Added value of I131 SPECT/CT imaging after I-131 ablation in patient with differentiated thyroid cancer

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Abstract

Aim:to evaluate the diagnostic value of I-131 SPECT/CT over traditional I-131 whole body planar scintigraphy during post-I-131 ablative dose imaging or during regular follow up of patient with differentiated thyroid cancer.

Material and methods:a total of 108 patients with differentiated thyroid were subjected to total or near total thyroidectomy and post-operative neck US to enroll status of residual disease together with base line serum TG. Planar I-131 whole body scan was done using dual head gamma camera. SPECT/CT was done by hybrid system composed of the gamma camera, used in planar whole body imaging, and integrated X-ray transmission device low dose CT .Neck and chest SPECT/CT was performed as well as on any other suspected areas of enhanced uptake seen in the planar imaging to assess the uptake of I-131 at the neck and rest of the body and to compare the whole body planar scintigraphy.

Results:Thyroid Bed: In 70 patients who performed post-therapy scan, there were 68 foci in the thyroid bed seen at both whole-body scintigraphy and SPECT/CT as being in the thyroid bed. Six foci which were interpreted as equivocal in whole body scans were seen in SPECT/CT as thyroid duct remnant. While in the 38 patients who had follow up diagnostic whole body scans, 8 foci were matched with SPECT/CT showing thyroid tissue uptake (residue in 5 and recurrence in 3), while SPECT/CT detected two more lesions in the thyroid bed that were false-negative in WBS in two patients. LN Metastases: In both post-therapy and diagnostic scans, a total of 24 radioactive foci were identified as potential LN metastases on whole-body scintigraphic images. Eight foci were believed to be clearly positive for uptake, while 10 were equivocal for LN metastasis. Six of the "positive nodal uptake" foci were confirmed to be accumulations within metastatic LNs. While the remaining 4 areas of uptake were shown to be due to uptake in saliva retained in the oral cavities (two foci), unilateral uptake in the submandibular glands (one focus) and skin contamination in the right site of neck (one focus) when the SPECT/CT image was reviewed. Distant Metastases: In both post-therapy and diagnostic scans, 28 areas of uptake were found and categorized as distant metastases on whole-body scintigraphic images (8 foci in lungs and 20 foci in bones). Fifteen of these 28 areas were believed to be positive findings. SPECT/CT showed that 15 of the 28 foci positive for uptake were metastases to the extrathyroidal organs, such as lungs (5 foci) and bones (10 foci). Thirteen foci were noted as equivocal for distant metastases by planar scans. SPECT/CT could localize 6 of 13 equivocal foci as definite metastases (3 in lungs and 3 in bones). The remaining 7 equivocal foci were shown to represent physiologic uptake or benign lesions, such as colons (two foci), breast uptake (two foci), stomach (one focus), and renal cyst (one focus) and the last one is an area of uptake that was believed to be positive for pelvic or femoral bone metastasis at whole-body scintigraphy was shown to be the uptake in a region of soft tissue inflammation in the right buttock at SPECT/CT . Overall, in a total of 31 radioactive foci in 17 patients, the interpretation of whole body scintigraphic findings was altered in light of SPECT/CT findings

Conclusion:SPECT/CT improved the detection and localization of LN metastases and distant metastases compared with whole-body scintigraphy and had a considerable effect on the management of patients with well-differentiated thyroid carcinoma.

Introduction

According to the American Cancer Society; ASCO in 2013, more than 60,000 new cases of thyroid cancer are diagnosed in USA every year with mortality rates approximately around 2000 annually. Thyroid cancer had a rising incidence in both genders and in all ethnic groups. [1]

Most of the thyroid gland tumors are of epithelial origin; papillary, follicular or anaplastic in nature. Papillary thyroid cancer represents 80-90% of all differentiated thyroid and is followed by follicular pathology in incidence [2, 3]. Risk factors of thyroid carcinoma are exposure to irradiation during childhood either accidentally or therapeutic neck irradiation in Hodgkin lymphoma or craniospinal irradiation of children [4]. Only in papillary thyroid cancer, there are proven link between positive history in the first degree relatives and disease risk. [5, 6]

