Original article

Utility of ^{99m}Tc-Hynic-TOC in 131I Whole-Body Scan Negative Thyroid Cancer Patients with Elevated Serum Thyroglobulin Levels

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Abstract

Several studies have reported on the expression of somatostatin receptors (SSTRs) in patients with differentiated thyroid cancer (DTC). The aim of this study was to evaluate the imaging abilities of a recently developed Technetium-99m labeled somatostatin analog, ^{99m}Tc-Hynic-TOC, in terms of precise localization of the disease. The study population consisted of 28 patients (16 men, 12 women; age range: 39-72 years) with histologically confirmed DTC, who presented with recurrent or persistent disease as indicated by elevated serum thyroglobulin (Tg) levels after initial treatment (serum Tg > 10 ng/ml off T4 suppression for 4-6 weeks). All patients were negative on the Iodine-131 posttherapy whole-body scans. Fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) was performed in all patients. SSTR scintigraphy was true positive in 23 cases (82.1%), true negative in two cases (7.1%) and false negative in three cases (10.7%) which resulted in a sensitivity of 88.46%, specificity of 100% and an accuracy of 89.2%. Sensitivity of ^{99m}Tc-Hynic-TOC scan was higher (93.7%) for patients with advanced stages, that is stages III and IV. ^{18}F-FDG showed a sensitivity of 93.7%, a specificity of 50% and an accuracy of 89.3%. ^{18}F-FDG PET was found to be more sensitive, with lower specificity due to false positive results in 2 patients. Analysis on a lesion basis demonstrated substantial agreement between the two imaging techniques with a Cohen's kappa of 0.66. Scintigraphy with ^{99m}Tc-Hynic-TOC might be a promising tool for treatment planning; it is easy to perform and showed sufficient accuracy for localization diagnostics in thyroid cancer patients with recurrent or metastatic disease.

Keywords: Fluorodeoxyglucose positron emission tomography, Hynic-TOC, single-photon emission computed tomography, thyroglobulin elevated, thyroid cancer, whole-body scan negative

Introduction

Most of the differentiated thyroid cancer (DTC) variants have a good prognosis, with a fair chance of complete cure, good overall survival and lower chances of locoregional and distant metastases, if treated adequately.[1] Routine postradioiodine ablation surveillance and follow-up in clinical setting is by serial serum thyroglobulin (Tg) measurement, which is highly sensitive as well as specific for DTC disease burden.[2-4] This situation is, however, complicated when a raised Tg level is accompanied by a negative ^{131}I/^{123}I whole-body scan (WBS). The potential explanation being the loss of ability of the underlying malignant cells to concentrate iodine. These patients belong to a cohort who may not benefit from radioiodine therapy. Thus, other imaging modalities like Fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) or different radiotracers like ^{99m}Tc-Sestamibi or ^{99m}Tc-Tetrofosmin or ^{201}Tl need to be used for disease localization. Treatment options would also vary depending on the site and extent of recurrent/metastatic disease.[5-8]

Despite being nonspecific tumor markers, with possible mitochondrial localization, single-photon emission computed tomography (SPECT) radiopharmaceuticals

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such as ^{201}Tl, ^{99m}Tc-Sestamibi or ^{99m}Tc-Tetrofosmin have reasonable accuracy.[9-11] However, they have been replaced by ^{18}F-FDG, which localizes in recurrent or metastatic tumors due to increased glucose demand and has proven to be very sensitive method in the follow-up algorithm of thyroid cancer patients. But above mentioned SPECT - radiopharmaceuticals are more economical than ^{18}F-FDG, are easily available, can be performed on suppressive thyroxine therapy, are easy to prepare and impart lower radiation dose to the patient than ^{18}F-FDG. Utility of ^{18}F-FDG PET, however has been proven even in clinical scenarios where conventional imaging (ultrasound, computed tomography [CT], magnetic resonance imaging [MRI]) is normal.[6-13]

