I-131 Postablation SPECT/CT Predicts Relapse of Papillary Thyroid Carcinoma more Accurately than Whole Body Scan

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Abstract. *Background/Aim:* The aim of the study was to prospectively compare I-131 postablation Whole Body scan (WBS) and Single Photon Emission Computerized Tomography/Computerized Tomography (SPECT/CT) scan on thyroid cancer patients. *Patients and Methods:* Overall, 58 patients with papillary thyroid carcinoma were submitted to total thyroidectomy and I-131 remnant ablation. Post-ablation WBS and SPECT/CT scans performed on the same day were compared. *Results of SPECT/CT* were confirmed by neck and upper mediastinum ultrasound scan and on specific cases by a fully diagnostic CT scan, other tests and definitive histology acting as the gold standard. A total of 36/58 patients were followed-up for 5 years to detect relapse. *Results:* Mac Nemar Chi square and Fisher's exact tests disclosed statistically significant differences between WBS and SPECT/CT scan, concerning cervical lymphadenopathy detection ($p=0.031$) and relapse prediction by NM stage ($p=0.033$), respectively; SPECT/CT was more accurate in both comparisons. *Conclusion:* In papillary thyroid carcinoma I-131 post-ablation SPECT/CT scan detects cervical lymphadenopathy and predicts relapse by NM stage more accurately than WBS.

I-131 post-ablation Whole Body scan (WBS) in patients with a well differentiated thyroid carcinoma (DTC) delivers more information than the pre-ablation diagnostic scan due to the high I-131 ablative dose delivered, and therefore is capable of altering stage and therapeutic management of patients (1, 2). However, planar WBS with I-131 in patients with DTC offers poor imaging data. On the contrary, a SPECT/CT scan obtains three dimensional images and offers accurate anatomometabolic information (3). There is growing evidence that SPECT/CT, especially with a dedicated hybrid device, contributes to a higher diagnostic accuracy by detecting infiltrated lymph nodes and distant metastases from DTC, accurately localizing the metastatic foci and differentiating physiological from pathological uptake of the radiopharmaceutical (3-6). This information contributes to a more accurate TNM staging and consequently to a better risk stratification of DTC patients and therapeutic management (3, 7). Therefore SPECT/CT has an increasing use in the detection of metastatic disease in DTC.

The aim of this study was to compare I-131 post-ablation SPECT/CT scan with planar I-131 post-ablation Whole Body scan (WBS) in restaging of patients with DTC after total thyroidectomy and ablation therapy, as well as in predicting relapse within a long period of follow-up. We planned a prospective study with a dedicated hybrid SPECT/CT device.

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Key Words: Papillary thyroid carcinoma, I-131 postablation scan, whole body scan, SPECT/CT.

Patients and Methods

Fifty-eight patients with DTC who had undergone total thyroidectomy followed by I-131 remnant ablation, were enrolled in the study between December 2011 and October 2018. All 58 patients, 25 men and 33 women aged 30 to 82 years, were diagnosed with DTC of the papillary type. After total thyroidectomy a diagnostic I-131 uptake measurement with 2.22 MBq (60 μ Ci) was performed, in order to appreciate remnant thyroid tissue presence. Thyroglobulin (Tg) levels and antithyroglobulin

antibodies (TgAb) were measured. I-131 ablative doses ranged from 2775 to 5550 MBqs (75-150 mCi). Five to seven days after the ablative dose a post therapy WBS was acquired using a SOPHA dual DST XLI Nuclear Gamma Camera. A SPECT/CT scan of the neck and thorax was performed on a Philips BrightView XCT device on the same day. Informed consent was obtained from all the enrolled patients and the protocol was approved by the Ethical Committee of Hygeia Hospital, adhering to the principles of the Declaration of Helsinki.

A subsequent neck and upper mediastinum U/S scan was performed on all patients, in order to evaluate thyroid and thyroglossal cyst remnants and abnormal cervical lymph nodes (8, 9). When distant findings were present on WBS of these 58 patients, an extra SPECT/CT study was performed to clarify these findings in the respective bed position. On dubious cases a fully diagnostic CT scan was planned, and occasionally another test. WBS and SPECT/CT scans were read separately and in comparison, by two experienced Nuclear Medicine physicians. As gold standard, we used surgery with definitive histology, a neck and upper mediastinum U/S on occasions of a fully diagnostic CT scan, as well as close clinical and radiological monitoring along with changes in Tg. The patients are followed up to this date. On thirty-six patients who completed a 5-year follow-up, the relapse rate was assessed.

