Evaluation of Diagnostic Value of SPECT/CT Imaging in Post-radioiodine Therapy in Thyroid Cancer

Asma Al Hatmi, *Anjali Jain, Alok Kumar Mittal, Samir Hussain

Department of Radiology and Molecular Imaging, Sultan Qaboos University Hospital, Muscat, Oman
*Corresponding Author’s e-mail: dranjalinm@gmail.com

Abstract

Objectives: The aim of this study is to investigate the value of Single Photon Emission Computed Tomography/ Computed Tomography (SPECT/CT) imaging in well differentiated thyroid cancer (DTC) after radioiodine ablation (I-131) therapy for clinical staging and risk stratification. To determine whether SPECT/CT would change management plan or predict the clinical outcomes of DTC patients. Methods: 78 DTC patients underwent first post radioiodine therapy “Whole body iodine- 131 scintigraphy (WBS) along with SPECT/CT” at Department of Radiology and Molecular imaging, Sultan Qaboos university Hospital between January 2014 and August 2017. Differences between WBS and SPECT/CT, change in clinical staging, risk stratification and management were recorded. Clinical outcome at 6-12 months was recorded. SPSS statistical software was used for collecting and analysing the data. A generalized McNemar test was used to assess disagreement between WBS and SPECT/CT. Results: American Thyroid Association (ATA) risk stratification falls into low (35.8%), intermediate (53.8%) and high risk groups (10.2%) on WBS, which changed to 44.8%, 38.4% and 16.6% respectively on SPECT/CT imaging. Overall change in risk stratification was noted in 16.6% and TNM stage in 11.5% of patients after SPECT/CT imaging. SPECT/CT changed therapeutic plan and clinical outcome in 19.2% of patients. Conclusion: SPECT/CT allows better detection and characterization of metastatic lymph nodes and distant metastasis in DTC patients compared to WBS imaging alone. It alters TNM
staging, ATA risk classification and management in significant number of patients. It is recommended that SPECT/CT should be done routinely along with WBS in well differentiated thyroid carcinoma.

**Keywords:** Thyroid cancer, Iodine, Ablation techniques, SPECT/CT

**Advances in Knowledge**
- This study has shown the significant clinical impact of SPECT/CT imaging in post radioactive iodine (RAI) therapy patients.
- SPECT/CT has influenced American thyroid association (ATA) risk stratification, TNM staging, management plan, and clinical outcome in thyroid cancer patients.
- This is the first study in the Gulf Cooperative Council (GCC) region which has compared wide clinical and imaging aspects of DTC management.

**Application to Patient Care**
- Our study recommends that SPECT/CT should be an integral part of Whole body I-131 scintigraphy (WBS) imaging protocol in differentiated thyroid cancer (DTC) patients.

**Introduction**
Thyroid cancer has a good prognosis and is considered a treatable disease. The 5-yr survival rates are 99.8% for localised disease, 97.0% for regional metastases, and 57.3% for distant metastases in well-differentiated thyroid cancer (DTC). In this study, we aim to evaluate the impact of SPECT/CT imaging in post-therapy planar whole body scintigraphy (WBS) which detects residual thyroid tissue, lymph nodes and distant metastasis.

This study has shown the significant clinical impact of SPECT/CT imaging in post radioactive iodine (RAI) therapy patients. SPECT/CT has influenced American thyroid association (ATA) risk stratification, TNM staging, management plan, and clinical outcome in thyroid cancer patients. This is the first study in the Gulf Cooperative Council (GCC) region which has compared wide clinical and imaging aspects of DTC management.