Utility of somatostatin receptor (SSTR) scintigraphy, which has become the gold standard for the diagnosis, staging and treatment response assessment in almost all neuroendocrine tumors,[14-18] has also been explored for various nonneuroendocrine tumors. Most of the studies reported earlier were using ^{111}In-diethylenetriaminepentaacetic acid (DTPA)-octreotide (octreoscan),[19-27] and could not clearly define the utility of this technique. In retrospect, it could be due to the inherent drawbacks of ^{111}In-isotope for imaging applications and small, nonhomogenous patient population with diverse histopathologiocal variants of DTC.[28]

In the present study, we have evaluated ^{99m}Tc-Hynic-TOC, prepared using an indigenously developed lyophilized kit,[29,30] in a clinical setting of noniodine concentrating DTC's with raised Tg levels. The advantages with this radiopharmaceutical include the use of ^{99m}Tc-isotope, which is having favorable nuclear characteristics for imaging applications when compared to ^{111}In, easy availability from ^{99}Mo/^{99m}Tc generator, ease of preparation, faster pharmacokinetics, improved background clearance, better image resolution, and lower cost.[31]

The purpose of this study was to evaluate the efficacy of ^{99m}Tc-Hynic-TOC for the detection of SSTR-positive lesions in patients who have had thyroidectomy, followed by radioiodine ablation and now presenting with raised Tg levels and negative follow-up whole-body radioiodine scans. In all patients, a correlative whole-body ^{18}F-FDG PET was also obtained to assess the tumor biology, aggressiveness and the feasibility of chemotherapy or peptide receptor radionuclide therapy (PRRT).

Materials and Methods

Patient eligibility criteria: A total of 28 patients (16 men, 12 women; age range: 39-72 years; mean age ± SD, 64.8 ± 7.6 years) with histologically confirmed DTC were included for this study.

The patients had undergone near-total thyroidectomy and immediate radioactive ablation between 4 and 12 weeks after surgery and presented with either recurrent or persistent disease as indicated by elevated Tg levels on routine follow-up (half-yearly) with negative ^{131}I WBS. None of the patients was treated with empiric oral ^{131}I following a negative low dose scan. Correlative ^{99m}Tc-Hynic-TOC scans were performed within 1-week of the ^{131}I WBS without restarting the patients on Thyroxine suppression. Raised Tg levels were confirmed on two separate occasions with or without thyroxine suppression.

Out of the 28 patients, 14 suffered from follicular carcinoma, 10 from papillary carcinoma and four from Hurthle cell carcinoma. The tumor node metastasis classification according to Union for Internationale Cancer Control,[32] edition 1997, was used to classify the primary tumor.

Initial pathologic tumor stages were as follows. T2 in 5 patients, T3 in 16 patients and T4 in 7 patients. Five patients were node negative (N0), 14 patients were node positive (N1a = 6, and N1b = 8) and 9 patients had no information concerning lymph node metastasis (Nx). Among the 28 patients, six initially had distant metastases (M1). The clinical staging represented the highest stage achieved during the patient's course and was determined according to the American Joint Committee on Cancer classification.[33] Stage I was present in 3 patients, stage II in 5 patients, stage III in 12 patients and stage IV in 8 patients. The frequency of metastatic disease was quite high in the patient group and Tg levels on T4 of far over 100 in 11 cases suggest a very advanced population that may be quite different from other groups described in the literature. Patient characteristics are summarized in Table 1. The study was approved by the local ethical committee and was performed in accordance with the declaration of Helsinki. All patients gave their written informed consent to participation.

Pretreatment evaluation and posttherapy scanning

Because of increasing serum Tg levels during thyroid stimulating hormone (TSH) suppression, patients were referred to our department for administration of high-dose radioiodine therapy under TSH stimulation. All patients had the scan after 4-6 weeks of L-thyroxine withdrawal. X-ray of the chest and ultrasound of the neck were regularly performed in all patients. CT of the chest (without contrast medium) was also obtained in all patients. Five patients had received a single sitting of high-dose Iodine-131 therapy, six patients had two sittings, 12 patients had three sittings, and five patients had four sittings of Iodine-131 therapy. WBSs were obtained with a double-headed camera (Siemens

Table 1: Patient characteristics and results in the patients without detectable pathology prior to ^{99m}Tc-Hynic TOC

