

Differentiated thyroid carcinoma: Incremental diagnostic value of ^{131}I SPECT/CT over planar whole body scan after radioiodine therapy

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Abstract The purpose of this prospective study was to determine the incremental diagnostic value of single photon emission computed tomography/computed tomography with iodine-131 over planar whole body scan in the staging of patients with differentiated thyroid carcinoma. A total of 365 patients (270 female, 95 male) with differentiated thyroid carcinoma were treated with radioiodine therapy for thyroid remnant ablation with radical intent after thyroidectomy between January 2013 and November 2014. In addition to planar whole body scan, single photon emission computed tomography/computed tomography of neck and chest were performed. Each radioactive focus at whole body scan was classified as positive or equivocal with respect of specific territories: thyroid bed, cervical lymph nodes and distant metastases. Whole-body scan detected focal uptake in 353 patients and no uptake in 12. The location was considered equivocal in 100. Single photon emission computed tomography/computed tomography detected focal uptake in 356 patients and no uptake in nine. In three patients with negative wholebody scan, single photon emission computed tomography/computed tomography provided information about residual activity in the thyroid bed. By single photon emission computed tomography/computed tomography the location was equivocal in 18

patients only. Single photon emission computed tomography/computed tomography was helpful in 82 out of 100 patients with equivocal findings by whole body scan allowing a correct identification of the uptake sites. In a great number of equivocal whole body scan, due to high remnant activity, single photon emission computed tomography/computed tomography was able to differentiate between thyroid remnant and lymph nodes uptake. In 22 out of 100 patients with doubtful whole body scan, single photon emission computed tomography/computed tomography correctly identified nodal or distant metastases, and in 2/100 patients, focal uptake classified as metastatic by whole body scan was reclassified as para-physiological by single photon emission computed tomography/computed tomography. The TNM classification changed in 13 out of 22 patients. Single photon emission computed tomography/computed tomography improves detection and localization of the iodine-131 uptake after thyroidectomy in patients with differentiated thyroid carcinoma and it is more accurate than whole body scan to evaluate lymph nodes and to identify and characterize distant metastases. Single photon emission computed tomography/computed tomography aids assessment of lower/upper stage in a significant number of patients with differentiated thyroid carcinoma and it can affect therapy decision-making and patient management.

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Abbreviations

SPECT/CT single photon emission computed tomography/computed tomography
WBS planar whole body scan
DTC differentiated thyroid carcinoma
LN neck lymph node

rhTSH	recombinant human thyrotropin
HEGP	high-energy general purpose
ABC	automatic body contouring

Introduction

Differentiated thyroid carcinoma (DTC) is the most common endocrine cancer accounting for 1 % of all cancers diagnosed each year [1]. Based on histology, thyroid cancer is classified as papillary (80.2 %), follicular (11.4 %), Hürthle cell (3.1 %), medullary (3.5 %), and anaplastic (1.7 %) [2]. Papillary and follicular carcinomas account for the majority of DTCs and these histological variants are characterized by radioiodine (^{131}I) uptake. The 5-year survival rates for well-differentiated thyroid cancer, are 99.8 % for localized tumors, 97.0 % for tumors with regional metastases, and 57.3 % for tumors with distant metastases [3]. Dinneen et al. reported that the 10-year overall and cause-specific survival rates decreased to 24 and 27 %, respectively, in patients with distant metastasis [4].

After initial thyroidectomy, ablation of thyroid remnants by ^{131}I is performed in the vast majority of patients. Treatment of regional and/or distant metastases by ^{131}I improves the prognosis of patients with metastatic disease [5–8].