A Mc Nemar chi square statistical test was used to determine whether I-131 planar WBS and SPECT/CT distributions had significant differences. Cohen's κ statistics was calculated in order to assess the agreement between the two methods. Fisher's exact test was used to assess differences in proportion of patients relapsing within five years by NM stage, as determined by WBS and SPECT/CT. All p -values reported were 2-sided. A p -value < 0.05 was considered significant. Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) version 20 software.

Results

Fifty-eight patients with papillary thyroid carcinoma underwent a post-ablation I-WBS and a SPECT/CT scan of the neck and thorax, respectively. Ten out of them required an additional SPECT/CT scan on another bed position, because of indeterminate findings in distant areas on the WBS. All patients had a pre-ablation TSH value above 30 mUI/l. TSH, Tg and postoperative uptake values are presented in Table I. Antithyroglobulin antibodies were present in four patients.

We used a focus-based and an NM stage-based patient analysis on our data. All radioactive foci on WBS and SPECT/CT were grouped into six categories, *i.e.*, presence/absence of thyroid remnant, thyroglossal cyst, thymus, cervical lymph nodes, mediastinal foci/nodes and distant metastases (Table II) (Figures 1a and b, 2a and b, 3a and b). Neck and upper mediastinum U/S, additional SPECT/CT views on other than neck and lung areas as well as a fully diagnostic CT scan helped in further characterizing foci as benign or malignant. In particular in four cases, three with lung metastases (Figure 2a and b) and one with an

Table I. Sample characteristics - TSH, Tg and post-op uptake (%) ($N=58$).

	Median (IQR)	Range
TSH (mUI/l)	83 (65, 112)	30.9, >200
Tg (ng/ml)	3 (0, 10)	<0.2, 47.1
Post-op uptake (%)	3 (1, 5)	0.5, 15.4

infiltrated pericolic lymph node (Figure 4), a fully diagnostic CT scan confirmed SPECT/CT findings. On a patient with abdominal foci and presumed bowel activity on SPECT/CT, a colonoscopy confirmed SPECT/CT results. Four patients staged as N0M0 on WBS and as N1M0 on SPECT/CT were submitted to lateral compartment cervical lymphadenectomy. Definitive histology showed infiltrated lymph nodes.

Concerning the focus-based analysis, on the total number of findings, WBS gave 27 false positive (7.76%) and 23 false negative (6.61%) results (Table II).

After performing SPECT/CT, several changes were induced in N and M staging in the framework of TNM classification, as compared with the initial stage estimation which comprised histopathology and WBS findings. On cross tabulation of NM stage through WBS and SPECT/CT only 24 patients with N0M0 stage and 6 patients with N1M0 stage were classified correctly in the same stage by both methods (Table III). Considering N stage, there were 14 cases of downstaging on SPECT/CT from N1 to N0 and 8 cases of upstaging from N0 to N1. Considering M stage, there were two cases of downstaging from M1 to M0 and 5 cases of upstaging from M0 to M1. Cohen's κ was 0.053 and not statistically significant ($p=0.307$), which signified that the degree of agreement between the two methods was very low. The accuracy of WBS in determining NM stage was low (51.72%), while that of SPECT/CT 100% respectively.

Mc Nemar chi square statistical analysis of our data revealed a statistically significant difference concerning the results of infiltrated cervical lymph nodes between the two methods ($p=0.031$). This means that SPECT/CT could detect infiltrated cervical lymph nodes more accurately than WBS, by decreasing false negative and false positive findings. No statistically significant difference between WBS and SPECT/CT distributions ($p>0.05$) concerning detection of thyroid remnant, thyroglossal cyst, thymus, mediastinal foci/lymph nodes and distant metastases was noticed.

Thirty-six out of fifty-eight patients were followed up for 5 years and the relapse rate by NM stage on WBS and SPECT/CT was assessed (Table IV). In total, four cases of relapse were observed. These cases of relapse were attributed to NM stages as classified by WBS and SPECT/CT. A 4.3% of patients in N0M0 stage by SPECT/CT presented with

Table II. Focus based analysis on WBS and SPECT/CT results. False-positive and false-negative results of WBS. All figures represent N (%).