Sex/age	Histology	TNM stage	Stage	TSH on T_4 (mU/l)	Tg on T_4 (ng/ml)	Tg-Ab	Findings	^{99m}Tc-TOC	^{18}F-FDG	Confirmation
Male/46	Follicular	pT3N0Mx	III	0.005	302	Negative	Lung, bone	TP	TP	CT
Female/54	Papillary	pT3aNxMx	III	0.02	16.8	Negative	Mediastinum	TP	TP	Biopsy
Male/39	Papillary	pT2NxMx	I	0.05	12	Negative	Lymph node	TP	FP	US, surgery
Female/48	Follicular	pT2NxMx	II	0.03	672	Negative	Lung	TP	TP	CT, biopsy
Female/54	Follicular	pT2NxMx	II	0.1	283.3	Negative	Mediastinum	TP	TP	Biopsy
Male/52	Hurthle	pT4N1bMx	IVa	0.01	8	Negative	Mediastinum	TP	TP	Biopsy
Female/42	Follicular	pT3N0Mx	I	0.02	37	Negative	Lung, brain	FN	FN	CT
Female/45	Papillary	pT3NxMx	I	0.003	26	Negative	Local recurrence	TP	TP	US, surgery
Female/44	Hurthle	pT2NxMx	I	0.02	106	Negative	Mediastinum	TP	TP	Surgery
Male/57	Papillary	pT4N1bMx	IVa	0.6	650	Negative	Lymph node	TP	TP	US, surgery
Male/56	Papillary	pT3N0M0	III	<0.05	62	Negative	Lymph node	TP	TP	US, surgery
Female/61	Follicular	pT3N1aM0	III	<0.1	6	Negative	Lymph node	TP	TP	US, surgery
Male/72	Follicular	pT3N0M0	III	0.2	322.4	Negative	Lung, mediastinum	TP	TP	CT
Male/67	Papillary	pT4N0M0	IVa	<0.5	10.2	Negative	Local recurrence	TP	TP	Surgery
Male/62	Follicular	pT3N0M0	III	0.002	602	Negative	Bone	TP	TP	MRI
Female/47	Follicular	pT4N0M0	IVa	0.005	9.4	Negative	No	TN	TN	15-month FU
Male/50	Papillary	pT4N1bMx	IVc	0.001	611.5	Negative	Local recurrence	TP	TP	12-month FU
Male/58	Follicular	pT3N0M0	III	<0.1	62.8	Negative	Lung	TP	TP	CT
Female/61	Follicular	pT4N0M0	IVc	<0.05	424.8	Negative	Local recurrence, bone	TP	TP	Surgery
Male/66	Papillary	pT2N1aMx	III	<0.1	87	Negative	Lymph nodes	FN	FP	13-month FU
Male/42	Hurthle	pT3NxMx	I	0.5	7	Negative	Local recurrence, lymph node	TP	TP	Biopsy
						Negative				
Female/62	Follicular	pT3NxMx	III	<0.1	13.2	Negative	No	TN	TN	15-month FU
Male/51	Papillary	pT3N1bMx	IVa	0.2	1102	Negative	Lymph node, Bone	TP	TP	US, surgery
Female/40	Follicular	pT3N0Mx	I	0.01	74	Negative	Lung	TP	TP	CT, FNAC
Male/43	Hurthle	pT4N1bMx	I	0.02	14	Negative	Local recurrence	TP	TP	US, surgery
Female/64	Follicular	pT3NxMx	III	0.005	226	Negative	Lung, mediastinum	TP	TP	CT
Male/59	Follicular	pT3NxMx	III	0.01	29	Negative	Lymph node	TP	TP	US, surgery
Male/60	Papillary	pT3N0Mx	III	0.1	8	Negative	Local recurrence	FN	TP	Surgery

TNM stage: Initial tumor stage; Stage: Highest tumor stage in the course of disease; Findings: All malignant involved tissue sites; FU: Follow-up; T4: Thyroxine; TP: True positive; TN: True negative; FP: False positive; FN: False negative; TNM: Tumor node metastasis; TSH: Thyroid-stimulating hormone; Tg: Thyroglobulin; Tg-Ab: Thyroglobulin antibodies; ^{18}F-FDG: Fluorine-18 fluorodeoxyglucose; CT: Computed tomography; FNAC: Fine-needle aspiration cytology; TOC: ^{99m}Tc-Hynic TOC

Symbia-T with high-energy collimator), 1 or 2 days after the oral administration of ^{131}I (1.5-3 mCi). WBS results were negative in all patients.