Our study recommends that SPECT/CT should be an integral part of Whole body I-131 scintigraphy (WBS) imaging protocol in differentiated thyroid cancer (DTC) patients.
The addition of Single photon emission computed tomography/Computed tomography (SPECT/CT) to planar WBS increases the diagnostic accuracy by improving the anatomic localisation of iodine uptake in the scan which changes the clinical stage and ATA risk classification.\textsuperscript{1,7} This further leads to alteration in management plan such as the need for additional imaging, biopsy, surgery and external beam radiation or other systemic therapies, etc.\textsuperscript{1,3}

In addition to excellent 3-dimensional localisation of abnormal iodine uptake, CT helps in attenuation correction and also detects non-iodine avid distant metastases, which has a tremendous impact on clinical outcome and rate of survival in DTC patients.\textsuperscript{3,8,9} Many institutions recommend I-131 SPECT/CT as part of imaging protocol in selected high-risk patients with inconclusive findings on planar imaging.\textsuperscript{1,2,3} We have studied the importance of SPECT/CT with I-131 WBS in Omani patients, as there was no such similar study done locally.

**Methods**

This retrospective study was conducted at Sultan Qaboos University hospital (SQUH), Muscat Oman, and was approved by the hospital Medical Research Ethical Committee and did not require informed consent. A computerized search of medical records of the patient database was made from the hospital information system (HIS) and Radiology information system (IntelliSpace PACS Enterprise, Philips Healthcare Informatics, Inc. USA). A total of 183 patients, who underwent post-RAI (ablation/therapy) whole body scintigraphy were recorded from January 2014 to August 2017.

The inclusion criteria are 1) Patients with histo-pathologically proven well-differentiated thyroid carcinoma, who underwent first RAI therapy after total Thyroidectomy. 2) Patients on whom both WBS planar and SPECT/CT were performed on the same day 3) Availability of 6-12 months follow-up with diagnostic I-131 WBS. 5 patients were excluded because they were not well-differentiated thyroid cancers on histopathology. 94 patients were excluded as SPECT/CT was not performed. Six patients were excluded because of the unavailability of 6-12 months follow up or diagnostic I-131 scan after the first therapy dose. Finally, a total of 78 patients were included in our study (Figure 1).
After thyroidectomy, all patients received high dose of radio-iodine for ablation/therapy. A diagnostic radioiodine scan was not performed as a protocol. Oral radioiodine dose was administered based on the surgical and pathological status of the tumour. Patients were classified into ATA low, intermediate and high-risk groups. 1.1 – 3.7 GBq of RAI was administered to low to intermediate risk group patients and patients with metastases as per departmental protocol. All patients were prepared with adequate thyroid hormone stimulation before the RAI therapy. Majority of these patients (83.4%) were kept off thyroxin for one month, while 16.6% patients received recombinant thyroid-stimulating hormone (TSH) injection for thyroid hormone stimulation. A low iodine diet was recommended one week before RAI therapy.

Whole-body I-131 imaging was performed 3-7 days post radioiodine dose on Symbia T-series dual-head SPECT gamma camera with multidetector CT scanner (Siemens Healthcare A/S, Denmark). Both WBS planar and SPECT/CT were acquired. Initially, anterior and posterior WB planar images were acquired at the speed of 12 cm/ minute with high energy parallel hole collimator, matrix of 256 x 1024, and photopeak at 364 KeV with 15% window. Additional planar anterior images of the neck and lateral images of the abdomen were also acquired as department protocol. At the same time, SPECT/CT images of the neck and chest were acquired from the skull base to the diaphragm. SPECT was acquired in step and shoot mode with 32 views and 180° rotation per detector. Acquisition time was between 30-60 seconds per step. Images were acquired with high energy parallel hole collimator with matrix of 128 x 128 and photopeak of 364 KeV with 15% window. CT images were acquired at 130 KeV, reference mAs 30 with 5 mm slice thickness. Axial, sagittal, and coronal reconstruction of images was done on Siemens workstation (symbia.net Siemens Healthcare A/S, Denmark).

Both WBS and SPECT/CT images were interpreted by a senior Nuclear Medicine physician, blinded to other laboratory and radiological image results. First planar images were interpreted. Any foci of uptake higher than the surrounding background (other than the physiological sites of uptake) were considered abnormal. Foci of abnormal iodine uptake in the medial portion of the lower neck, approximately in the thyroid bed were categorized as positive for residual thyroid tissue.