Focus	Both +	Both –	FP	FN
Thyroid remnant	50 (86.21%)	5 (8.62%)	2 (3.45%)	1 (1.72%)
Thyroglossal cyst	11 (18.97%)	36 (62.07%)	6 (10.34%)	5 (8.62%)
Thymus	2 (3.45%)	53 (91.38%)	1 (1.72%)	2 (3.45%)
Cervical lymph nodes	6 (10.34%)	33 (56.90%)	14 (24.14%)	5 (8.62%)
Mediastinal foci/Nodes	1 (1.72%)	50 (86.21%)	2 (3.45%)	5 (8.62%)
Distant metastases	0 (0.00%)	51 (87.93%)	2 (3.45%)	5 (8.62%)
All foci	70 (20.11%)	228 (65.52%)	27 (7.76%)	23 (6.61%)

Table III. Cross tabulation of N, M Stage by SPECT/CT vs. WBS (N=58). Cohen's κ statistics assesses agreement between the two methods.

	N, M Stage - WBS				<i>p</i> -Value (Cohen's κ)
	N0M0 N (%)	N1M0 N (%)	N0M1 N (%)	Overall N (%)	
N, M Stage - SPECT/CT					0.307 (0.053)
N0M0	24 (70.6)	14 (63.6)	2 (100.0)	40 (69.0)	
N1M0	7 (20.6)	6 (27.3)	0 (0.0)	13 (22.4)	
N0M1	2 (5.9)	0 (0.0)	0 (0.0)	2 (3.4)	
N1M1	1 (2.9)	2 (9.1)	0 (0.0)	3 (5.2)	
Total	34 (58.6)	22 (37.9)	2 (3.45)	58 (100.0)	

relapse, while for patients with a higher than N0M0 stage by SPECT/CT, the proportion was 23.1%. In particular, in patient group N0M0, one out of 23 patients had a relapse, in the N1M0 group one out of 8 and in the N1M1 group two out of three (Table IV).

Fisher's exact test pointed the statistical differences in the proportion of patients relapsing within 5 years by NM stage as determined through WBS and SPECT/CT. There was a statistically significant difference in relapse proportion by NM stage when assessed with SPECT/CT ($p=0.033$), while with WBS this difference was not significant ($p=0.209$) (Table IV).

Discussion

The established way of staging a DTC postoperatively is by planar I-131 WBS together with serum thyroglobulin measurements (10). This helps evaluate thyroid remnant and presence of regional and distant metastases. Post-ablation WBS with thyroglobulin levels are also used for restaging and follow-up (11, 12). However, SPECT/low dose CT discloses more foci in comparison with planar WBS and U/S and offers a more accurate localization of the foci. SPECT/CT allows a differentiation between physiological

uptake of the radiopharmaceutical and malignant uptake, leading to a more effective therapy (3, 13). In comparison with WBS, SPECT/CT improves diagnostic performance because it reveals more pathological lesions, reduces false positive and equivocal findings, alters nodal stage and risk stratification of the patients, and has therefore a significant impact on early risk stratification, therapy, management and prognosis of DTC (3, 5, 7, 14-24). In addition, SPECT/CT can clarify false positive uptake of I-131 due to sodium iodide symporter expression by tissues and consequent trapping to inflammation/infection, and to increased perfusion etc. (25, 26). In cases with negative I-131 WBS and elevated serum thyroglobulin FDG-PET could detect all patients with metastatic cervical lymph nodes, while technetium-99m tetrofosmin SPECT as well as technetium-99m methoxyisobutylisonitrile SPECT could detect only a proportion of the affected patients (27, 28).

Due to all the above mentioned reasons, we chose to perform a SPECT/CT scan on all our studied patients. Results of SPECT/CT were confirmed by neck and upper mediastinum U/S scan and on specific cases by a fully diagnostic CT scan. In one patient an additional colonoscopy confirmed the presence of bowel activity as pointed by

Figure 1. Thyroglossal cyst remnant on SPECT/CT. a: Increased radioactive uptake is seen on WBS in an area considered as thyroid remnant. b: On SPECT/CT the same area is a thyroglossal cyst remnant (white arrow).

Figure 2. False-negative WBS. *a*: WBS showing high radioactive uptake corresponding to the thyroid remnant (white arrow). No pathological uptake is seen elsewhere. *b*: SPECT/CT on the same patient shows areas of high radioactive uptake corresponding to the thyroid remnant, a right regional cervical lymph node and two lung foci, one right and one left.

SPECT/CT. In patients who received a lateral compartment lymphadenectomy, histology confirmed SPECT/CT results.

