

The role of technetium Tc99m-tetrofosmin as head and neck tumor-seeking agent: a preliminary report

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ABSTRACT

Aim: To evaluate the diagnostic value of technetium Tc99m-tetrofosmin (^{99m}Tc-TF) in primary cancers of the head and neck. **Methods:** Single photon emission computer tomography with planar imaging of the neck for primary site evaluation and whole body scanning for assessment of metastases in 12 patients with newly diagnosed head and neck cancer. Tumor-to-background index (T/Bg) was derived in patients with positive findings (tumor or lymph nodes). **Results:** The tomographic images showed increased tracer uptake in pathological sites (primary tumor or lymph node) in 9 patients (overall sensitivity 75%). Primary tumor was visualised in 7 patients (sensitivity 58%) and infiltrated lymph nodes in 4 out of 7 patients (sensitivity 57%). Mean values for T/Bg index were 5.44 ± 1.28 for primary tumor and 4.25 ± 1.67 for lymph nodes. Mean values for T/Bg index were 4.5 ± 0.71 for patients with *in situ* and grade I carcinoma and 6.68 ± 0.36 for patients with tumor grade II and III ($P = 0.034$, Mann-Whitney *U* test). **Conclusion:** The present study demonstrates that ^{99m}Tc-TF is a valuable radiotracer for head and neck cancer imaging. To determine the potential role of this imaging protocol in clinical practice will require a larger sample size.

Key words: Head and neck cancer; radionuclide imaging; single photon emission computer tomography; ^{99m}Technetium-tetrofosmin

INTRODUCTION

Malignant tumors of the head and neck are among the six most common forms of tumors in the body. Head and neck cancer include neoplasms of the upper respiratory tract (nasopharynx, oropharynx, larynx) salivary glands, and soft tissue of the neck with squamous cell carcinoma being the most frequent histological type. Diagnosis of this type of cancer is based on endoscopy and biopsy of the suspicious lesion.^[1] Staging and evaluation of the extent of disease involves the use of computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET).^[2] Follow-up evaluations after surgery and/or radiotherapy and differential diagnosis of disease relapse from radiation necrosis is more difficult to assess,

due to extensive distortion of the normal anatomy, and may require a combination of different imaging tests,^[3-7] such as PET scan.^[8-11] However, its availability is limited by the need for a cyclotron that produces ¹⁸Fluorodeoxyglucose (¹⁸FDG) and its increased cost. In addition, in many countries, PET is not widely available so other methods are needed for tumor-imaging assessment.

When a PET scanner is not available, nuclear medicine still plays a crucial role in the initial staging of the disease and for follow ups. Lymph node cancerous involvement at initial presentation may be difficult to assess by conventional

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imaging methods based only on morphology and size. Functional nuclear medicine imaging has the unique advantage of assessment of the metabolic state of lymph nodes. Currently, the agents employed are Thallium-201 (²⁰¹Tl) and the two technetium-99m labelled compounds Sestamibi (MIBI) and Tetrofosmin.^[2]

^{99m}Tc-MIBI and Tc^{99m}-tetrofosmin (^{99m}Tc-TF) are two lipophilic cationic complexes, which were originally employed in myocardial perfusion imaging, but later were found to possess tumor-seeking properties in the evaluation of diverse human malignancies.^[12] The diagnostic value of ^{99m}Tc-TF could hold promise as a head and neck cancer tracer, although limited data exist in clinical research.^[13,15] In the present study the diagnostic utility of ^{99m}Tc-TF prior to surgery of head and neck neoplasms was assessed and correlated with the ^{99m}Tc-TF uptake of histological grade, and tumor and lymph node size.

METHODS

Prior to surgery, 12 subjects (11 males and 1 female) of median age 65.5-year-old (48-83) with suspected head and neck cancer had ^{99m}Tc-TF planar and Single photon emission computer tomography (SPECT) imaging of the neck and whole body scanning for metastatic evaluation. None of the patients had received treatment prior to scintigraphy, except for patient twelve, who had surgery, radiotherapy and chemotherapy, one year prior to scintigraphy. This patient had scintigraphy because of a tumor relapse at the primary tumor.

All patients were interviewed before ^{99m}Tc-TF imaging and the patients' age, height, weight, smoking habits, and alcohol consumption were noted. Data from the CT findings included the anatomical location and size of the tumor, as well as the existence and size of lymph nodes. Correlation of SPECT imaging with the tumor histopathology diagnosis and grade was performed after the original tumor was excised and the pathology was established. The protocol was approved by the Hospital Research and Ethics Committee. Informed consent was obtained from all patients. Clinical trial registration was not required for this small study.