An abnormal focus of uptake in the lateral part of the neck was considered as lymph node metastases. Foci of uptake very close to the medial part of the neck were equivocal for lymph
node metastases. When more than one foci of uptake were seen in the medial part of the neck, the one with prominent uptake was considered as a residual tissue, and the rest of the foci were interpreted as equivocal for lymph node metastases. (Figure 2) Foci of abnormal iodine uptake in mediastinum were categorized as mediastinal lymph node metastases, while abnormal foci adjacent to mediastinum were considered equivocal for lymph node metastases. Abnormal uptake in lung fields was considered as positive or equivocal for lung metastases. All areas of abnormal uptake beyond the neck and chest were also considered as positive or equivocal for metastatic foci and possible locations (bone, brain, liver, etc) were also recorded.

Findings were recorded as positive, negative, and equivocal for thyroid bed, lymph node metastasis and distant metastasis. SPECT/CT images were also reviewed as a second step at the same time. Similarly, SPECT/CT images were also interpreted as positive and negative for thyroid bed, lymph node metastases and distant metastases. Non-Iodine avid lesions seen on CT were also recorded. Changes observed in the interpretation of WBS planar and SPECT/CT were noted. Changes in ATA risk stratification and TNM staging were recorded. All patients were grouped into ATA low, intermediate, and high-risk groups and also categorized into 4 stages according to the 8th edition of the AJCC/TNM staging of thyroid cancer. Changes in management plans like biopsies, additional cross-sectional imaging, and further therapies were recorded. Clinical outcome like complete remission or additional treatment were noted on the 6-12 month follow-up.

A database in the SPSS program, version 23 on the computer was created for statistical analysis. By using generalized McNemar test, disagreement between WBS planar and SPECT/CT was assessed in three groups; including thyroid bed, lymph node metastases and distant metastasis. A P-value of < 0.05 was considered significant.

**Results**

Among the 78 patients included in our study, 64 (82%) were females and 18 were males (18%). The age of the patients ranged from 7 years to 76 years with a mean age of 41.6 +/-16 (standard deviation). Papillary carcinoma was the most common histopathology forming 96% of patients compared to follicular forming 3% and papillary carcinoma with poorly differentiated component forming 1% of patients. These included 9 patients of mixed papillary with follicular carcinoma, 2 patients with oncocyic variant, 1 with diffuse...
sclerosing type, and 1 with Hurthle cell carcinoma. 14% patients had a background of multinodular goitre (MNG), 6% had Graves’ disease, 10% had Hashimoto thyroiditis, and 19% lymphocytic thyroiditis. The patients’ demographic data is shown in table (1). TSH levels for all patients during iodine administration were more than 30 mIU/L. Thyroglobulin (TG) levels ranged between 1 to 67795 ug/L and TG antibodies were positive in 20.5 % of patients. Patients received high doses of radioactive iodine with activities ranging from 980 to 7900 MBq.

**Change in residual thyroid tissue uptake**

There was total agreement between WBS planar and SPECT/CT image findings in residual thyroid tissue uptake. Out of 78 patients, 77 showed positive iodine uptake in thyroid bed on both WBS planar and SPECT/CT images, suggesting residual thyroid tissue. One patient didn’t show any iodine uptake in the thyroid bed on both planar and SPECT/CT images.

**Change in locoregional Lymph node Metastases**

There was a significant difference noted between the WBS planar and SPECT/CT images pertaining to lymph node metastases. On WB planar imaging, 22 patients, out of 78 patients, were positive for lymph node metastases. 17 patients were equivocal for lymph node metastases. Out of the 22 patients (positive for lymph node metastases on WB planar imaging), 12 were positive on SPECT/CT images. In the remaining 10 patients (with false-positive lymph nodal uptake on WB planar images) uptake was seen in thyroid bed on SPECT/CT images. These 10 patients showed complete remission on 6-12 months follow-up with no requirement for a second RAI dose. All equivocal lymph node metastases on WB planar images were negative for lymph node metastases on SPECT/CT. There were no equivocal cases for lymph node metastases on SPECT/CT images. The remaining 39 patients were negative for lymph node metastases on both WBS planar and SPECT/CT. There is a statistically significant difference between WBS planar and SPECT/CT imaging for lymph node metastases with P<0.01. (Figure 2)

