^{99m}Technetium Pertechnetate Thyroid Scan for Remnant Thyroid Tissue Detection Among Post-Thyroidectomy Patients at Jose R. Reyes Memorial Medical Center: A Retrospective Analysis

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ABSTRACT

This study aims to determine the diagnostic value of a ^{99m}Tc-pertechnetate (^{99m} TcO-4) thyroid scan among patients with DTC who underwent thyroidectomy to assess functioning thyroid remnants before radioactive iodine therapy. A retrospective non-experimental cross-sectional design was done to compare the results of the ^{99m} TcO-4 thyroid scan with the patient's post-RAI scan. A review of all our patients' charts was done for eight years, and after excluding those that did not fit the criteria, 70 patients were included in the study. Data collected was analyzed on a "per patient" basis– where patients either had a "positive scan" or "negative scan", and on a "per lesion" basis – where every lesion's presence and size were compared on both modalities. ^{99m} TcO-4 thyroid scan in the "per patient" analysis showed a sensitivity of 73.91%, specificity of 100%, positive predictive value (PPV) or 100%, and accuracy of 74.29%, however, negative predictive value was determined to be 5.26%. In the "per lesion" analysis, the scan had a less favorable performance with the computed sensitivity of 61.69%, PPV of 94.93%, and accuracy at 59.41%. It was then concluded that 99mTc-pertechnetate scan may be useful in determining functioning remnant thyroid tissue and subsequent management of DTC patients after thyroidectomy, but must take note of its low negative predictive value.

Keywords: *Thyroid cancer, ^{99m}Tc-pertechnetate scan, ^{131}I post-therapy scan, Thyroid remnants*

INTRODUCTION

Thyroid cancer cases have been on the rise and is estimated globally to have 586,202 new cases in 2020, where 43,464 have succumbed to the disease [1]. The increase in the trend of diagnosed thyroid cancer patients was suggested to have been contributed by increasing early detection with the use of evolving technology and surveillance [2]. In the Philippine Interim Clinical Practice Guidelines for the Diagnosis and Management of Well-Differentiated Thyroid Cancer released in 2021, thyroid cancer in the Philippines ranked as the 6th most common cancer, ranking 21st as the cause of cancer-related mortality [3].

Currently, the management for well-differentiated thyroid cancer is mainly surgical. This may be followed with a conservative approach (monitoring and surveillance) or adjunctive/ablative radioactive iodine therapy. The Philippine Interim CPG recommends the consideration of the post-operative disease status of the patient as the attending physician decides on the next steps in the management of the patient [3]. The 2015 ATA guidelines report that post-operative imaging can change clinical management as it can modify the status assessment based on the results of the scan. Should RAI be considered, a pre-ablation low-dose ^{131}Iodine whole body scan is ideal to guide the clinician in prescribing the dose, along with other diagnostics such as neck ultrasound, serum tumor markers, and thyroid stimulating hormone [4].

Unfortunately, the low-dose ^{131}Iodine scan comes with its issues. Multiple studies have shown that diagnostic radioactive iodine is associated with an increased risk of ablation failure or "stunning" as mentioned in the 2015 ATA Guidelines [4]. A study by Park and colleagues showed that in patients who underwent diagnostic 131Iodine scan (dose of 3 to 10 mCi), there were 20 out

26 patients that showed impairment of radioiodine uptake on post-therapy scans compared to the group that used ^{123}Iodine [5]. To address this, the guidelines recommend using a lower dose of ^{131}Iodine (1-3 mCi) or an alternative radioisotope such as ^{123}Iodine to minimize the risk of ablation failure [4]. At present, ^{123}Iodine is not locally available in the Philippines. In our institution, as an alternative to ^{123}Iodine, the ^{99m} TcO-4 thyroid scan was used to assess for functioning tissue remnants, although not particularly mentioned in the existing clinical guidelines. Given the pathophysiology of the well -differentiated tumor, its use appears plausible, with the additional benefit of its favorable cost and availability and the absence of possible "stunning." On literature review, other institutions have also employed ^{99m} TcO-4 thyroid scan with the same objectives and have also attempted to determine the accuracy of this scan in determining thyroid tissue remnants. Their data showed promising results, but due to their limited sample size, there is still a lack of robust evidence to support its reliability. Several of them have yielded values for sensitivity of 77-81% (patient-based) and 59-61% (lesion-based), with PPV of 100% (patient-based) and 81-99% (lesion-based) [6]. Other studies reported less impressive data, with a sensitivity of only 13% for ^{99m} TcO-4 thyroid scan – significantly inferior to a diagnostic radioactive iodine scan having 67% sensitivity [7].

