Technetium-99m-Tetrofosmin SPECT Imaging of Lung Lesions: A Not-So-Negative Study

TO THE EDITOR: We read with great interest the article by Kao et al. (*1*) on the use of ^{99m}Tc-tetrofosmin SPECT imaging in the evaluation of single solid lung masses, based on the findings of chest radiographs. They evaluated 49 patients, 41 with malignant lung lesions and 8 with benign ones, and reported a diagnostic sensitivity, specificity and accuracy of 61%, 50% and 59%, respectively. On the basis of these results, the authors state that ^{99m}Tc-tetrofosmin SPECT of the chest is of little or no value for differentiating malignant from benign lung lesions and for the detection of cancer when diagnosing single solid lung masses.

The clinical usefulness of ^{99m}Tc-tetrofosmin as a tumor-seeking agent in lung cancer is currently under investigation in several institutions, mirroring previous experiences with ^{201}Tl and ^{99m}Tc-sestamibi. As cited in the study of Kao et al. (*1*), we reported on the use of ^{99m}Tc-tetrofosmin SPECT in patients with radiological evidence of lung lesions (*2*), obtaining a sensitivity of 95% (18/19) for the detection of primary lung cancer and a specificity of 100% (no pathological accumulation of the radiopharmaceutical was observed in the 6 patients with benign lesions). On the basis of these preliminary but encouraging findings, we investigated the role of ^{99m}Tc-tetrofosmin SPECT in a larger series of patients with lung lesions to better evaluate its diagnostic accuracy. To date we have studied a total of 67 patients, 46 with malignancies and 21 with benign lung lesions; sensitivity, specificity and accuracy of ^{99m}Tc-tetrofosmin imaging in the detection of lung cancer have been 93%, 86% and 91%, respectively (unpublished data). These results are similiar to those reported by other authors both for sensitivity and specificity (*3–5*); nevertheless other studies yielded a comparable high sensitivity but a lower specificity (*6,7*).

In contrast with these findings, the sensitivity found by Kao et al. (*1*) is quite low compared with that obtained in other studies using ^{99m}Tc-sestamibi. In fact, only their previous article (*8*) reports a low sensitivity (65%), whereas sensitivities obtained in the works of Hassan et al. (*9*) and Lebouthillier et al. (*10*), which were cited by Kao et al. (*1*), are clearly higher (91% and 96%, respectively). Although we agree with the conclusion of Kao et al. (*1*) that a different P-glycoprotein expression may explain this discrepancy, in our opinion, tumor size is also important for detection. Their results show that sensitivity is 74% (17/23) for cancers >4 cm and only 44% (8/18) for those ≤4 cm.

With regard to specificity, the small number of benign lesions in the study by Kao et al. (*1*) has to be taken into account when considering their findings. Moreover, the intrathoracic goiter (Patient no. 45), which demonstrated positive ^{99m}Tc-tetrofosmin uptake, must not be considered to be a solid lung mass; in fact, a chest CT would have simply clarified its nature.

In conclusion, we think that the negative conclusions of Kao et al. (*1*) regarding the usefulness of ^{99m}Tc-tetrofosmin SPECT imaging in patients with lung lesions are premature. The results of various studies (*2–7*) indicate that this radiopharmaceutical is highly sensitive in the detection of lung cancer. Because of the small total number of patients with benign lesions considered, larger series are required to finally determine the clinical role of ^{99m}Tc-tetrofosmin imaging in differentiating malignant from benign lung lesions and its specificity.

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Technetium-99m-Tetrofosmin Scintigraphy, P-Glycoprotein and Lung Cancer

TO THE EDITOR: We read with interest the article by Kao et al. (*1*) that referred to the study of lung masses by means of SPECT imaging of the chest using ^{99m}Tc-tetrofosmin (TF). They evaluated ^{99m}Tc-TF for its ability to differentiate between malignant and benign lesions in single solid lung masses. They conclude by saying that, "^{99m}Tc-TF SPECT of the chest is of little or no value for the detection of lung cancer from single solid lung masses." We would like to express some additional considerations concerning the kinetics and uptake of this radiopharmaceutical in lung cancer and communicate our experience.

In vitro studies involving cultured tumor cell lines, uptake of ^{99m}Tc-TF and ^{99m}Tc-hexakis-isobutyl isonitrile-2-methoxyisobutyl isonitrile (MIBI) has been shown to be rapid during the first few minutes, after which time it continues to increase gradually during the first hour of incubation, at which time it reaches a plateau of at least 4 hr duration (*2*). Thus, the assessment of in vivo studies should not be based exclusively on early images (15–30 min). A later acquisition would also allow clearance of the circulating vascular background. Kao et al. (*1*) assessed a single study performed 15–30 min postinjection, which may have influenced their findings.

