# Diagnostic value of [$^{99m}$Tc]Tc-HYNIC-TOC scintigraphy in the management of differentiated thyroid cancer with elevated thyroglobulin and negative radioiodine whole-body scan

Original Article

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## ABSTRACT

**Introduction:** Negative radioiodine ($^{131}$I) whole-body scan with elevated serum thyroglobulin (Tg) level are found in 20% of patients with differentiated thyroid cancer (DTC), which can be a diagnostic challenge. We evaluated the efficacy of Technetium-99m-Hydrazinonicotinyl-Tyr3-Octreotide ([$^{99m}$Tc]Tc-HYNIC-TOC) somatostatin receptor scintigraphy (SRS) for detection of non-iodine-avid metastases and its impact on staging and management of these patients.

**Methods:** The study population consisted of 35 DTC patients (25 females; PTC = 88.2%, FTC = 11.8%) who had elevated serum Tg levels despite negative post-ablation radioiodine whole-body scan. All patients underwent whole body SRS 3-4 hours after intravenous injection of 20mCi (740 MBq) of [$^{99m}$Tc]Tc-HYNIC-TOC. Sites of suspected radiotracer accumulation were confirmed with anatomic imaging. Ultimately, corresponding changes in the staging and management were recorded.

**Results:** SRS was positive in 27 (77.1%) cases. Patients with positive scan had significantly higher Tg levels at the time of scan, compared to those with negative scans (154.5±188.6 vs. 28.2±32.7 ng/mL, p-value = 0.005). Interestingly, previous history of neck external beam radiation therapy (EBRT) was significantly correlated with [$^{99m}$Tc]Tc-HYNIC-TOC avidity (Likelihood ratio = 11.2, p = 0.005). Addition of SSTR scintigraphy changed overall staging and management in 11% and 32.4% of the patients, respectively.

**Conclusion:** SRS can be a useful diagnostic adjunct in DTC patients with highly elevated Tg and negative radioiodine whole-body scan. The likelihood of positive findings on [$^{99m}$Tc]Tc-HYNIC-TOC was higher in cases with previous history of EBRT or high Tg levels (i.e. suppressed-Tg >80 ng/mL) at the time of scan.

**Key words:** [$^{99m}$Tc]Tc-HYNIC-TOC; Somatostatin receptor scintigraphy; Differentiated thyroid carcinoma; TENIS syndrome

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## INTRODUCTION

Thyroid carcinoma is the common endocrine malignancy [1]. The majority of cases of thyroid cancers can be categorized into papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC). These histological categories are collectively known as differentiated thyroid cancers (DTC) [2].

Considering the nature of DTCs as well as the available treatment options, recurrence and distant metastases happen in only a small fraction of cases. The 10-year survival of DTCs are >90% with an increasing trend in the survival rate in the last decade [3]. However, after 10 years, local recurrence and distant metastases might happen for about 20% and 10% of patients, respectively. There are various therapeutic methods for these patients including radioiodine (RAI), external beam radiotherapy (EBRT), and metastasectomy [4]. However, one-third of these cases achieve a complete response and two-thirds of the patients will become RAI-refractory, with a reduced overall prognosis [5]. Another scenario that might arise during management of thyroid cancer is lack of RAI uptake in up to 30% of the cases [6-8]. These cases may manifest with clinical, laboratory, or radiological evidence of disease progression. Serum thyroglobulin (Tg) levels are usually detectable and elevated in these cases. This situation is known as thyroglobulin elevated negative iodine scintigraphy (TENIS) syndrome which results in biochemical signs of recurrent or persistent thyroid cancer associated with high Tg amounts without any apparent disease to treat with radioiodine ($^{131}$I) [9-10]. To detect these patients, $^{18}$F-Fluoro-deoxyglucose ([$^{18}$F]FDG) PET/CT is the commonly used imaging modality. [$^{18}$F]FDG PET/CT is the main imaging modality for evaluation of patients with TENIS syndrome [11]. Unlike RAI, [$^{18}$F]FDG uptake can show more aggressive disease with acceptable, if not excellent, accuracy [11-14]. However, its utility is hampered by high costs [15, 16].