Locally, there is no established data on the clinical utility of ^{99m} TcO-4 scan. As mentioned above, it is still being utilized as an alternative to an ^{131}Iodine diagnostic scan despite the scarcity of information concerning its accuracy. This study then aims to compare ^{99m}TcO-4 scan with the post-RAI scans and determine its sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in detecting remnant thyroid tissue in well-differentiated thyroid cancer patients. In doing this, we hope to contribute relevant information concerning the utility of this easily accessible and inexpensive diagnostic test to guide our Nuclear Medicine physicians in their practice.

MATERIALS AND METHODS

Patients and Data Collection

A retrospective, non-experimental, cross-sectional study

design was used for this study. A review of records of thyroidectomized patients who have undergone their first RAI remnant ablation or adjunctive therapy for the past eight years was done (January 2015 - August 2022). Included in the data pool are patients aged 19-90 years old with histopathologically proven well-differentiated thyroid cancer (Papillary Thyroid Cancer or Follicular Thyroid Cancer), excluding patients with known distant metastases. We excluded those with distant metastases since most of these patients almost always warranted subsequent RAI therapy, with their post-operative stratification being high risk [3,4]. This means that the presence or absence of residual disease in the neck area may have less gravity in the decision-making process in this population versus those who are at low to intermediate risk. Those included in the study must also have undergone one of the following operations: 1) Near -Total, 2) Total Thyroidectomy, and/or 3) Completion Thyroidectomy, since patients who have undergone partial thyroidectomy or lobectomy are not recommended to undergo RAI [3,4]. A total of 256 patient records were initially reviewed. After eliminating pediatric patients, those with high-risk stratification, and those with no existing record of ^{99m} TcO-4 thyroid scan or post-therapy scans, a total of 70 patients remained to be part of the analysis. Figure 1 illustrates the selection process of eligible records.