**Change in Distant metastases**

WB planar imaging has shown distant metastases in 5 patients while 2 patients were equivocal for distant metastases. The most common site of metastases was the lung followed by bone and liver. SPECT/CT confirmed distant metastases in 5 patients, while 2 equivocal findings on WB planar imaging turned out to be negative on SPECT/CT. There is a
statistically significant difference between WBS and SPECT/CT imaging in distant metastases with P value of < 0.01. (Figure 3)

In addition; the CT part of SPECT/CT also detected lung nodules in 7 patients. These nodules did not show any iodine uptake on post therapy scan. 2 of these patients showed complete resolution of nodules in the 6-12 months follow-up diagnostic I-131 WBS with normal TG levels (< 1 ug/L), denoting these nodules were likely to be inflammatory. However; 5 patients in the 6-12 months follow-up showed persistent lung nodules with raised TG levels and were therefore suspicious for metastases. Histopathologically, 2 patients were papillary carcinoma with an oncocytic variant, 1 with poorly differentiated component, 1 follicular carcinoma, and 1 papillary carcinoma. These patients were further evaluated by F-18 Fluoro-deoxyglucose Positron Emission Tomography/ computed tomodgraphy (FDG PET-CT) scan, which revealed abnormal increased FDG uptake and was considered as distant metastases of DTC. All of these patients were referred to an oncology centre and they were treated with other systemic therapies (3 patients) and radiotherapy (2 patients). (Figure 4)

The difference between WBS Planer imaging (A) and SPECT/CT imaging (B) categorizing in the thyroid bed, neck lymph node, and distant metastasis is well demonstrated in (Figure 5)

Change in ATA thyroid cancer risk stratification and TNM staging
8 out of 10 patients with negative lymph node metastases on SPECT/CT imaging were restratified from intermediate to low-risk group. Risk stratification in 2 patients did not change due to the presence of extra thyroidal tumour extension. 5 out of 7 patients with non-iodine avid metastases were restratified to high risk group.

ATA thyroid cancer risk stratification in these patients was falling into low (35.8%), intermediate (53.8%), and high-risk groups (10.2%) on planar imaging, which changed to 44.8%, 38.4%, and 16.6% respectively after SPECT/CT imaging. The overall change in risk stratification was noted in 13 (16.6%) out of 78 patients. (Table 1)

The percentage of change in TNM staging was smaller than the change in risk stratification. Out of 10 patients with negative lymph nodes on SPECT/CT, staging didn’t change in 8 patients. These patients were <55 years and continued to be categorised as stage I according to TNM staging for thyroid cancer. SPECT/CT downstaged the disease in 2 patients as they
were >55 years of age. The status of 7 patients with non-iodine avid lesions changed from M0 to M1, thus upstaging the disease. The overall change in clinical staging was seen in 9 (11.5%) patients.

All patients showing change in TNM stage and risk classification were from intermediate to high risk groups.

Change in the management plan and clinical outcome
12 patients with positive lymph nodes metastases on SPECT/CT imaging did not show remission at 6-12 months follow up. These findings were correlated with neck USG and CT scans. Out of these 12 patients, 1 patient underwent re-surgery for complete lymph nodal dissection after confirmation of disease on FNAC. The rest of the patients underwent second RAI therapy. 10 false-positive lymph node metastases on WBS planar imaging (negative on SPECT/CT) showed complete remission on 6-12 months follow up and did not require further RAI therapy, leading to change in clinical outcome. All 5 patients with non-iodine avid metastases on SPECT/CT (proven with F-18 FDG PET/CT) were upstaged from M0 to M1, which has resulted in a change in the management plan. A total of 15 (19.2%) patients out of 78 showed changes in clinical outcome and management plan. 10 patients with negative lymph nodes went into remission on follow up, while 5 patients with non-iodine avid metastases required further treatment in terms of systemic therapy and radiotherapy.