Protocol

All patients were injected with a dose of 740 MBq (20 mCi) bolus ^{99m}Tc-TF; and immediately after injection patients drank 5 mL of lemon juice to stimulate salivary glands. Lemon juice stimulation achieves the lowest possible uptake of radiotracer in the salivary glands (normal distribution of ^{99m}Tc-TF) during imaging. Scintigraphy was performed with patients in a supine position. Anterior planar images were acquired 5-10 min post injection, using a zoom factor of 2.66. Tomography was acquired 15 min post-injection with the dual-head camera at 6°-angles (60 stops) and 30 s per projection (30 projection/head) over

a 360° arc, using a low-energy, general purpose collimator. Acquisition was obtained with a matrix size of 64 × 64 × 16, 1.85 zoom factor, and a 15% symmetric window at 140 keV (no contour). Reconstruction method was filtered back projection (filter butterworth, cut-off frequency 0.5, power 7.0). No attenuation correction was used. Finally, whole body scan was acquired in all patients for possible distant metastases evaluation.

Two nuclear medicine specialists visually evaluated the planar, tomographic and whole body images, which were compared to the CT scans. Increased uptake in SPECT images (in a site of pathological finding on CT (primary tumor or lymph node) was considered a positive finding. A region of interest (ROI) was drawn on the relative coronal image. Background (Bg) ROI was drawn over the apex of the right lung. T/Bg index for tumor and lymph nodes was derived in all patients with positive findings. Patients with no significant uptake on pathological sites were considered negative.

Table 1: Physical characteristics of the patients and tumor anatomical location

Characteristics	Patients
Gender	11 M/1 F
Mean age (years)	65.75 ± 11.8 (48-83)
Height (cm)	166.75 ± 8.9 (155-184)
Weight (kg)	69.25 ± 9.5 (55-82)
BMI (kg/m ²)	25.00 ± 3.8 (16.2-32.4)
Smoking	11/12 (91.7%)
	* 0: 1/12 (8.3%)
	* 1: 0/12 (0.0%)
	* 2: 11/12 (91.7%)
Alcohol	8/12 (66.7%)
	** 0: 4/12 (33.3%)
	** 1: 2/12 (16.7%)
	** 2: 6/12 (50.0%)
Anatomical location of tumor	
Eepiglottis	1/12 (8.3%)
Vocal cord	2/12 (16.7%)
Base of tongue	2/12 (16.7%)
Pharyngeal wall	1/12 (8.3%)
Tonsil	1/12 (8.3%)
Submandibular gland	1/12 (8.3%)
Soft palate	1/12 (8.3%)
Pyriform fossa	2/12 (16.7%)
Nasopharynx	1/12 (8.3%)
Histopathological findings	
Squamous cell	10/12 (83.3%)
Adenoid cystic cell	2/12 (16.7%)

M: male; F: female; BMI: body mass index; * Smoking habits: 0 = no smoking; 1 = less than 500 cigarettes/year; 2 = more than 500 cigarettes/year; for more than 2 decades. **Alcohol consumption: 0 = no alcohol consumption, 1 = alcohol consumption no more than 2-3 times in week; 2 = every day consumption of alcohol

Table 2: Tumor and regional lymph node characteristics in patients with head and neck cancer

Patient	Tumor diameter: cm (max)	LN diameter: cm (max)	T/Bg Index	LN/Bg index	Histological Grade*
1	3	5	5.2	5.18	I
2	2.5	No LNs	3.52	No LNs	0
3	2	No LNs	4.57	No LNs	0
4	4.5	4.5	4.72	3.17	I
5	2	2	-	-	0
6	3	3	6.44	-	III
7	2.5	2.5	-	2.55	III
8	2.5	4	-	6.1	II
9	6	No LNs	6.5	No LNs	III
10	4.5	2	-	-	III
11	2.5	No LNs	-	No LNs	0
12	5.5	No LNs	7.1	No LNs	III

D: diameter; LN: lymph node; T/Bg: tumor-to-background; LN/Bg: lymph node-to-background; *Histopathological grade 0: *in situ*

Table 3: Tumor and lymph node uptake of ^{99m}Tc-TF and uptake sensitivity according to tumor grade and size and lymph node size in patients with head and neck cancer

Patients	Patients No.	TF uptake sensitivity (%)	P	Mean T/Bg ± SD	P
<i>In situ</i> and Grade I	4/6	66.7%		4.05 ± 0.71	
Grade II and III	3/6	50.0%	0.343	6.68 ± 0.66	0.034*
Total	7/12	75.0%		5.44 ± 1.28	
Tumor size < 3cm	2/6	33.3%		4.05 ± 0.74	
Tumor size ≥ 3cm	5/6	83.4%	0.074	5.99 ± 0.99	0.053
Total	7/12	75.0%		5.44 ± 1.28	
LN size < 3 cm	1/3	33.3%		2.55	
LN size ≥ 3 cm	3/4	75.0%	0.32	3.99 ± 1.5	0.180
Total	4/7	57.0%		4.25 ± 1.67	