Patient Preparation and Tc-99m Pertechnetate Scan

Our patients had their post—thyroidectomy ^{99m}TcO-4

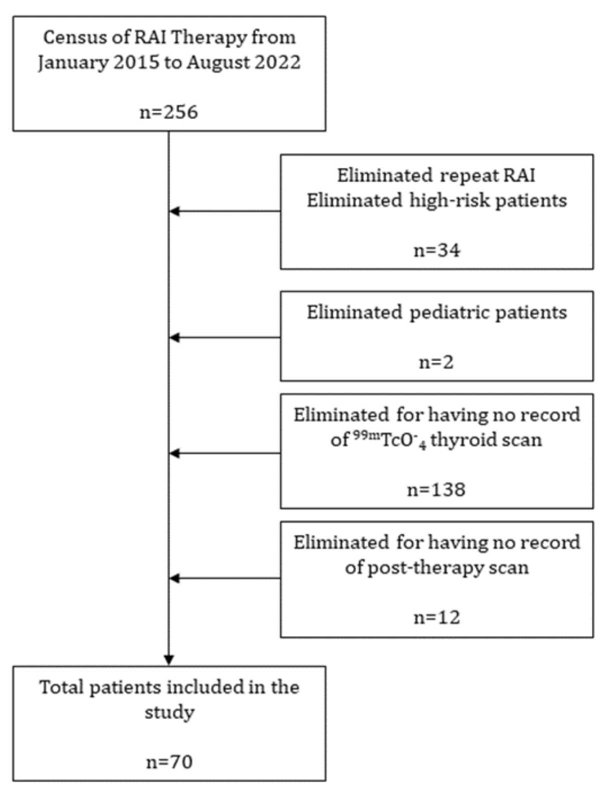

FIGURE 1. . Patient Selection Flow Chart

thyroid scan acquired at least 4-6 weeks after the operation. For patients who were already on thyroid hormone replacement therapy, the thyroid scan was further delayed for 4-6 weeks after cessation of the medication. The patients were also put on a low-iodine diet at this time. A dose of 259 MBq (7 mCi) of ^{99m}TcO-4 was given intravenously and was imaged 20 minutes after. Imaging was done using a Mediso Anyscan SPECT gamma-camera using a low energy high-resolution parallel-hole collimator at 20% energy window centered at 140 keV (frame size 256 X 256). Anterior, right anterior oblique, and left anterior oblique static views with markers on surgical scars and the sternal notch was acquired. The images were processed using the InterViewXP Clinical Processing System.

Post-Radioactive Iodine Therapy Whole Body Scan

Prior to therapy, TSH values were measured. At serum TSH of 30 mIU/L, they then proceeded to RAI therapy. A post-therapy whole body scan was done after 72-168 hours post oral administration of RAI. Our patients received doses ranging from 1850 to 5550 MBq (50-150 mCi) of ^{131}I. Whole-body scan acquisition was done using the Mediso Anyscan SPECT gamma-camera using a high energy parallel-hole collimator at 20% energy window centered at 364 keV (frame size 256 X 256). An additional view of the thyroid bed anteriorly using the high-energy parallel-hole collimator was also acquired.

Data Analysis

The images were again reviewed and blindly interpreted by us. The lesions were also individually remeasured blindly by 1) an experienced nuclear medicine technologist and 2) repeated by us. The average of the two values were used for data analysis.

The data gathered was analyzed on a "Per-Patient" and "Per-Lesion" basis. For the purposes of this study, the ^{131}I post-therapy scans of the patients were regarded as the "gold standard" to compute for the sensitivity, specificity, PPV, NPV, and accuracy of ^{99m}TcO-4 thyroid scan.

For the "Per-Patient" analysis, A ^{99m}TcO-4thyroid scan was deemed "positive" if at least one lesion was present in the scan. A lesion is any abnormal uptake in the neck area. The same method was used to identify a positive scan for a post-^{131}I post-therapy scan. The results of the ^{99m}TcO-4 thyroid scan were compared with the patient's radioactive iodine (RAI) post-therapy scan using a paired T-test. For the "Per-Lesion" analysis, lesion presence and size were compared in both scans. Lengths and widths (in centimeters) of the lesions were measured. Lesions that were not present in either scan had measurements of 0 cm. A paired T-test was applied to compare the length and width of ^{99m}TcO-4 and post-therapy scan results. Analysis was done using Medcalc Statistical software with a significance level set at 0.05

RESULTS

Seventy patients fulfilled the inclusion and exclusion criteria and were included in the study. The majority of the patients were females (77.1%). Most of our patients were post-operatively stratified as low risk, and RAI therapy doses ranged from 1,850 MBq to 5,550 MBq, as seen in Table 1.

Table 2 shows the 2 x 2 contingency table of the patients' thyroid and post—therapy scans. A total of 69 patients presented with positive post - therapy scans. Among these, 51 patients concordantly had positive thyroid

TABLE 1. Demographical and Clinical Characteristics

Age (years), mean ± sd	46.5 ± 13.7	
Sex, n, %		
Male	16 (22.9%)	
Female	54 (77.1%)	
Risk Stratification	**RAI Dose in MBq (mCi)**	**n, %**
Low-risk	1,850 (50)	10 (14.3%)
	3,700 (100)	46 (65.7%)
Intermediate-risk	5,180 (140)	2 (2.86%)
	5,550 (150)	12 (17.14%)

scans (true positive), and 18 had negative thyroid scans (false negative). One patient demonstrated both negative ^{99m}TcO-4 and ^{131}I scans (true negative).

The sensitivity, specificity, PPV, NPV, and accuracy of the ^{99m}TcO-4 thyroid scan in detecting the presence of thyroid remnants are shown in Table 3. The data reveals that the sensitivity of the 99mTcO-4 thyroid scan in predicting a positive 131I Scan is 73.91%, specificity of 100%, positive predictive value of 100%, negative predictive value of 5.26%, and accuracy of 74.29%.

