and physical examination. A central decrease of uptake in the mass was indicative of central tumor necrosis. B. Tc-99m MIBI SPECT showed a similar finding but found an additionally abnormal uptake in the right sub-mandible region, recurrence with extension to the opposite site was highly suggested. The patient has been followed up for 1 month, showing a bulging mass in the area as seen on Tc-99m MIBI SPECT that was not identified by concomitant anatomic image or Tl-201 SPECT.

ADD FIGURES HERE!





結論與建議

Tc-99m MIBI SPECT might be useful to delineate location and extension of the oral cavity SCC when the anatomic images are equivocal. It is especially true when the bulk tumor can not be completely removed by surgical operation and receives alternative radiotherapy. As comparison with another tumor agent- Thallium-201 (Tl-201), Tc-99m MIBI provided less uptake in inflammatory lesions, either acute or chronic. This enabled us to discriminate benign natures such as wound infection, effects of operation or radiotherapy from tumor residual or recurrent. However, we still found 4 clinically mis-matched cases. Two of them with positive Tc-99m MIBI SPECT but no evidence of tumor recurrence which might be contributed from inflammatory process or salivary gland uptake distorted by tumor compression. The other 2 cases with negative Tc-99m MIBI SPECT but positive evidence of tumor recurrence seen on Ct or MRI and finally proved by clinical follow-up, in-homogenous tumor expression in the lesions after radiotherapy or too small in size might be responsible. More works in this regard was warranted.

On the other hands, it appeared that SPECT provided more information regarding location and extension of residual or recurrent tumor. SPECT can provide higher target to noise ratio and clearer delineation of tumor margin. However, there are two pitfalls of Tc-99m MIBI in the detection of residual or recurrent oral cancer. First, normal physiological uptake in the sub-mandible salivary glands may mask the presence of nodal disease in the sub-mandible regions. Second, the lack of structural delineation makes precise anatomical localization of lesions difficult. Using SPECT/CT

camera or co-registration of images of SPECT and CT or MRI may overcome these pitfalls. Owing to number of cases recruited for the study was limited, we did not calculate the sensitivity, specificity, accuracy, and positive and negative predictive values for identifying recurrent oral cavity SCC. Further study with larger number of cases is needed.

No major complaint or objectively side effect was told or found, either during or two days after imaging. Our observations support the safety of the radiopharmaceutical and imaging procedures in the clinical subjects.

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