LN: lymph node; T: tumor; Bg: background; TF: ^{99m}Tc-TF; *: < 0.05

Statistical analysis

Data are presented as mean (± standard deviation). Uptake of ^{99m}Tc-TF (T/Bg index) in tumors, as well as sensitivity, was correlated to tumor histological grade, and the tumor and regional lymph node size. For statistical analysis, the software “SPSS for Windows” ($P \leq 0.05$ was considered as statistically significant). Non parametric statistics was applied. The Mann-Whitney *U* test compared means and the chi-square test to compare frequencies.

RESULTS

The characteristics of the twelve patients and the tumors are summarized in [Table 1].

Among them, 4 patients had *in situ* carcinomas, 2 patients grade I carcinoma, 1 patient grade II and 5 patients grade III carcinoma. The smallest measurable tumor was 2.0 cm, and the largest 5.5 cm. Pathological enlarged lymph nodes were noted in 7 patients with sizes between 2 cm and 5 cm [Table 2].

Tomographic images showed increased tracer uptake in pathological sites (primary tumor or lymph nodes) in 9 patients, with an overall disease detection sensitivity of 75% [Figure 1]. Primary tumor was visualised in seven patients (sensitivity 58%) and infiltrated lymph nodes in 4

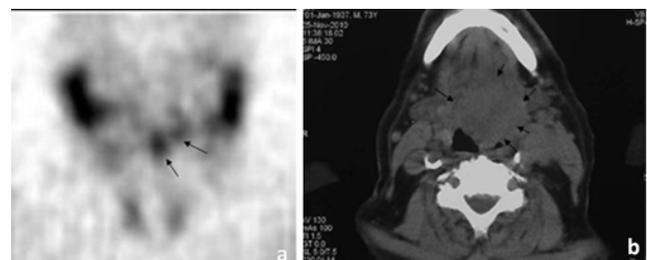


Figure 1: Patient No. 4 with base of tongue cancer: (a) SPECT coronal slice (arrows showing the ^{99m}Tc-TF uptake); (b) relevant CT slice (arrows showing the tumor)

out of 7 patients (sensitivity 57%) [Table 3]. According to histological tumor grade, 4 (66.7%) patients with *in situ* or grade I and 3 (50%) patients with grades II or III had higher ^{99m}Tc-TF tumor uptake ($P = 0.373$) than the counterparts. Scintigraphic sensitivity was lower with tumor size < 3 cm (33.3%) compared to tumor size ≥ 3 cm (83.4%) sensitivity. The statistical analysis found a trend towards a positive correlation with tumor size in radiotracer uptake, although the results did not reach statistical significance ($P = 0.079$) [Table 3]. In addition, one patient with tumor size of 4.5 cm had no uptake [Table 2]. Among the 7 patients with ^{99m}Tc-TF uptake in primary tumor, 4 patients exhibited increased ^{99m}Tc-TF uptake in the regional infiltrated lymph nodes. One of them had lymph node size < 3, while the other patients had lymph node sizes larger than 3 cm. Two of the

5 patients with no primary tumor uptake had uptake in the lymph nodes [Table 2].

Mean values for T/Bg index in all patients was 5.44 ± 1.28 for primary tumor and 4.25 ± 1.67 for lymph nodes. Statistical difference was found with histological grade, after categorizing the patients according to their grade, tumor and lymph node size. Thus, concerning histological grade, patients with tumor grades 0 or I had mean values for 4.5 ± 0.71 , whereas patients with tumor grades II or III had T/Bg indexes of 6.68 ± 0.36 . Statistically significant difference between the 2 groups was found ($P = 0.034$, Mann-Whitney U test) [Table 3]. Regarding tumor size, T/Bg index was lower in tumors < 3 cm (4.05 ± 0.74) than in tumors ≥ 3 cm (5.99 ± 0.99). After statistical analysis, there was a trend towards a positive correlation of T/Bg index with increasing tumor size ($P = 0.053$) [Table 3]. Mean values for T/Bg index of lymph nodes < 3 cm were 2.55, and in lymph nodes ≥ 3 cm, was 3.99 ± 1.5 . There was no statistical difference ($P = 0.180$), possible due to the small number of cases [Table 3]. No metastatic lesions were found on whole body images.