Table 4 shows the 2 x 2 contingency table for the lesions that were detected in both ^{99m}TcO-4 and ^{131}I post-therapy scans. The ^{99m}TcO-4 thyroid scan detected 107 lesions, while 164 were noted in the ^{131}I post-therapy scans. One hundred-one lesions were detected in both scans (true positives), with a congruence of 101/170 (59.4%).

Table 5 shows the diagnostic accuracy parameters analyzed on a per-lesion basis. The sensitivity and specificity of ^{99m}TcO-4 thyroid scan on a per lesion basis are 61.69% and 0%, respectively. A high PPV was noted at 94.39% and an NPV of 0%. Of note are the six lesions that were present in the ^{99m}TcO-4 thyroid scan but not in the post-therapy scan. The computed accuracy was 54.91%. The specificity and NPV of 0 in this instance are irrelevant as it is impossible to quantify lesions that truly do not exist.

To measure if there is a significant difference in the dimensions of lesions detected in both scans, only lesions that were present in both the ^{99m}TcO-4 thyroid scan and ^{131}I Post-Therapy Scan were analyzed. Table 6 reveals that there was a significant difference in the lengths obtained by ^{99m}TcO-4 thyroid scan (M=1.98, SD=0.98) and lengths measured in the post-therapy scans (M=2.70, SD=2.49, $p < 0.05$). Similarly, there is a significant difference in the width of lesions measured in ^{99m}TcO-4 thyroid scan (M=1.48, SD=0.69) compared to the widths measured in the post-therapy scans (M=2.26, SD=0.88, $p < 0.05$). These results suggest that the dimensions of the lesions measured are significantly larger in the post-therapy scans compared to the ^{99m}TcO-4 thyroid scan.

DISCUSSION

Per Patient Analysis

Our data shows that the ^{99m}TcO-4 thyroid scan is 74.29% accurate in determining thyroid remnants in post-thyroidectomy patients. Its computed sensitivity is at

TABLE 2. Contingency Table for Per Patient Analysis

	Positive ^{131}I Scan	*Negative ^{131}I Scan*	*Total*
Positive $^{99m}TcO^-_4$ Scan	51 (TP)	0 (FP)	51
Negative $^{99m}TcO^-_4$ Scan	18 (FN)	1 (TN)	19
Total	69	1	70

TABLE 3. Diagnostic accuracy of ^{99m}TcO-4 thyroid scan (Per Patient)

		95% CI
Sensitivity	51/69 (73.91%)	(61.94 to 83.75%)
Specificity	1/1 (100%)	(2.50 to 100%)
PPV	51/51 (100%)	
NPV	1/19 (5.26%)	(3.60 to 7.63%)
Accuracy	74.29%	(62.55 to 83.99%)

TABLE 4. Contingency table for the Per Lesion analysis

	Positive in ^{131}I Scan	*Negative in ^{131}I Scan*	Total
Positive in $^{99m}TcO^-_4$ Scan	101 (TP)	6 (FP)	107
Negative in $^{99m}TcO^-_4$ Scan	63 (FN)	0 (TN)	63
Total	164	6	170

TABLE 5. Diagnostic accuracy of ^{99m}TcO-4 thyroid scan (Per Lesion)

		95% CI
Sensitivity	61.69%	53.68 to 69.09%
Specificity	0	0 to 45.93%
PPV	94.39%	93.72 to 95%
NPV	0	
Accuracy	59.41%	51.63 to 66.86%

TABLE 6. Comparison of lengths and widths of lesions present in both ^{99m}TcO-4 thyroid scan and ^{131}I post-therapy scan

	n	*Tc-99m Thyroid Scan*			*Post-Therapy Scan Result*			*p value*
		Mean	SD	Median	Mean	SD	Median	
Overall Length	101	1.98	0.97	1.72	2.70	0.95	2.49	0.0001
Overall Width	101	1.48	0.69	1.37	2.26	0.88	2.13	0.0001

73.91%, which does not fare differently from the results of similar studies, which showed sensitivities of 72.2%-81% [6,8,9]. The positive predictive value of 100% is likewise similar or identical to the results of the same publications. Our data suggests that a fair number of patients with positive ^{131}I post-therapy scans can be predicted by the ^{99m}TcO-4 thyroid scan among patients with low to intermediate-risk DTC.