Discussion
SPECT/CT has become very popular in recent years. With the availability of hybrid cameras, it is being used frequently in nuclear medicine departments. Both functional and structural imaging can be performed at the same time, giving maximum benefit in terms of diagnosis and further management. SPECT/CT is also being used with WB planar imaging in DTC resulting in substantial advantage for diagnosis and localization of the disease. In our study, we have included all patients with DTC, who underwent both WB planar and SPECT/CT imaging after the first RAI therapy. All the patients with only thyroid bed residual uptake showed no contradiction between WB planar and SPECT/CT findings. Previously in some studies SPECT/CT was acquired only in cases of diagnostic uncertainty and was not performed for clear thyroid bed residual uptake. In our study, all patients with residual thyroid bed tissue also underwent SPECT/CT and they had complete
remission after first RAI therapy. Another study has shown similar results in thyroid bed uptake with no significant disagreement seen.

Different studies in the literature have shown the advantage of SPECT/CT over planar imaging in lymph node metastases, distant metastasis and in management of DTC patients. In our study there was disagreement in nodal metastases between WBS planar and SPECT/CT imaging with P<0.01. These patients with false-positive nodes on WBS planar were downgraded on SPECT/CT images with complete remission of disease on 6 months follow up. On WBS planar these areas of iodine uptake were seen in the lateral or superior part of the neck and were interpreted as lymph node metastases, while they could be anatomically localised as residual thyroid tissue on 3-dimensional tomographic acquisition of SPECT/CT images. Similarly, foci of uptake equivocal for lymph node metastases on WBS planar could also be delineated as residual thyroid tissue in the thyroid bed on SPECT/CT. In total 34% of lymph nodal disease status was changed with SPECT/CT, which is similar to previously reported in literature. These studies changed and reclassified the lymph nodal status in 34% to 36.4% of patients with SPECT/CT. However; these studies also interpreted lymph nodal disease from N0 status N1 and from Nx status to N1. In our study, lymph nodal status changed only from N1/Nx to N0. This could be explained either by differences in interpretation of findings on WBS planar with high suspicion of lymph nodal metastases in our study, or may be due to difference in surgical techniques and higher number of neck dissection during surgery in our study, reducing the possibility of residual lymph nodal disease.

Findings with distant metastases have also shown disagreement between WBS planar and SPECT/CT imaging with P<0.01. 2 patients in our study with equivocal finding of distant metastases were found negative on SPECT/CT. As shown by other authors SPECT/CT reduces the number of indeterminate foci of metastases and also differentiates benign physiological uptake from pathological uptake. In our study, one of the foci in mediastinum was localised to be oesophageal uptake. In another patient, diffuse linear uptake of iodine was seen in the lung, which was characterised as infective on CT images and showed resolution after a course of antibiotic. This is possible as CT part of SPECT/CT not only localises foci of uptake but also characterises the disease. Maruoka et al have shown alteration of equivocal findings to benign findings on 38% of patients. Our study also shows a similar finding, although our number is much smaller. The detection of non-iodine avid lesions is
very important in management since these patients cannot be treated with radioactive iodine and would need other treatment options. Diagnosis of these lesions on post-therapy scan would save time and cost of additional imaging and would direct the patient to proper management. Non-iodine lesions are also of prognostic significance and have a worse prognosis. In one of the studies,² authors have seen non-iodine avid lesions in 21% of patients, while in our study it was 9%. According to literature, dedifferentiated thyroid cancer can show non-iodine avid metastasis in 30% of cases and it is highly associated with certain aggressive histopathology like solid, insular, trabecular variants of poorly differentiated cancer, Hürthle cell carcinoma, papillary thyroid cancer with cribriform, columnar, or tall cell variants.¹

Our study has shown a significant difference in WBS planar and SPECT/CT imaging in ATA risk stratification, TNM staging and management, and thus the outcome of DTC. Our findings are similar to other studies ²,¹⁷,²⁷ where risk classification was changed in 6.4%, 25%, and 35.6% of patients respectively after SPECT/CT and change in TNM stage was seen in 6.1% ³, 25.9%²⁷ and 21%²¹ patients. Similarly, change in therapeutic plan was changed in 2.0%, 24%, and 19.4% of patients ³,⁷,²⁰ after SPECT/CT. This variability in results may be explained due to differences in the qualitative assessment of image findings, patient population, age, histopathologies, and variation in study protocols. Some studies have performed diagnostic ¹³¹-I scan before RAI therapy, however others did not, some have performed SPECT/CT only in equivocal cases, while some studies did not include low-risk patients, as these patients were not treated with RAI. There were differences in study samples and type of analyses (lesion based vs patient-based).