Papillary thyroid cancer is characterized by being multifocal, un-capsulated, partially cystic with cells containing big, oval and crowded nuclei beside areas of micro classification foci; psammoma bodies [7-9]. However, follicular thyroid cancer might be either well-differentiated or poorly differentiated and carry worse prognosis than papillary thyroid cancer. [10]

The management of thyroid nodules are always a matter of important. The clinical examination, the ultrasonography and the TSH level are the standard for their evaluation. [11] High or normal TSH level might raise consideration for Fine needle aspiration. [12]

The American Thyroid Association (ATA) developed a risk stratification system. Low risk patients are those having papillary thyroid cancer confined to the thyroid with low risk of recurrence at 6%. Intermediate risk patients are those having regional metastasis in the LNs, worrisome histology, vascular or extracapsular extension with risk of recurrence at 21%. High risk patients are those with tumor infiltrating extra-thyroid area or distant metastasis and risk of recurrence at 68%. [13]

The standard surgical procedure are the total thyroidectomy which included; removal of the entire thyroid gland or near total thyroidectomy with preservation of the posterior thyroid capsule beside therapeutic lymph node dissection is intermediate and high risk patients. [14, 15].

Radioactive iodine ablation aims to destroy any remaining post-resection residual thyroid tissue. The I^{131} ablation depends on delivering high doses of radioactive iodine more than 80 mCi aiming to reduce 10 years recurrence risk by 30% [16-18]. Stimulation of remnant thyroid tissue and metastatic disease by higher levels of TSH is necessary before delivery of RAI to enhance its killing potential [19].

Following total thyroidectomy, TSH suppression through levothyroxine replacement therapy is of extreme necessary to reduce risk of disease activation [20]. Serum thyroglobulin and anti-thyroglobulin were the best molecular marker to monitor disease response to treatment.[21]

Material and methods

The aim of this work was to evaluate the diagnostic value of I-131 SPECT/CT over traditional I-131 whole body planar scintigraphy during post-I-131 ablative dose imaging or during regular follow up of patient with differentiated thyroid cancer.

This was a study reviewing a total of 108 patients with differentiated thyroid cancer referred to Nuclear Medicine Units of South Egypt Cancer Institute (from January 2015 to February 2016), as well as patients referred to Kasr Alainy Center of Oncology and Nuclear Medicine, Cairo University (NEMROCK, from March 2016 to December 2016).

All these patients were subjected to total or near total thyroidectomy and post-operative neck US to enroll status of residual disease together with base line serum TG.

Inclusion criteria should include pathological confirmation of differentiated thyroid carcinoma papillary and follicular thyroid carcinoma and surgical resection in the form of total or near total thyroidectomy.

The patients followed a low-iodine diet for 2 weeks in preparation for radioiodine administration beside withdrawal of L-thyroxin for 25-40 days before I-131 administration. Serum TG level was evaluated for all patients before scintigraphy or iodine therapy. Post- operative neck US was done and I-131whole body imaging was done for all patients (diagnostic, 48-72 hrs after dose of 3-5 mci or and 5-7 days post-therapy). The administered dose of I-131 ranged from 50-200 mCi (1.8 to 7.4 GBq).

Exclusion criteria included undifferentiated thyroid carcinoma, evidence of other malignancy.

Data of the studied patients included; patient name, ID, age. Sex, Scan type, RAI dose, TG and TSH at time of scan, nodal positivity, histology, vascular invasion, tumor focality, patient' risk, residual on neck ultrasonography post-operatively .

Planar I-131 whole body scan was done in both anterior and posterior projection using dual head gamma camera at aspeed 15cm/min

SPECT/CT was done in the same session by hybrid system composed of the gamma camera, used in planar whole body imaging, and integrated X-ray transmission device low dose CT .Neck and chest SPECT/CT was performed as well as on any other suspected areas of enhanced uptake seen in the planar imaging to assess the uptake of I-131 at the neck and rest of the body and to compare the whole body planar scintigraphy.