The specificity of ^{99m}TcO-4 thyroid scan was computed to be 100%. Our data was significantly greater compared to another study, which showed specificity estimation of 70.5% [8]. However, it is important to consider that only one was truly negative, and was the only value used to compute for the specificity. Similar studies conducted by Kueh [6] and Tsai [9] could not produce estimates for specificity since their study samples all had positive post-therapy scans. NPV was likewise not possible to compute in their studies.

Our negative predictive value was computed to be 5.26%. This was expected given that there were 18 (26.1%) patients with negative ^{99m}TcO-4 thyroid scans that were positive in their post-thyroidectomy scans. This shows then that a negative ^{99m}TcO-4 thyroid scan is unlikely to indicate the absence of a thyroid remnant tissue.

Per Lesion Analysis

It was found that the ^{99m}TcO-4 thyroid scan had a sensitivity of 61.69% and a positive predictive value of 94.39%. This indicates that only a little more than half of the lesions can appear in the ^{99m}TcO-4 thyroid scans, but its presence in the ^{99m}TcO-4 thyroid scan almost guarantees its uptake in the subsequent post-therapy scan. A representative image from a patient in Figure 2 demonstrates lesions not detected in the ^{99m}TcO-4 thyroid scan, which then appeared in the post-therapy scan.

This was almost similar to the results of Tsai [9] which were 59% (sensitivity) and 100% (PPV). The specificity and negative predictive value were both 0, as expected. A limitation in this analysis was the absence of lesions in our gold standard that can only be quantified as 0 and would mathematically give us no value. Interestingly, six false-positive lesions were identified in the ^{99m}TcO-4 thyroid scan, which was not identified in the post—thyroidectomy scan. A study by Long similarly encountered false positive lesions in their study, which also compared a ^{99m}TcO-4 scan with post-therapy scans.

One focus of ^{99m}TcO-4 uptake was seen in the axillary lymph nodes and was speculated to be lymphatic drainage of the radiotracer from the injection site [10]. This might not be a plausible explanation for our case since we only assessed the neck area, and it is unlikely that the tracer will concentrate in the cervical nodes. It may be possible that interpretation error may be involved, such as physiologic ^{99m}TcO-4 uptake in the salivary glands, or may also be explained by increased tracer accumulation secondary to an inflammatory process [9].

The lesion dimensions measured in the 99mTcO-4 scan and post-therapy scans were also compared, showing a

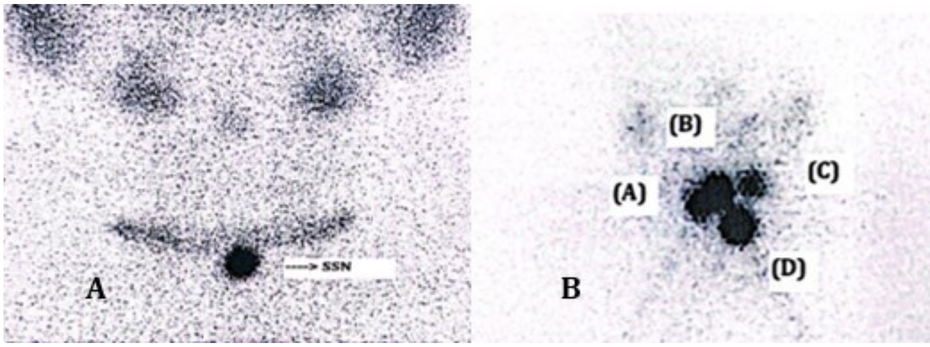

FIGURE 2. False negative lesions. **A.** $^{99m}TcO^{-}_{4}$ thyroid scan shows a mild uptake in the midline; **B** Post-RAI scan in the same patient showing four foci of intense iodine uptake in the neck

significant difference in the lesion length and width. Although statistically different, scintigraphic images are unreliable in measuring organ volume. A communication by Tanahill revealed that thyroid scintigraphy thyroid measurement using ^{99m}TcO-4 did not correlate to ultrasound, surgical specimens, or clinical palpation [11]. This disagreement on size measurement may be operator-dependent but may be addressed by concomitant anatomic imaging such as SPECT/CT. Size measurement is vital as it can impact subsequent management. To illustrate, a study comparing thyroid volume measurement using radioiodine versus ultrasonography found that scintigraphic volume estimation using the Himanka formula overestimated the thyroid volume by 53% in patients with diffuse goiter dose. The variability in computed volume using scintigraphy also resulted in differences in therapeutic radioiodine dose [12].