Accurate diagnosis of neck lymph node (LN) and distant metastases is mandatory for treatment planning and follow-up. The extent of localized neck nodal disease or distant metastases has a major prognostic impact [9]. Planar ^{131}I WBS, in association with serum thyroglobulin measurement, is considered the routine diagnostic procedure in patients with DTC for diagnostic work-up after thyroidectomy [10]. ^{131}I scintigraphy integrates morphologic imaging modalities, such as ultrasonography, computed tomography, and magnetic resonance imaging, for staging of patients with DTC. In restaging, treatment of metastases and long-term follow-up WBS can be useful, in addition to neck ultrasound and serum thyroglobulin, in selected patients (e.g., metastatic patients and patients with antithyroglobulin antibodies).

^{131}I scintigraphy is conventionally performed as a whole body planar scan in anterior and posterior projections. The limitations of this technology are related to the absence of reliable anatomical references, to the overimposition of different anatomical structures and to physiologic other than pathologic uptake. A sensitivity of 45–75 % has been reported in the literature for diagnostic planar ^{131}I WBS in detecting recurrences or metastases from DTC [11, 12].

Hybrid Single photon emission computed tomography/computed tomography (SPECT/CT) with ^{131}I provides metabolic and morphological information, allowing

accurate alignment of anatomical and functional findings. The incremental diagnostic value of SPECT/CT in the management of DTC patients has been investigated in several studies [13–16]. The cost-effectiveness of SPECT/CT was evaluated as well [17].

Purpose of this prospective study was to evaluate the incremental diagnostic value of ^{131}I SPECT/CT over conventional planar WBS in clarifying equivocal findings in a large cohort of consecutive patients. Moreover, the efficacy of SPECT/CT in the prognostic stratification and, as a consequence, in the assessment of therapeutic strategy and planning in DTC patients was investigated.

Materials and methods

From January 2013 until November 2014 we enrolled, prospectively, 365 consecutive patients (270 female and 95 male) after total or nearly total thyroidectomy for DTC. They were admitted to the Nuclear Medicine Department of our Institution for the ablation of thyroid remnant and for ^{131}I WBS.

The patients age ranged from 16 to 83 years with a mean age of 51 ± 14 years. All patients had histopathologically diagnosed DTC: 150 papillary carcinoma, 118 follicular variant of papillary carcinoma, 53 aggressive papillary variants (tall cell, columnar cell or diffuse sclerosing variants), 37 follicular, 5 papillary plus follicular variant of papillary and one papillary plus follicular type. Two hundred and forty-four patients underwent L-thyroxine withdrawal for 40 days, replaced by L-triiodothyronine in the first 20 days.

In 121 patients recombinant human thyrotropin (rhTSH—Thyrogen, Genzyme Corporation) was administered intramuscularly at a dose of 0.9 mg on 2 consecutive days during treatment with levothyroxine, and radioiodine was administered on the day after the second injection. All patients followed a low-iodine diet for 2 weeks in preparation for radioiodine administration. In all patients the serum thyrotropin concentration was higher than 30 m UI/L before ^{131}I administration.

Serum thyrotropin, fT3, fT4, thyroglobulin, antithyroglobulin antibody levels, and ioduria were measured before ^{131}I therapy.

The administered dose of ^{131}I ranged from 1.1 to 4.2 GBq (average 2.6 GBq), that was defined according to the risk class based on the TNM staging of the American Joint Committee on Cancer/International Union against Cancer, currently in the seventh edition [18].

Typically, 1.1 GBq [30 mCi] were administered to low risk patients, 1.85 GBq [50 mCi] to intermediate risk patients, and a high dose (3.7 GBq [100 mCi]) to high risk patients.

All patients underwent WBS followed SPECT/CT scanning on the same day.

The imaging was acquired 3–4 days after ^{131}I administration, by hybrid dual-detector SPECT/CT (Infinia Hawkeye II, GE Healthcare, Haifa Israel), equipped with 1 inch StarBrite™ Crystal and a high energy collimator. The StarBrite™ Crystal has a sensitivity more than two folds higher than that provided by a 3/8 inch crystal without a significant loss in resolution, therefore contributing to improve the reliability of SPECT with ^{131}I .