A promising substitute can be somatostatin receptor scintigraphy (SRS). Somatostatin receptors (SSTR) are surface cell G-proteins expressed in various malignancies with a role in regulation of cell proliferation. Utilizing radiolabeled somatostatin analogs can disclose SSTRs on tumor cells and therefore might be helpful in peptide receptor radionuclide therapy and molecular imaging [11, 17]. One such peptide with a high affinity for SSTRs is $^{99m}$Tc-Hydrazinonicotinyl-Tyr3-Octreotide ([$^{99m}$Tc]Tc-HYNIC-TOC) which is considered an economical and logistically practical element for scintigraphy of neuroendocrine tumors with excessive expression of SSTR that permits high quality and more rapid whole body imaging [18]. Since DTC tumors express SSTRs on their cell walls, [$^{99m}$Tc]Tc-HYNIC-TOC can be an auxiliary and complementary diagnostic method in DTC patients with TENIS syndrome [19]. Therefore, in the current study, we aimed to determine the diagnostic value of [$^{99m}$Tc]Tc-HYNIC-TOC in patients with TENIS syndrome.

## METHODS

This study was conducted in the nuclear medicine department at Ghaem hospital of Mashhad, Iran from 2016 to 2020. The study population consisted of 35 patients with TENIS subtype of DTC previously undergone thyroidectomy and received at least two doses of radioiodine with high Tg levels and negative radioiodine whole-body scan. The negative radioiodine whole-body scan was defined as the absence of an abnormal uptake in whole body iodine scan, either in the neck region or other body parts. Tg levels were measured using radioimmunoassay kits (Medipan Inc.). High stimulated Tg levels were defined as >10 ng/mL (off-levothyroxine) or >5 ng/mL (rhTSH protocol).

After explaining the benefits and logistics of performing [$^{99m}$Tc]Tc-HYNIC-TOC scan for the patients, they were referred to the nuclear medicine center for whole body and single photon emission tomography acquisition. The [$^{99m}$Tc]Tc-HYNIC-TOC kit was purchased from Pars Isotope company. The kits were labeled with 20 mCi (740 MBq) of pertechnetate milked from a $^{99m}$Mo/$^{99m}$Tc generator in a pyrogen-free manner according to the manufacturer's protocol. Quality control and verification of the radiochemical purity of >90% was performed using an instant thin layer chromatographic system. After intravenous injection of the radiotracer, adverse reactions were monitored and recorded.

Each imaging session consisted of whole-body scanning at 2 and 4 hours after radiopharmaceutical injection from the anteroposterior views (12 cm/min per bed position, matrix size of 256 × 1024 pixels) and SPECT images (64 projections, 20 sec/frame) from the neck and chest at 4 hours after injection. The intensity of SSTR uptake was assessed as described previously [20]. Briefly, each scan was scored as 0 (no uptake), 1 (very low, equal to the mediastinal uptake), 2 (≤ liver uptake), 3 (< splenic uptake), and 4 (> splenic uptake) by two nuclear medicine experts. In cases of discrepant results, consensus was made. Foci with suspicious uptake were correlated with anatomic imaging and/or biopsy if needed. We considered the possibility of false positive results due to EBRT-induced inflammation in reporting the scan findings and also performed whole body scanning at least 8 months after the completion of radiation therapy. We considered Krenning score 1 as an abnormal scan threshold, after ruling out the possible inflammatory processes or other false positive etiologies like contamination, artifacts, etc.

## Ethics approval and consent to participate

Prior to enrollment in the study and after providing a complete explanation of the study, written consent was obtained from all patients. They were assured of a fully voluntary participation in the study, of confidentiality during the study period and of anonymity. This research was approved by the Ethics Committee of Mashhad University of Medical Sciences under the code of ethics of IR.MUMS.fm.REC.1396.04.

# RESULTS

## Patients' demographic data

The present study evaluated 35 DTC patients (25 females) with TENIS syndrome. The mean age of the patients was 55.2±15.5 years (range: 25-78 years).

## Patient's cancer-related data

88.6% of the subjects were suffering from PTC and 11.4% from FTC. Most of the patients were in stage I or IV of the disease (34.3% for each). Majority of the cases were $T_{3a}$ (25.7%), $N_{1b}$ (71.4%), and $M_0$ (65.7%) according to the eighth version of TNM staging (Table 1). First serum Tg and first anti-Tg Ab levels were 342.5 ± 616.6 and 123.6±257.2 ng/mL, respectively (Table 2).