Radiopharmaceutical preparation

Lyophilized Hynic-TOC kit vials were obtained as a gift from Radiopharmaceuticals Division, Bhabha Atomic Research Centre, Mumbai. Detailed procedure for the preparation lyophilized Hynic-TOC kit will be reported elsewhere.[34] Each lyophilized kit vial contains Hynic-TOC (30 ug), EDDA (10 mg), tricine (20 mg), sodium phosphate dibasic heptahydrate (4.5 mg), sodium phosphate monobasic (1 mg) and stannous chloride dehydrate (40 ug). The lyophilized kits were subjected to thorough quality control checks, including bacterial endotoxin test and sterility test, at the manufacturer's end before releasing for clinical use.

The radiolabeling procedure was performed under aseptic conditions. ^{99m}Tc-Hynic-TOC was prepared by adding 10-60 mCi (370-2220 MBq) of freshly eluted sterile ^{99m}Tc-sodium pertechnetate in 1-3 ml of sterile saline, obtained from ^{99}Mo/^{99m}Tc alumina column generator (Radioisotope Center POLATOM), into the kit vial and heating the vial in boiling water bath for 20 min.

The radiochemical purity of ^{99m}Tc-Hynic-TOC determined by standard quality control procedure was between 92% and 98%, with the free pertechnetate content in the range of 2.93-1.54%.

Imaging protocols

About 740 MBq - 925 MBq (20-25 mCi) of ^{99m}Tc-Hynic-TOC was administered in each patient which corresponded to ~10 ug of Hynic-TOC. First image was acquired ~1.5 h postinjection. In select cases, when there was difficulty in the evaluation of the abdominal region due to the elimination of the radiopharmaceutical via the gastrointestinal tract, a second image was acquired after waiting for another 2 h. A WBS as well as SPECT of the region where the tumor was located (e.g. head, neck, thorax, abdomen, pelvis) was also acquired. No contrast agent was used. The whole-body images were acquired at a table speed of 8 cm/min in a dual-headed

gamma camera (Siemens Symbia T equipped with an LEHR collimator, with energy peak of 140 KeV ± 15% window level).

In the SPECT/CT system, the CT acquisition was performed with a slice thickness of 4 mm and a pitch of one on a helical dual-slice CT unit. Images were acquired using a matrix of 512 × 512 pixels and a pixel size of 1 mm. SPECT data were acquired using a matrix of 128 × 128 pixels and a slice thickness of 1.5 mm. CT-based attenuation correction of the emission images was used. SPECT images were reconstructed by iterative method ordered subset expectation maximization (OSEM) (two iterations and eight subsets).

Fluorine-18 fluorodeoxyglucose positron emission tomography

All patients received 370 MBq (10 mCi) ^{18}F-FDG after a fasting period of 5-12 h while they are off thyroxine therapy. Trans axial imaging was performed using a PET-CT scanner (Siemens Biograph 6, Germany) at 45 and 90 min after intravenous injection of the tracer. The emission scan was acquired from the head to upper legs with five to six bed positions (4 min/bed position). Iterative image reconstruction was performed with an OSEM algorithm (two iterations, 28 subsets). Abdominal, chest and head CT-scanning was performed with 3-mm contiguous sections using a 512 × 512 matrix, without infusion of contrast medium.