SPECT/CT proved particularly helpful in cases considered as indeterminate on WBS, *i.e.* cases with

significant thyroid remnant and doubtful presence of cervical lymph nodes, increased Tg which could not be justified by the existing thyroid remnant, suspicion of presence of a thyroglossal cyst and lastly in cases with

Figure 3. *False-positive WBS. a: WBS demonstrates an area of high radioactive uptake in the upper mediastinum to the left of the midline (black arrow). b: SPECT/CT of the thorax on the same patient shows that the high uptake area corresponds to oesophageal activity.*

dubious uptake in the abdominal area and other distant areas not attributable to physiologic or pathologic activity with certainty.

In our study, by comparing WBS with SPECT/CT in the same patients we concluded that SPECT/CT is significantly more accurate in demonstrating infiltrated regional cervical lymph nodes, by reducing false-positive and false-negative

results provided by WBS. On the other hand, SPECT/CT disclosed infiltrated mediastinal lymph nodes and distant metastases, thus reducing false negatives, but not to a statistically significant degree. In the cervical lymph node work up, hybrid imaging clarified the poor imaging results of planar WBS. Due to low dose CT the anatomic information on the exact number of infiltrated cervical

Figure 4. High radioactive uptake is seen on SPECT/CT corresponding to a right paracolic lymph node (white arrow on CT). The same area of increased uptake on WBS was considered physiological bowel uptake.

lymph nodes was limited, however, on some occasions we did not wish to increase the radiation dose absorbed by the patients with an additional fully diagnostic CT. On WBS the streak artifact from a thyroid remnant may cover up malignant lesions in the mediastinum and ribs and since differentiation between skeletal and soft tissue structures by low dose CT is satisfactory, SPECT/CT was proven accurate in disclosing a rib bony metastasis. In addition, SPECT/CT could demonstrate uptake on metallic dental restorations mostly in the mandibular bone and in the left maxillary sinus due to infection, leading to downstaging of the patient (6, 29, 30).

Concerning radioactive contamination, SPECT/CT could differentiate contamination from malignant bone involvement which is difficult on planar WBS, since it requires washing of

Table IV. Proportion of patients relapsing within 5 years by N, M Stage (N=36).

	Relapse		Overall N (%)	p-Value
	No N (%)	Yes N (%)		
N, M Stage- WBS				0.209
N0M0	21 (95.5)	1 (4.5)	22 (100.0)	
N1M0	9 (75.0)	3 (25.0)	12 (100.0)	
N0M1	2 (100.0)	0 (0.0)	2 (100.0)	
N, M Stage - SPECT/CT				0.033
N0M0	22 (95.7)	1 (4.3)	23 (100.0)	
N1M0	7 (87.5)	1 (12.5)	8 (100.0)	
N0M1	2 (100.0)	0 (0.0)	2 (100.0)	
N1M1	1 (33.3)	2 (66.7)	3 (100.0)	

the respective area, additional projections and delayed acquisitions. Finally, SPECT/CT helped clarify the presence of thyroid remnant, thyroglossal cyst and thymus (31).

Considering the statistical analysis performed, a statistically significant difference was found between the two methods only in the results concerning infiltrated cervical lymph nodes ($p=0.031$). In addition, staging performed by SPECT/CT was significantly associated with a probability of relapse ($p=0.033$), whereas this was not the case with WBS results ($p=0.209$).

The advantages of our study are the following: We planned a prospective study on 58 DTC patients with a planar WBS and a SPECT/CT scan on a dedicated hybrid device and compared the results. To our knowledge this is the first Greek study concerning post-ablation SPECT/CT in papillary thyroid carcinoma. Our study was focus-based so that we could sum up all false negative and false positive findings, but it was also NM stage-based, especially in terms of follow-up (13).

In conclusion the results of our study showed that in patients with DTC, post-ablation I-131 SPECT/CT was superior to WBS in determining cervical lymphadenopathy and in predicting relapse by NM stage classification to a statistically significant degree.

Conflicts of Interest

The Authors of this study declare no conflicts of interest.

Authors' Contributions

Doctors J. Koutsikos and S. Giourgouli recruited the 58 patients of the study. They performed I-131 diagnostic uptake measurements, administered the I-131 therapeutic dose and performed the WBS. They follow up patients till now; Doctors V. Prassopoulos, Th. Pipikos and F. Vlachou performed SPECT/CT studies on all 58 patients. Doctors Prassopoulos and Koutsikos read all WBS and SPECT/CT scans separately and in comparison; Dr J. Malamitsi processed the data and wrote the manuscript; Dr S. Zachaki performed the statistical analysis of the data.

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