**Table 1:** TNM staging of the patients enrolled in the study (n=35).

| Category/Stage | | No. (%) |
|---|---|---|
| T-category | $T_{1a}$ | 7 (20.0) |
| | $T_{1b}$ | 3 (8.6) |
| | $T_2$ | 7 (20.0) |
| | $T_{3a}$ | 9 (25.7) |
| | $T_{3b}$ | 2 (5.7) |
| | $T_{4a}$ | 4 (11.4) |
| | $T_{4b}$ | 4 (11.4) |
| | $T_x$ | 1 (2.9) |
| N-category | $N_{0a}$ | 3 (8.6) |
| | $N_{0b}$ | 2 (5.8) |
| | $N_{1a}$ | 5 (14.3) |
| | $N_{1b}$ | 25 (71.4) |
| M-category | $M_0$ | 23 (65.7) |
| | $M_1$ | 12 (34.3) |
| Overall staging (before somatostatin receptor scintigraphy) | I | 12 (34.3) |
| | II | 6 (17.1) |
| | III | 5 (14.3) |
| | IV | 12 (34.3) |

**Table 2:** Pertinent laboratory and SSRT data of the patients enrolled in the study (n=35).

| Characteristics | Mean ± SD |
|---|---|
| Cumulative dose until octreotide scan (mCi) | 343.2 ± 198.1 |
| Time passed until loss of iodine uptake (years) [a] | 3.2 ± 2.3 |
| fTg (ng/mL) | 342.5 ± 616.6 |
| f-anti-Tg (ng/mL) | 123.6 ± 257.2 |
| Tg at the time of SSTR scintigraphy (ng/mL) | 154.0 ± 191.2 |
| anti-Tg at the time of SSTR scintigraphy (ng/mL) | 243.2 ± 714.1 |

f-anti-Tg: first anti-thyroglobulin antibody; fTg: first thyroglobulin; Tg: thyroglobulin; SSRT: somatostatin receptor
[a]Assessed as interval from first radioiodine treatment to the first negative radioiodine whole body scan

**Table 3:** Summary of the data of SSTR imaging and its comparison with anatomical findings (n=35).

| Characteristics | No. (%) |
|---|---|
| Management change after octreotide scan | 11 (31.4) |
| Changing the disease stage after octreotide scan | 4 (11.4) |
| Anatomic vs. SSTR imaging: | 33 of 35 (94.3) [a] |
| Octreotide = Anatomic | 14 (42.4) |
| Octreotide < Anatomic | 8 (24.2) |
| Octreotide > Anatomic | 6 (18.2) |
| Completely discordant | 1 (3) |
| Partially discordant | 4 (12.1) |

SSTR: somatostatin receptor
[a]Anatomic data was not available for two patients. Valid percent is mentioned for the next rows.

## Patients' iodine status

Of those treated with RAI (34 of 35), one-year response assessment after first RAI therapy was available for 33/34 patients. According to the ATA definitions, 3.0%, 51.5%, and 45.5% of these patients showed excellent, biochemical incomplete and structural incomplete, respectively [4]. The initial iodine dose was 30 mCi (1.11 GBq) in 20.0%, 150 mCi (5.55 GBq) in 71.4%, and 200 mCi (7.4 GBq) in 5.7 % of subjects of which, post-treatment radioiodine whole-body scan show RAI-avid areas in 31 (91.2%) of the patients.

The cumulative dose of RAI until negative radioiodine whole-body scan was 343.2 ± 198.1 mCi (12.7 GBq ± 7.3 GBq). The loss of RAI uptake occurred 3.2 ± 2.3 years after first RAI dose. Both Tg and anti-Tg values remained high despite being evaluated in on-levothyroxine status (Table 2). Neck external beam radiation therapy (EBRT) had been performed in 42.9% of the cases. Patients with history of EBRT were more likely to have positive SRS (Likelihood ratio = 11.2, p = 0.005).

## Patients' anatomical imaging data

The [$^{99m}$Tc]Tc-HYNIC-TOC scan findings were correlated with neck ultrasound, chest CT scan, brain MRI, RAI SPECT/CT, and CXR in 94.3%, 51.4%, 8.6%, 2.9%, and 8.6% of patients, respectively, considering the location of abnormal uptake. The mentioned anatomical imaging found the abnormal site of uptake in 54.3% of the patients.