Image and data analysis

The images obtained were interpreted by two nuclear medicine physicians (AS., KK.) blinded to the results of conventional or PET/CT examinations. Any focal tracer accumulation exceeding normal regional tracer uptake was rated as a pathological finding (tumor uptake). In relevant areas, SPECT images were available to the physicians. All data were analyzed on a SIEMENS SYMBIA system. In both groups, readers of the scans were blinded to the underlying pathology and to the results of the standard staging procedures, including PET data. All images were visually evaluated and abnormal scintigraphic findings were classified according to the sites typical for recurrences or metastases (local recurrence, lymph node of the neck, mediastinum, lungs and bone structures) and other sites. The reference standard against which the results of the ^{99m}Tc-Hynic-TOC procedure were measured was based on the results of all of the imaging procedures which include serial follow-up, morphological imaging and histopathology of surgical specimens or biopsy (12 patients). All patients underwent ultrasound of the neck and imaging with CT and MRI (n = 2). ^{18}F-FDG PET was performed in all patients. The time interval between ^{99m}Tc-Hynic-TOC scintigraphy and ^{18}F-FDG PET did not exceed 2 weeks and both techniques were prospectively compared. The viewers of the studies were blinded to findings of other methods.

Thyroglobulin measurement

Blood samples for measuring serum Tg were taken during suppression therapy as well as prior to scintigraphy off - Thyroxine therapy. The Tg levels were determined in duplicate by a sensitive, commercially available radio-immunoassay.

Statistical analysis

^{99m}Tc-Hynic-TOC images were classified as true positive (TP), true negative (TN), false positive (FP) or false negative (FN) comparing with the gold standard (histopathology or other imaging techniques), as described above. The Chi-square test for independence, or the Fisher exact test when appropriate, was used to evaluate differences in lesion-detectability with ^{99m}Tc-Hynic-TOC when subgroups of the patients being investigated were statistically compared. All $P < 0.05$ were considered to be statistically significant. The McNemar test of correlated properties was used to assess the statistical significance of the difference between the scintigraphic results of ^{99m}Tc-Hynic-TOC and ^{18}F-FDG PET. Analysis was performed both on a lesion and a patient basis. Two-sided $P < 0.05$ were considered as significant. Statistical analysis was carried out with SPSS software (Statistical Package for Social Sciences).

Results

Table 1 summarizes the clinical information of each patient. Among the 28 cases, SSTR scintigraphy was TP in 23 (82.1%), TN in 2 (7.1%) and FN in 3 (10.7%) cases. No FP results were observed. Overall, the sensitivity of ^{99m}Tc-Hynic-TOC for identification of thyroid cancer was 88.46% (95% CI 69.82-97.42) on a patient basis, with a specificity of 100% and an accuracy of 89.2%. Sensitivity of ^{99m}Tc-Hynic-TOC scan was higher (93.75%) for (n = 17) with advanced stages, that is stages III and IV, than for stage I and II (n = 11) disease, in which sensitivity was 80%. These findings are summarized in Table 2.

Site-related findings are listed in Table 3. When ^{99m}Tc-Hynic-TOC was correlated with other imaging

Table 2: ^{99m}Tc-Hynic TOC results in early versus late stages

Parameter	Stage I and II	Stage III and IV
Sensitivity %	80.00	93.75
Specificity %	100.00	100.00
Positive predictive value %	100.00	100.00
Negative predictive value %	33.30	50.00
Negative likelihood ratio	0.2	0.06

TOC: ^{99m}Tc-Hynic TOC

Table 3: Scintigraphic findings: Analysis per lesion

	Local recurrence	Neck (lymph node)	Mediastinum	Lung	Bone	Overall
^{99m}Tc-Hynic TOC+	6	14	12	48	21	101
^{99m}Tc-TOC	1	3	2	8	3	17
Number of lesions	7	17	14	56	24	118

TOC: ^{99m}Tc-Hynic TOC

modalities or histopathology for analysis on a lesion basis, 101 tumor foci were localized in 23 patients, affecting the following five tissues: Local recurrence (n = 6 patients), lymph node metastases in the neck (n = 14), mediastinum (n = 12), pulmonary metastases (n = 48) and bone (n = 21). In addition to pulmonary metastasis and local tumor recurrence as assessed by biopsy, ^{99m}Tc-Hynic-TOC identified a solitary brain metastasis in one patient. These findings are summarized in Table 4.