<u>Data Analysis</u>

Whole-body scintigraphic and SPECT images were reviewed by two nuclear medicine physicians involved in patient care. The reviewers were blinded to prior interpretations and results of prior imaging studies. First, all whole-body scintigraphic planar images were evaluated for foci with I-131 uptake higher than the surrounding background. Foci localized on the medial portion of the neck were categorized as positive for thyroid bed uptake while located laterally were categorized as positive for uptake of LN metastases. Foci in the mediastinal region were categorized as positive for LN metastases. Uptake in the lung fields was considered positive for lung metastases. Even if diffuse pulmonary uptake was found, these were counted as one metastasis for each lung.

SPECT/CT findings were next described with the anatomic localization of I-131 uptake. The change in the interpretations of foci from whole-body scintigraphic to SPECT/CT images was analyzed in the thyroid bed, LN, and distant metastases. Considering the reference standard mentioned below, the lesions determined to be positive for uptake with SPECT/CT but negative for uptake with whole-body scintigraphy (false-negative findings) were also evaluated.

The reference standard was at least one of the following methods: histopathologic diagnosis in three patients with accessible cervical LNs uptake; diagnostic imaging by using other modalities of US and/or diagnostic CT in 33 patients, fluorine 18 (18F) fluorodeoxyglucose positron emission tomography (PET)/CT in 2 patients; clinical follow-up from 6 to 18 months in the rest of patients.

Statistical analysis

Initial data exploration was performed via determining the mean, median, standard deviation. Regression analysis was done for scale data. Initial hypothesis testing of quantitative data was done by the methods of comparing means (Independent-samples T-Test) while for categorical data; Chi-Square test was used. For bivariate analysis, Pearson correlation was used. Significant statistical findings were considered when a date posed < 0.05 probability of occurrence of an event when null hypothesis was assumed. Significant variables were subjected to multivariate analysis for extraction of true independent variable with their hazard ratio.

Table 1.1 – patients charcteristics

Parameter	All patients (N=108)	Post-therapy (N=70)	Diagnostic (N=38)
Age (years)			
Range	16-73	24-73	16-67
Mean	41.2±14.4	39.7±14.4	43.9±14.1
SEX			
Female	78 (72.2%)	48 (68.6%)	30 (78.9%)
Male	30 (27.8%)	22 (31.4%)	8 (21.1%)
Pathology			
Papillary thyroid carcinoma	84 (77.8%)	56 (80%)	28 (73.7%)
Follicular thyroid carcinoma	24 (22.2%)	14 (20%)	10 (26.3%)
TG (uIU/L)			
Range	0.2-652	0.6-652	0.2-600
Mean	87.3	86.6	88.5
TSH (mU/L)			
range	14-100	14-100	27-100
Mean	68±27.0	69.7±27.0	67.2±27.2

Results

The study included 108 patients; 30 males (27.8%) and 78 females (72.2%) with range of age 16-73 years with mean age of 41.2±14.4 years. Papillary thyroid carcinoma was the commonest pathological type representing 77.8% (84 patients). 20.4% of the patients are of low risk, 68.5% were classified as intermediate risk while 11.1% are high risk ones.

I-131 whole body and SPECT/CT scans were performed 5-7 days after therapeutic dose in 70 patients and 2-3 days after diagnostic dose (mean dose of 148.6±44.2 mCi (range 50-200 mCi) in 38 patients coming for follow up. Patients demographics are mentioned in the table 1.1.