## The findings of SSTR imaging

SSTR imaging was positive in 77.1% of the patients (score 1, 2, and 3 in 9/35, 16/35 and 2/35, respectively). The scan findings changed the patient's management in 31.4% and altered the disease stage in 11.4% of the patients. Of 33 patients with available both anatomic and SRS data, 28 (84.8%) showed concordant results (Table 3). No adverse reaction related to SSTR imaging was observed. Figure 1 shows the whole body and SPECT images of one of our patients.

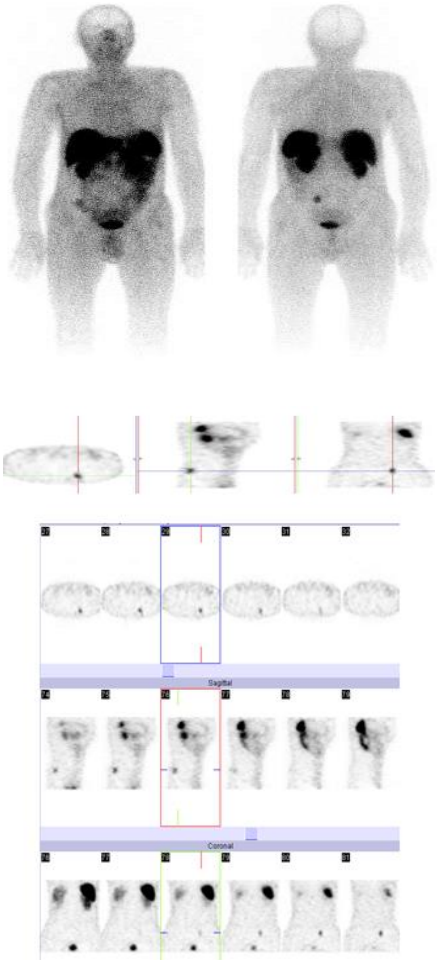

**Fig 1.** A 78 years old male with history of papillary thyroid cancer with elevated thyroglobulin (Tg=199) and negative iodine scan. Whole Body [$^{99m}$Tc]Tc-HYNIC-TOC scan (above) and SPECT images (below) showed a zone of increased tracer uptake in the right sacroiliac region.

### Optimal Tg cutoff for prediction of SRS positivity

The ROC curves were drawn for first Tg (fTg) and Tg at the time of SRS to predict the positive results of the imaging. The area under the curves were 0.685 and 0.643 for Tg at the time of SRS and fTg, respectively (Figure 2A and 2B, respectively). fTg values >140 ng/mL and Tg values at the time of SRS >80 ng/mL were predictive of positive results (i.e. Krenning score ≥1) with sensitivity of 50%, and 47.6% and specificity of 85.7%, 93%, respectively.

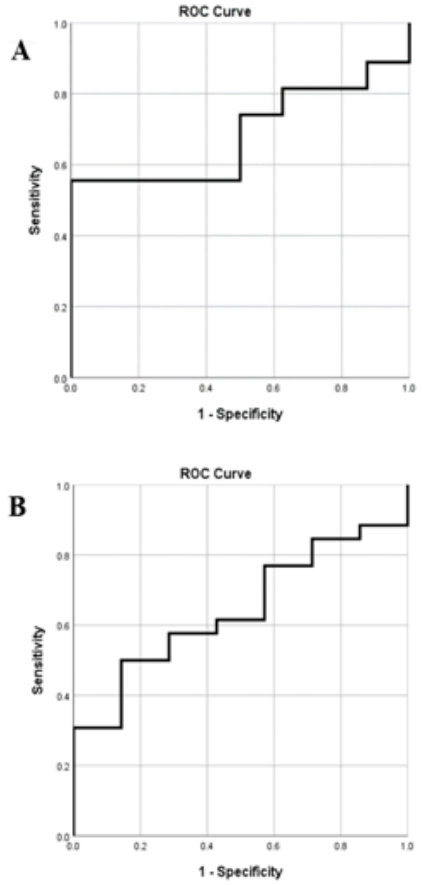


**Fig. 2.** ROC curve analysis for prediction of positive SSTR results. (A) Area under curve (AUC) for serum thyroglobulin (Tg) levels at the time of SSTR scintigraphy (0.685), and (B) AUC for first serum Tg (0.643).