^{99m}Tc-Hynic-TOC and thyroglobulin evaluation

Patients were categorized into two groups in order to evaluate the influence of the current Tg level on lesion-detectability with ^{99m}Tc-Hynic-TOC. First group had initial serum Tg levels of <30 ng/ml (n = 12) and with the second group had the initial serum Tg levels of >30 ng/ml (n = 16). In the group with elevated Tg levels (>30 ng/ml) (n = 16), the scan result was true positive in 15 cases and FN in 1. In the 12 patients with Tg levels lower than 30 ng/ml, scanning was negative in four patients, which include three TN and 1 FNs. Eight cases were true positive.

The fraction of true positive ^{99m}Tc-Hynic-TOC uptake in lesions was positively correlated with elevated Tg levels (>30 ng/ml), showing a significant difference (P < 0.01). The lowest Tg level with unequivocal positive ^{99m}Tc-Hynic-TOC findings was 6.7 ng/ml (in whom lymph node involvement was revealed), and the highest Tg level with FN ^{99m}Tc-Hynic-TOC scintigraphy was 137 ng/ml. This patient presented with multiple pulmonary metastases, all of which were smaller than 1 cm.

Comparison of results between ^{99m}Tc-Hynic-TOC and ^{18}F-FDG PET are given in Table 3. In five cases (17.8%), ^{99m}Tc-Hynic-TOC scintigraphy was negative, while ^{18}F-FDG PET was negative in three cases (10.7%). In two of the five patients with negative ^{99m}Tc-Hynic-TOC scans, further clinical examinations did not reveal any pathological findings and serum Tg levels remained stable for at least 1-year. These cases were considered TN. 26 of the 28 patients (92.8%) were proven to have disease, which confirms the advanced nature of our patient group. False negative ^{99m}Tc-Hynic-TOC scan were obtained in three cases (10.7%) while a single FN scan (3.5%) was observed with ^{18}F-FDG PET in a patient with lung and cerebral metastases. Per patient analysis comparing the scan results of ^{99m}Tc-Hynic-TOC and ^{18}F-FDG showed no significant difference between PET and ^{99m}Tc-Hynic-TOC imaging (P = 0.6) using the McNemar test. Illustrative examples of HYNIC TOC and FDG PET CT scans in patients presenting with thyroid bed recurrence, cervical node, lung , mediastinal and skeletal metastases are shown in Figures 1- 4.

Table 4: ^{99m}Tc-Hynic TOC and ^{18}F-FDG results

Parameter	^{99m}Tc-TOC %	^{18}F-FDG %
Sensitivity	88.46	95.80
Specificity	100.00	50
Accuracy	89.20	89.20
Positive predictive value	100.00	92.00
Negative predictive value	40.00	66.70
Positive likelihood ratio	-	1.9
Negative likelihood ratio	0.12	0.08

^{18}F-FDG: Fluorine-18 fluorodeoxyglucose; TOC: ^{99m}Tc-Hynic TOC

In addition, a site-specific evaluation was performed. Tissue-related abnormal uptake is reported in Table 2. Analysis on a lesion-by-lesion basis also emphasized substantial agreement between the imaging techniques.

Twelve patients were referred for receptor-mediated radionuclide therapy using ^{177}Lu-DOTA TATE or ^{90}Y-DOTA TATE, or a cocktail therapy with both, based on the uptake observed with ^{99m}Tc-Hynic-TOC radiopharmaceutical found in tumor lesions. All patients had extended disease with more than one affected tissue site. Each of them responded under this therapy regimen and stable disease was achieved for at least 6 months in all patients. Each patient was well informed about this new treatment option, and the therapy was well-tolerated.