Overall, additional SPECT/CT imaging improves diagnostic accuracy, anatomic localization and helps in further characterization of lesions, especially equivocal areas of iodine uptake and non-avid iodine lesions. This alters the TNM staging and initial risk stratification of the patients. The management plan also changes accordingly and it avoids additional imaging in most of the cases.

Our study has limitations. It was a single-centre retrospective study with a small sample size with short term follow-up. Secondly, metastases were diagnosed on thyroglobulin levels and imaging results, while histopathology was not always available. Another limitation in our study was interpretation of WBS planar images with multiple foci of uptake in neck, where
one prominent uptake was considered residual thyroid tissue and rest of them as lymph node metastases due to limitation of planar images to localise the area of uptake. It has been seen on SPECT/CT images that residual thyroid tissue can be seen as multiple foci of uptake.

**Conclusion**
SPECT/CT is a powerful diagnostic tool that allows better detection and further characterization of lymph node and distant metastasis of well-differentiated thyroid carcinoma compared to WBS planar imaging alone. It also alters risk stratification and clinical staging and management plan of patients. It is recommended that SPECT/CT should be routinely performed in the evaluation of well-differentiated thyroid carcinoma patients after radioiodine therapy.

**Conflict of Interest**
The authors declare no conflicts of interest.

**Funding**
No funding was received for this study.

**References**


11. Michael Tuttle, Bryan Haugen, Nancy D. Perrier. The Updated AJCC/TNM Staging System for Differentiated and Anaplastic Thyroid Cancer (8th edition): What changed and why?. Thyroid © Mary Ann Liebert, Inc. DOI: 10.1089/thy.2017.0102


14. Tharp K, Israel O, Hausmann J, Bettman L, Martin WH, Daitzchman M et al. Impact of 131I-SPECT/CT images obtained with an integrated system in the follow-up of


Figure 1: Patients enrolment chart
Figure 2: Thyroid bed Vs lymph nodal metastases in a 76 years old male patient a) Anterior, b) posterior I-131 Whole body planar images reveal multiple foci of iodine uptake in medial and right lateral neck region consistent with thyroid bed residual and neck lymphadenopathy c) Coronal SPECT/CT images of the neck shows Iodine avid foci are localised in post-operative thyroid bed with no neck lymph nodal metastasis.
Figure 3: Iodine avid distant metastases in 67 years old female patient a) Anterior, b) posterior I-131 Whole body planar images reveal multiple areas of abnormal iodine avid distant metastases. c) SPECT/CT coronal image shows iodine avid multiple lung, liver, and skeleton distant metastases.
Figure 4: Non-iodine avid distant metastases in 73 years old male patient a) Anterior and b) Posterior I-131 Whole body planar images do not reveal any abnormal distant metastases. c) SPECT/CT axial image shows non-avid multiple small pulmonary nodules, d) 18-F FDG PET-CT axial fused image shows avid pulmonary nodules consistent with distant metastases.
**Figure 5:** The bar graph showing a comparison of results between a) WBS Planer imaging and b) SPECT/CT imaging. No discrepancy in thyroid bed residual tissue, while a significant change in interpretation of neck lymph node and distant metastasis.

**Table 1:** Change in risk stratification after SPECT/CT.

<table>
<thead>
<tr>
<th>Thyroid cancer risk stratification (%)</th>
<th>Whole body planar imaging</th>
<th>SPECT/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>35.8</td>
<td>44.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>53.8</td>
<td>38.4</td>
</tr>
<tr>
<td>High</td>
<td>10.2</td>
<td>16.6</td>
</tr>
</tbody>
</table>

*SPECT/CT: Single photon emission computed tomography- Computed tomography*