## DISCUSSION

Since SSTRs are expressed in DTCs, some have suggested possible utilities for SRS in these types of cancer [21-24]. Previously, studies aimed to evaluate the diagnostic performance of SRS in DTCs. For example, Gabriel et al. compared [$^{18}$F]FDG PET with SRS in 54 DTC patients. This study showed sufficient accuracy (66.7%) and sensitivity (62.5%) for octreotide scintigraphy, albeit lower than that of [$^{18}$F]FDG PET (83.3% and 87.5%, respectively) [25]. Other studies employed SRS in the diagnosis of DTC patients with TENIS syndrome, which has been associated with variable detectability, sensitivity, and specificity [26-28]. The current study also highlighted the usefulness of SRS in patients with TENIS syndrome.

The present study did not aim to assess the sensitivity and specificity of SRS as compared to the standard of truth. There is a wide range of disparities regarding the diagnostic performance of SRS in DTCs in the literature [29-31]. For example, Shinto et al. examined patients with thyroid cancer using [$^{99m}$Tc]Tc-HYNIC-TOC scan and reported the sensitivity and specificity of 88.5% and 100%, respectively [28]. In contrast, in the study of Czepczyński et al., sensitivity and specificity were 69% and 78.6% for this modality, respectively [32].

Some factors may influence the detection rate of SRS, of which disease stage at the time of SSTR imaging and Tg levels definitely play a role. In the present study majority of the cases in advanced stages deemed positive on SRS (data not shown). Also, the patients with history of EBRT were more likely to have a positive SRS. This can be explained by the fact that EBRT is usually reserved for advanced cases of DTC [4]. We have also previously described a case of poorly differentiated DTC with high [$^{99m}$Tc]Tc-octreotide avidity [33]. Similarly, Shinto et al. reported that the sensitivity of [$^{99m}$Tc]Tc-HYNIC-TOC scan was higher for patients with advanced stages (93.7%), including stages III and IV [28]. We also observed that the patients with suppressed-Tg levels >80 ng/ml had higher chance of SRS positivity. Similarly, Czepczyński et al. stated that the positive scans were found in patients with higher Tg levels (133 ± 144 versus 33 ± 54 ng/ml) [32]. Gabriel et al. also stated that the true positive [$^{99m}$Tc]Tc-octreotide findings were directly correlated with elevated Tg levels (i.e. >30ng/ml) [25]. Therefore, our result is line with earlier research claiming a correlation between somatostatin receptor scintigraphy positivity and elevated Tg levels [34].

Previous investigations reported that there is no correlation between the expression level of somatostatin receptors and Tg levels at the time of SRS [22, 35]. This is also true for in the current study since there was no correlation with Tg levels at the time of SRS and Krenning score (data not shown).

SRS changed staging in a minority of patients with DTC. However, considering that patients with positive SRS may benefit from treatment with peptide receptor radionuclide therapy, up to one-third of the patients had changes in their management [36].

It can be stated that the [$^{99m}$Tc]Tc-HYNIC-TOC scan can be an appropriate alternative in countries that do not have easy access to PET-CT scan or when [$^{18}$F]FDG PET is negative. Hopefully, these two diagnostic imaging modalities does not require levothyroxine discontinuation, contrary to radioiodine

whole-body scan [28]. Since the [$^{18}$F]FDG PET scan is expensive and not an easily available diagnostic method for most patients in the country, SRS with [$^{99m}$Tc]Tc-HYNIC-TOC can be used instead of PET in patients with TENIS syndrome.

### Study limitations

This study has certain limitations including small sample size, unavailability of comparative anatomic imaging in many patients, no assessment regarding the role of TSH stimulation on SSTR expression and lack of facilities to perform [$^{18}$F]FDG PET in selected patients. We recommend further studies with larger sample size along with controlled correlative imaging studies to achieve better and more accurate results.

## CONCLUSION

The [$^{99m}$Tc]Tc-HYNIC-TOC scan may be helpful in finding metastases in thyroid cancer patients with TENIS syndrome. Since the [$^{99m}$Tc]Tc-HYNIC-TOC scan is an affordable, low-cost, and easy-to-use imaging procedure, its use for metastases detection can be especially of importance in developing countries where there is no easy access to PET/CT and budget constraint is of major concern.

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