Discussion

In DTC patients, imaging with ^{111}In-DTPA-Octreotide has demonstrated high uptake in some cases, but the reported sensitivities vary significantly among different studies.[28] This study was specifically designed to evaluate the clinical potential of ^{99m}Tc-Hynic-TOC for tumor localization in WBS negative DTC patients with elevated Tg levels under TSH stimulation.[31]

Our results demonstrate reasonably accurate and favorable imaging ability of this new tracer in DTC

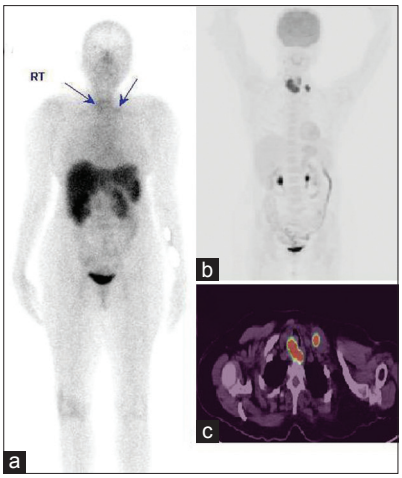

Figure 1: Whole-body Hynic-TOC anterior image (a) showing moderate uptake in the recurrence in the thyroid bed and cervical nodes, whole-body fluorodeoxyglucose-positron emission tomography/computed tomography (CT) maximum intensity projection image (b) intense uptake in the right neck nodes. Fused Hynic-TOC single-photon emission computed tomography/CT (c) uptake in the right level II cervical nodes and thyroid bed

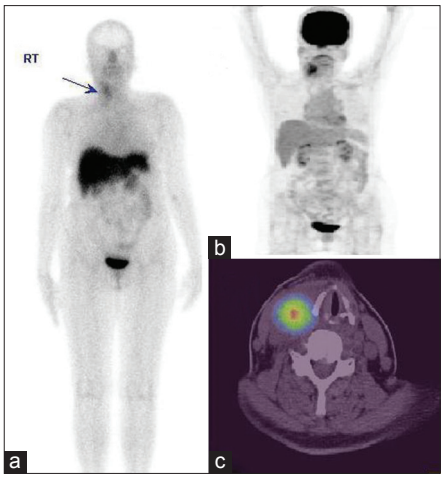

Figure 2: Whole-body Hynic-TOC anterior image (a) showing moderate uptake in the right cervical node, whole-body fluorodeoxyglucose-positron emission tomography/computed tomography (CT) maximum intensity projection image (b) intense uptake in the right neck nodes and Fused Hynic-TOC single-photon emission computed tomography/CT(c) uptake in the right level II cervical nodes

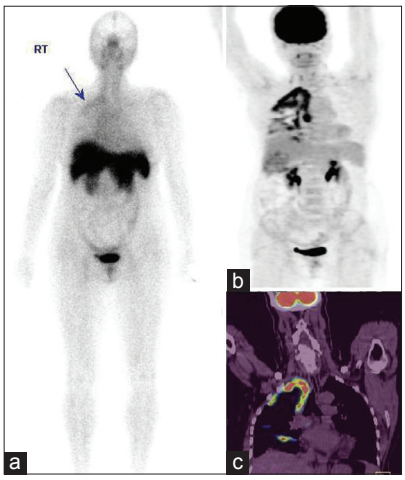

Figure 3: Whole-body Hynic-TOC anterior image (a) showing mild uptake in the right pleural thickening, whole-body fluorodeoxyglucose-positron emission tomography/computed tomography (CT) maximum intensity projection image (b) intense uptake in the right pleural thickening and Fused Hynic-TOC single-photon emission computed tomography/CT (c) uptake in the right pleural thickening

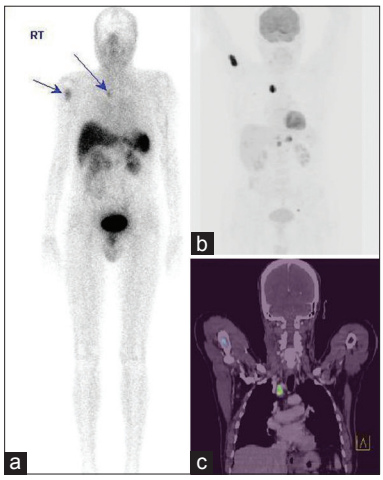

Figure 4: Whole-body Hynic-TOC anterior image (a) showing uptake in the right humerus and mediastinal nodes. Whole-body FDG PET/CT maximum intensity projection image (b) intense uptake in the right humerus, lung nodules, mediastinal, abdominal and aortocaval lymph nodes and fused Hynic-TOC single-photon emission computed tomography/CT (c) uptake in the shaft of right humerus and mediastinal nodes