DISCUSSION

The study showed as sensitivity of SPECT in pathological sites (either primary tumor or regional lymph nodes) of 75%. SPECT sensitivity for only primary tumor diagnosis was 58% while for infiltrated lymph nodes it was 57%. In accordance with our findings, a previous study in 10 patients with nasopharyngeal carcinoma reported the ^{99m}Tc -TF uptake in 7 out of 10 patients (70%).^[15] Fattori *et al.*^[14] studied exclusively patients with laryngeal cancer using ^{99m}Tc -TF and reported 96% sensitivity for detecting the primary mass and 50% for lymph node involvement. Variations of sensitivities using ^{99m}Tc -TF uptake in primary cancers of the head and neck between studies may be caused by a small study sample, but it may be higher in patients with exclusively laryngeal cancer according to other trials.^[14]

In another study of 21 patients with nasopharyngeal carcinoma that evaluated ^{99m}Tc -MIBI, sensitivity was 97% and specificity 100%.^[16] A study that compared ^{99m}Tc -MIBI to ^{99m}Tc -TF in nasopharyngeal cancers found that both radiotracers detected all primary tumors, ^{99m}Tc -MIBI was superior in detecting pathological lymph nodes (sensitivity 95% vs. 79%).^[13] The same authors also reported better sensitivity for ^{99m}Tc -MIBI compared to ^{201}Tl during monitoring response to radiotherapy.^[17] Similarly, another study reported a limited role of ^{201}Tl in detection of the primary tumor with a sensitivity of 54%, specificity 75% and accuracy 57%.^[18]

In contrast, Wang *et al.*^[19] reported that ^{201}Tl was more sensitive than ^{99m}Tc -MIBI, with ^{201}Tl SPECT identifying 94% of the primary lesions in head and neck cancers with

different sites, and all of the positive and two negative lymph nodes.^[20]

Another study found a higher percentages for sensitivity (88%) and specificity (94%).^[21] Shiao *et al.*^[22] reported a 64% sensitivity for ^{99m}Tc -MIBI in primary tumor detection and 73%^[23] for tumor recurrence. Shen *et al.*^[15] reported higher specificity, but lower sensitivity for ^{99m}Tc -TF, as compared to CT. Finally, other researchers suggested that both ^{201}Tl and ^{99m}Tc -MIBI have the same accuracies in locating primary, recurrent and lymph node involvement and thus could also be valuable.^[24]

In the study, no relation of the ^{99m}Tc -TF sensitivity with the pathological grade of the tumor was observed, but there was a potential correlation of ^{99m}Tc -TF sensitivity with tumor size. Thus, it appeared to be a trend toward positive uptake with increasing tumor size, which did not reach statistical significance, probably a result of a relatively small number of cases. In contrast, ^{99m}Tc -TF result from previous studies with ^{99m}Tc -MIBI did correlated tumor size, stage, or histology and it did not affect the tracer uptake.^[25] Five patients did not have any ^{99m}Tc -TF uptake and no tumor was visualized. All but one of these tumors had a size < 3 cm and were in the pharyngeal wall, with close proximity to the tonsils and the pyriform fossa. Lower sensitivity in this area could be due to the complex anatomy and physiological uptake, which make tumor distinction more difficult. Although not verified in the present study, another possibility for negative radiotracer uptake by some tumors could be a possible molecular mechanism that pumps the radiopharmaceutical out of the tumor cells.^[26] Such mechanisms attributed to membrane multidrug resistance proteins have been associated with resistance to chemotherapy,^[27-29] and or linked to limited or no radiotracer uptake in a variety of tumors.^[30-33] if this mechanism proves to be significant in head and neck cancers, then the ^{99m}Tc -TF scintigrams may be useful in therapy planning for these patients.

Although the tumor grade was not correlated to radiotracer uptake sensitivity, it was positively correlated to T/Bg index. In another study, false-positive cases were reported when T/Bg index were ≤ 1.7 .^[13] In our study, no patient with radiotracer uptake had a T/Bg index ≤ 1.7 .

In conclusion, the study showed that ^{99m}Tc -TF SPECT had an overall sensitivity for visualization of a head and neck primary cancer site of 58%. However, sensitivity was lower for certain tumor locations than others. For example, patients with tonsillar and pyriform fossa tumors didn't have any uptake (false negative exam). Since these sites are difficult to assess, even with SPECT, the results in these locations should be interpreted with caution. Generally, SPECT should be accurate for visualization of tumors of > 3 cm in any other location. The T/Bg ratio was correlated with malignancy grade. Larger studies will help to increase the statistic power (as well as comparison with

¹⁸FDG PET/CT) to establish a role for ^{99m}Tc-TF SPECT in therapy, as well as prognosis of head and neck cancers.

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Conflicts of interest

There are no conflicts of interest.

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