There were a significant positive association both modalities and serum TG level. The positivity of SPECT/CT was significantly associated with patient's risk stratification in detection of thyroid bed residue, LNs, lung and bone metastases. On the other hand, planar finding was significantly associated with risk of patient in thyroid bed residue detection only. There was non-significant association between both modalities and the type of pathology. Table 1.2

Scan type	Clinical Parameter	Pathology P value	Risk P value	TG P value
SPECT/CT	thyroid bed	Not Significant	0.001	0.001
	LNs	Not Significant	0.03	0.003
	lung metastases	Not Significant	0.02	0.04
	bone metastases	Not Significant	0.04	0.02
Planar	thyroid bed	Not Significant	0.001	0.001
	LNs	Not Significant	NS	0.004
	lung metastases	Not Significant	NS	0.004
	bone metastases	Not Significant	NS	0.01

Lesion based analysis

Thyroid bed

In 70 patients who performed post-therapy scan, there were 68 foci in the thyroid bed seen at both whole-body scintigraphy and SPECT/CT as being in the thyroid bed. Six foci which were interpreted as equivocal in whole body scans were seen in SPECT/CT as thyroid duct remnant in two sites, pretracheal LNs uptake in two foci and skin contamination in the other two lesions.

While in the 38 patients who had follow up diagnostic whole body scans, 8 foci were matched with SPECT/CT showing thyroid tissue uptake (residue in 5 and recurrence in 3), while SPECT/CT detected two more lesions in the thyroid bed that were false-negative in WBS in two patients. The intensity of the radioactive uptake in the thyroid bed of these two patients was too faint to detect at whole-body images, but at SPECT/CT, an uptake in the thyroid remnant was obviously identified.

Therefore, there were a total of eight patients (6 in post-therapy scans and 2 in diagnostic scans) in whom the whole-body scintigraphic interpretations of uptake in the thyroid bed were corrected after addition of SPECT/CT findings (Table 6). However, there was no significant disagreement between whole-body scintigraphic and SPECT/CT findings in thyroid bed uptake (P >0. 05).

LN Metastases

In both post-therapy and diagnostic scans, a total of 24 radioactive foci were identified as potential LN metastases on whole-body scintigraphic images. Eight foci were believed to be clearly positive for uptake, while 10 were equivocal for LN metastasis. Six of the "positive nodal uptake" foci were confirmed to be accumulations within metastatic LNs. Most of these metastatic LNs were located close to the thyroid bed, and the accumulations in the LNs were masked by intense thyroid bed uptake at whole-body scintigraphy.

While the remaining 4 areas of uptake were shown to be due to uptake in saliva retained in the oral cavities (two foci), unilateral uptake in the submandibular glands (one focus) and skin contamination in the right site of neck (one focus) when the SPECT/CT image was reviewed. There was a significant difference between the whole-body scintigraphic and SPECT/CT detectability of cervical LNs metastases ($P < 0.05$).

Distant Metastases

In both post-therapy and diagnostic scans, 28 areas of uptake were found and categorized as distant metastases on whole-body scintigraphic images (8 foci in lungs and 20 foci in bones). Fifteen of these 28 areas were believed to be positive findings. SPECT/CT showed that 15 of the 28 foci positive for uptake were metastases to the extrathyroidal organs, such as lungs (5 foci) and bones (10 foci). Thirteen foci were noted as equivocal for distant metastases by planar scans. SPECT/CT could localize 6 of 13 equivocal foci as definite metastases (3 in lungs and 3 in bones). The remaining 7 equivocal foci were shown to represent physiologic uptake or benign lesions, such as colons (two foci), breast uptake (two foci), stomach (one focus), and renal cyst (one focus) and the last one is an area of uptake that was believed to be positive for pelvic or femoral bone metastasis at whole-body scintigraphy was shown to be the uptake in a region of soft tissue inflammation in the right buttock at SPECT/CT due to repeated intramuscular injection and finally resolved by means of treatment with antibiotics on clinical follow up of the patient. There were significant differences in the findings between whole-body scintigraphy and SPECT/CT as regards distant metastases detection (P <0.05).