patients with an overall sensitivity comparable and specificity higher than ^{18}F-FDG PET. The results obtained indicate that, with time, lesions that lose their ability to concentrate iodine have a higher glucose uptake rate, at the same time a significant percentage of such lesions still retain their ability to express SSTR. In comparison to similar studies, the overall sensitivity of ^{99m}Tc-Hynic-TOC in our study is better than previously reported with ^{111}In-DTPA-Octreotide as well as with the same agent (19, 20, 23, 25-27). This favorable result could be due to the fact that imaging was carried out at the time of TSH stimulation. It was also shown that there was a higher probability for a positive scan result in patients with higher Tg levels exceeding 30 ng/ml, which might be mainly attributed to the tumor load.

Another interesting finding is that ^{18}F-FDG PET outperformed ^{99m}Tc-Hynic-TOC tracer in detecting lesions, especially smaller than 1 cm in size, and more so in the case of pulmonary metastases. These patients had a very high Tg level and tumor load, but no SSTR uptake, which could be due to a higher state of de-differentiation resulting in high-grade ^{18}F-FDG uptake. Another possible explanation is the higher spatial resolution of PET. Thus,

^{99m}Tc-Hynic-TOC and ^{18}F-FDG PET have completely different mechanisms of localization and could be considered complimentary in assessing the tumor biology and aggressiveness. This potentially explains the findings in patients in whom ^{18}F-FDG PET picked up lesions not demonstrated on ^{99m}Tc-Hynic-TOC.[35]

In the present study, though the statistical diagnostic efficacy was higher for ^{18}F-FDG PET than for ^{99m}Tc-Hynic-TOC, there were two FP findings with the former, which were negative on ^{99m}Tc-Hynic-TOC. Findings were comparable with a substantial overlap in the lesions detected by each modality, which implies a high degree of agreement between the metabolic pattern and the SSTR status in noniodine-avid lesions.

From a practical and clinical point of view, both techniques can easily be performed without withdrawal of L-thyroxine. Although there is no evidence that serum TSH levels influence the rate of SSTR expression, higher glucose consumption in tumor foci can be observed under TSH stimulation, which could improve the accuracy of ^{18}F-FDG PET.[36,37] As a corollary, a higher sensitivity of ^{99m}Tc-Hynic-TOC scans reported in our series could also be due to increased SSTR expression under TSH stimulation, though it has not been verified or reported. It is important to note that ^{99m}Tc-Hynic-TOC scans will not replace ^{18}F-FDG PET as the primary imaging modality in this clinical scenario due to less signal to background ratios, less resolution, as well as lack of widespread radio-pharmaceutical availability. Thus ^{99m}Tc-Hynic-TOC shall remain a significant option only in countries with no easy access to PET CT scanners or when ^{18}F-FDG PET scanning is negative. SSTR imaging could have a higher clinical impact with the added ability to plan for PRRT or cold somatostatin therapy.

Use of a long-acting Octreotide analogue in patients with metastatic thyroid cancer that exhibited SSTR s have been tried and seem promising.[38,39] High expression of SSTRs in thyroid carcinoma lesions also offers another treatment option using PRRT, e.g. ^{177}Lu or ^{90}Y based SSTR analogues.[40] We have treated 12 patients with advanced tumor stage who had a very high tumor load. These patients showed good SSTR expression in the lesions on ^{99m}Tc-Hynic-TOC.Thus, ^{99m}Tc-Hynic-TOC can aid in identifying patient suitable for both types of therapy in different clinical scenarios.

Conclusion

Somatostatin receptor imaging using ^{99m}Tc-Hynic-TOC demonstrates promise as a cost effective, easy to perform and widely available imaging tool in DTC patients with elevated Tg levels and negative WBS. With ongoing research into the utility of somatostatin analogs and PRRT in palliative therapy, SSTR imaging is likely to play a significant role in clinical decision making. The impact of ^{99m}Tc-Hynic-TOC would be higher in developing countries with many centers having no PET/CT facility and when budgetary constraints dictate the type of imaging algorithm followed.

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