They mention the possible mechanisms of ^{99m}Tc-TF uptake by tumor cells (*1*). These mechanisms, like those of ^{99m}Tc-MIBI, are related to the number of mitochondria in the cells. Thus, uptake is observed in those tissues whose cells present elevated energy requirements, whether they be tumor cells, inflammatory cells or cells of some other type (which explains their use in myocardial perfusion). Kao et al. (*1*) observed uptake by 4 of 8 benign lesions corresponding to granulation tissue, mucormycosis, fungal abscess and intrathoracic goiter. In a preliminary study involving the use of ^{99m}Tc-TF in 5 patients with lung cancer (*3*), we also observed a false-positive result in the mediastinum that was caused by tuberculous lymphadenitis. The key to differentiating between malignant and benign lesions probably lies in the analysis of the amount of radiopharmaceutical deposited in the target tissue with respect to healthy tissue (tumor-to-healthy tissue ratio). This semiquantitative analysis has already proved its utility in other studies involving ^{99m}Tc-MIBI (*4*).

We recently carried out a broader study dealing with 62 resected lung masses (49 malignant and 13 benign) and ^{99m}Tc-TF SPECT (*5*). The histopathologic findings in the benign lesions in that series were as follows: 6 tuberculomas, 4 hamartomas, 1 aspergilloma, 1 hydatid cyst and 1 fibrotic nodule. None of the lesions had greater uptake than the contralateral symmetrical healthy tissue, although low-intensity uptake was visible. That is to say, the tumor-to-healthy tissue uptake ratio was less than or equal to 1. All the lung masses studied were resectable, not including lesions that showed no morphological or clinical evidence of malignant disease. Kao et al. (*1*) examined the images visually, a circumstance that, together with the early SPECT acquisition and the fact that not all of the lesions they studied were resectable, could explain the discrepancy between their study and ours with respect to uptake by benign lesions.

With respect to malignant lesions, we observed a tumor-to-healthy tissue ratio of greater than 1 in 30 of the 49 lesions. As indicated by Kao et al. (*1*), the absence of uptake by the remaining tumors can be explained by the presence of P-glycoprotein (Pgp) in the tumor cells. Pgp is encoded by the multidrug resistance gene (mdr1). Its overexpression by cancer cell lines is associated with an increased efflux of many cytotoxic drugs from the cells. Many of the drugs that are Pgp substrates are lipophilic cations at physiological pH (*6*), a condition that is fulfilled by both ^{99m}Tc-MIBI and ^{99m}Tc-TF and, in fact, both radiopharmaceuticals are Pgp substrates (*7,8*). On the basis of these premises, we studied 11 patients with non-small cell lung carcinoma (*9*). Our objective was to determine the Pgp distribution in resected tumor tissue samples by flow cytometry and to correlate it with preoperative ^{99m}Tc-TF scintigraphy. Depending on the Pgp expression revealed by flow cytometry, we classified the lung tumors as Pgp-positive or Pgp-negative. The ^{99m}Tc-TF uptake ratio in Pgp-positive tumors was 1.302 (0.232), whereas in Pgp-negative tumors it was 1.845 (0.348). The difference in the ^{99m}Tc-TF uptake ratio between Pgp-positive and Pgp-negative tumors was statistically significant ($p = 0.016$). These data suggest that the absence or low rate of uptake in a pulmonary mass histologically diagnosed as lung cancer is related to the presence of Pgp in the tumor.

In conclusion, ^{99m}Tc-TF SPECT and the determination of ^{99m}Tc-TF uptake ratio, in a selected group, differentiates between malignant and benign disease in the presence of uptake. Like ^{99m}Tc-MIBI (*7*), it also provides a functional image of mdr, with resulting prognostic and therapeutic implications of this information (*10*).

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Drug Labeling Changes

TO THE EDITOR: The Pharmacopeia Committee of the Society of Nuclear Medicine wishes to pass on the following safety-related drug labeling changes approved by the U.S. Food and Drug Administration in October 1997: "For nuclear medicine procedures involving withdrawal and reinjection of blood with the potential of transmission of blood-borne pathogens, procedures should be implemented to avoid administration error and viral contamination of personnel during blood product labeling. A system of checks similar to the ones used for administering blood transfusions should be routine."

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