Location	Post-therapy (70 patients)		Diagnostic (38 patients)	
	SPECT/CT findings	Planar findings	SPECT/CT findings	Planar findings
Thyroid bed (no of lesions)				
- Positive	70	68	10	8
- Equivocal	0	6	0	0
- Negative	4	0	0	2
Total	74	74	10	10
LNs metastases (no of lesions)				
- Positive	10	6	4	2
- Equivocal	0	8	0	2
- Negative	8	4	2	2
Total	18	18	6	6
Distant metastases (no of lesions)				
- Positive	17	12	4	3
- Equivocal	0	8	0	5
- Negative	3	0	6	2
Total	20	20	10	10

Overall, in a total of 31 radioactive foci in 17 patients, the interpretation of whole body scintigraphic findings was altered in light of SPECT/CT findings

Discussion

The clinical utility of SPECT/CT for the diagnosis of well-differentiated thyroid carcinoma patients is still growing and under research. Referring to previous studies, The diagnostic value of SPECT/CT has varied widely from 15% in 25 patients to 73.9% in 148 patients [22, 23]; these percentages represent patients who had findings with variable interpretations between whole-body scintigraphy and SPECT/CT. In the current study, the findings of diagnostic whole-body scintigraphy were altered in 10 (9.2%) of 108 patients in light of SPECT/CT findings. In addition, in our study a high-activity of I-131 (30-200 mCi) in post-therapy scans could yield a higher detection rate of radioactive foci than a low-activity diagnostic I-131 (3-5 mCi) scans. Higher radioactive iodine activity and a longer interval between radioactive iodine administration and imaging acquisition on post therapy scans would result in an increased target-to-background ratio [24, 25]. Therefore, the results of the studies using diagnostic scans, post-therapy scans, or a combination of both might be different. [23, 26-29]

Based on our study; in 70 patients who performed post-therapy scan; 22 equivocal foci in the form of 6 foci in the thyroid bed, 8 equivocal foci in cervical LNs and 8 foci in extrathyroidal (distant) sites were reevaluated after SPECT/CT compared with only 7 foci in the 38 patients who performed diagnostic scans in the form of 2 negative foci in the thyroid bed, 2 equivocal foci in cervical LNs and 5 distant foci.

For LNs and distant metastases, a significant difference was demonstrated between the interpretations of whole body scintigraphic and SPECT/CT findings ($P<0.05$). With SPECT/CT, the site of radioactive uptake was clearly identified, and the location of uptake believed to be equivocal at whole-body scintigraphy could be defined. This was obviously seen in SPECT/CT of a case with skin contamination in the neck falsely interpreted as neck LNs uptake in whole body scan and in another patient with bilateral breast uptake misinterpreted as bi. A SPECT image, instead, is a tomographic image that reduces summation artifacts and more clearly defines the spatial (depth) localization of hot spots. Moreover, CT fused with SPECT provides much higher-resolution images than does simple SPECT and can help identify the anatomic location of radioactive uptake, which might be difficult to recognize at whole-body scintigraphy [30].

Various sources of false-positive uptake, including physiologic accumulation in I-131 scintigraphy, have been reported [31, 32]. Such uptake can be found in various locations of the body and sometimes leads to diagnostic error. Differentiation of pathologic uptake from physiologic accumulation is difficult on whole body scintigraphic images, in these situations SPECT/CT fusion images are extremely helpful.

another two patients were also altered to be physiologic uptake (in salivary and submandibular glands) with addition of SPECT/CT findings. Therapeutic planning was changed in 4 patients with extrathyroidal equivocal lesions seen in whole body images, iodine therapy had been given to one patient with lung metastases and had been terminated in 3 patients with physiologic uptake.

SPECT/CT had a significant positive association with serum TG level and patient's risk stratification in detection of thyroid bed residue as well as lymph nodes, lung and bone metastases. This was expected as the increase in both the risk and serum TG may raise the possibility of presence of functioning metastatic sites that could not be resolved in whole body scan and better detected in SPECT/CT. [30].

Conclusion:

SPECT/CT improved the detection and localization of LN metastases and distant metastases compared with whole-body scintigraphy and had a considerable effect on the management of patients with well-differentiated thyroid carcinoma. Patients with higher serum TG and higher risk stratification would be the target patients who may have great benefit for adding SPECT/CT technique to their scans especially when whole body imaging is negative or equivocal.SPECT/CT should be routinely performed in the evaluation of high-risk well-differentiated thyroid carcinoma patients after radioiodine therapy or during routine follow up especially if serum thyroglobulin is significantly elevated.

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