Limitations and Pitfalls

The ^{99m}TcO-4 scintigraphy may show uptake of remnants due to its ability to be taken up by functioning thyroid tissue through the sodium iodide transporters and trapped without proceeding to organification. It is also more accessible and has more favorable imaging characteristics (i.e., half-life of 6 hours and a photopeak of 140 keV) compared to the ^{131}Iodine [13]. However, our data has shown its limitations in its ability to demonstrate all functioning thyroid tissue, and while focal uptake in the thyroid bed is considered a remnant, certainty of its histology is not certain due to the lack of corresponding anatomical imaging. In this case, the addition of SPECT/CT may give us more valuable information in the same way it has in other literature. A study conducted by Chantadisai, which investigated the usefulness of a whole body ^{99m}TcO-4 imaging with SPECT/CT to detect remnants and metastasis, has shown that out of the 111 positive foci of ^{99m}Tc-pertechnetate, 106 were seen in the thyroid bed, two foci in the lymph nodes and one bone lesion [14]. Another study was likewise able to identify extrathyroidal ^{99m}Tc-pertechnetate uptake, with high sensitivity for regional nodal metastasis but low sensitivity for distant metastasis. SPECT/CT for patients with equivocal ^{99m}Tc-pertechnetate scans was done and ultimately confirmed mediastinal uptake in 2 patients and only physiologic esophageal activity in 2 other patients [15]. Utilization of SPECT/CT is recommended if ^{99m}Tc-pertechnetate thyroid scan is contemplated, and especially if a ^{99m}Tc-pertechnetate whole body scan being considered.

We focused mainly on thyroid remnant tissue and did not attempt to evaluate distant metastases, so we only included patients with low to intermediate-risk stratification. Our investigation is also limited to well-differentiated thyroid carcinoma, and patients demonstrating dedifferentiation will entail an entirely different study.

Impact on Management

The ^{99m}Tc-pertechnetate scan may help determine the following steps after confirming functioning thyroid remnant post-thyroidectomy. Although remnant ablation in low-risk patients is not always recommended, it was reported that more than 90% of post-thyroidectomy patients across the Asia-Pacific region are treated with radioactive iodine ablation therapy [16]. This may be due to the higher risk of recurrence in this population, resulting in a more aggressive approach. It was also reported that Filipinos are more at risk for disease recurrence [3]. A retrospective study by Lo concluded that Filipinos are associated with a more aggressive papillary thyroid cancer disease course. However, follicular thyroid cancer patients did not have any significant risk compared to other populations. It was also found that their patients who underwent RAI therapy, along with surgical management and TSH suppression therapy achieved a disease-free status on long-term follow-up.[17] With this knowledge, identifying the presence of thyroid remnants can aid the physician in weighing the risk and benefits of an ablative RAI .

CONCLUSION

^{99m}Tc pertechnetate thyroid scan has a high sensitivity and predictive value for determining thyroid remnants on per-patient and per-lesion analyses. However, its low negative predictive value warrants cautious utilization of the ^{99m}Tc pertechnetate thyroid scan, and must not be complacent about the absence of remnants in a negative thyroid scan. The significant difference in lesion size measurements between the ^{99m}Tc pertechnetate thyroid and post-therapy scans suggests that this may not accurately measure the remnants. To address the limitations of ^{99m}Tc pertechnetate thyroid scan, we recommend the addition of SPECT/CT and further exploring its utility in determining regional and distant metastases. Overall, the ^{99m}Tc-pertechnetate scan is useful in determining functioning remnant thyroid tissue and subsequent management of DTC patients after thyroidectomy.

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