The WBS was performed in continuous mode with high-energy general purpose (HEGP) parallel holes collimator, 364-keV photopeak with $\pm 10\%$ energy windows setting and scatter correction. The infrared-based real-time automatic body contouring system was activated for simultaneous dual view (anterior/posterior) scans with a matrix of 256×1024 . The scan speed was 11 cm/min for injected activities ranging from 1100 to 1850 MBq and 15 cm/min for 3700 Mbq.

Hybrid SPECT/CT scans from skull base to the lung bases were routinely obtained in all patients and additional SPECT/CT scans of other areas were performed depending on whole body scintigraphy findings. SPECT images were acquired with HEGP collimator, matrix size of 128×128 , 364-keV photopeak with $\pm 10\%$ energy and scatter windows, dual-detector 180° acquisition, angular step of 3° , $15''$ time per step/view. The CT parameters were 140 kV, 2.5 mA, $30''$ rotation speed, 10 mm slice thickness, 256×256 matrix. CT acquisition was performed with a 2-slices elicoidal acquisition. An ordered subset expectation maximization iterative reconstruction with CT-based attenuation correction and scatter correction was performed.

The studies were performed for clinical purposes, according to the institutional ethical committee rules. All patients provided written, informed consent.

Data analysis

WBS were considered positive when one or more areas of ^{131}I uptake higher than background activity were identified. A hot nose was considered normal, as well as symmetrical uptake of the salivary glands of the gastrointestinal tract and urinary bladder. Focal uptake localized on the medial portion of the neck was categorized as positive for thyroid bed uptake; foci laterally located in the neck or apart from the medial portion or in the mediastinal region were categorized as positive for LN metastases; foci adjacent to the medial portion but not clearly localized, or streak artifacts, commonly observed with high activity of radioiodine, were interpreted as equivocal for thyroid bed uptake or LN. Foci whose location could not be differentiated between the mediastinum and lung were categorized as equivocal for LN metastases or distant metastases. Uptake in the lung fields,

or in the skeleton or in other areas, when they were not clear physiologic accumulation, was categorized as positive for distant metastases.

Planar images were compared with SPECT/CT: Changes in the interpretations from WBS to SPECT/CT were analyzed in the thyroid bed, LN, and distant metastases.

Moreover, we evaluated the change in TNM stage [18].

Statistical analysis

Data were analyzed using cross-tabulation for categorical data in order to examine relationship between variables.

Data analysis was performed using SPSS (Version 20.0 for Mac OS X).

Results

In planar imaging neck focal uptake was observed in 353/365 patients, whereas no uptake was found in 12 (with no correlation with tumor histology). Three hundred and fifty-six SPECT/CT studies were positive and nine were negative, thus documenting thyroid remnant not seen by WBS in three patients.

One hundred planar studies showed equivocal radioactive foci, which could not be interpreted as thyroid remnant, LN, distant metastases, or physiologic uptake.

SPECT/CT studies were conclusive in 82/100 patients with equivocal radioactive foci at WBS (22.5 % of total patients). In detail, in 60 patients (16.4 %) SPECT/CT confirmed thyroid remnant uptake, excluding extra-thyroidal uptake; in 22 (6.0 % of total patient group) SPECT/CT documented or excluded nodal (Fig. 1) or distant lesions. Specifically, in 20/22 subjects SPECT/CT demonstrated nodal or distant metastases and 2/22 demonstrated para-physiological uptake in a hiatal hernia (Fig. 2) and in a bowel diverticulum. In 18 patients SPECT/CT also was inconclusive (uncertain anatomical attribution). Table 1 summarizes the detailed data for 22 patients for whom additional conclusive information was provided by ^{131}I SPECT/CT fusion imaging after planar imaging.

In 13 subjects out of 22 with equivocal planar WBS, SPECT/CT findings modified the TNM stage and consequently the treatment planning were changed in 13/365 patients, 3.6 % of the patients studied. The results of the study are summarized in Fig. 3.

Discussion

Thyroid cancer is the most frequently occurring endocrine cancer [19], with an incidence of 1 % of all cancers

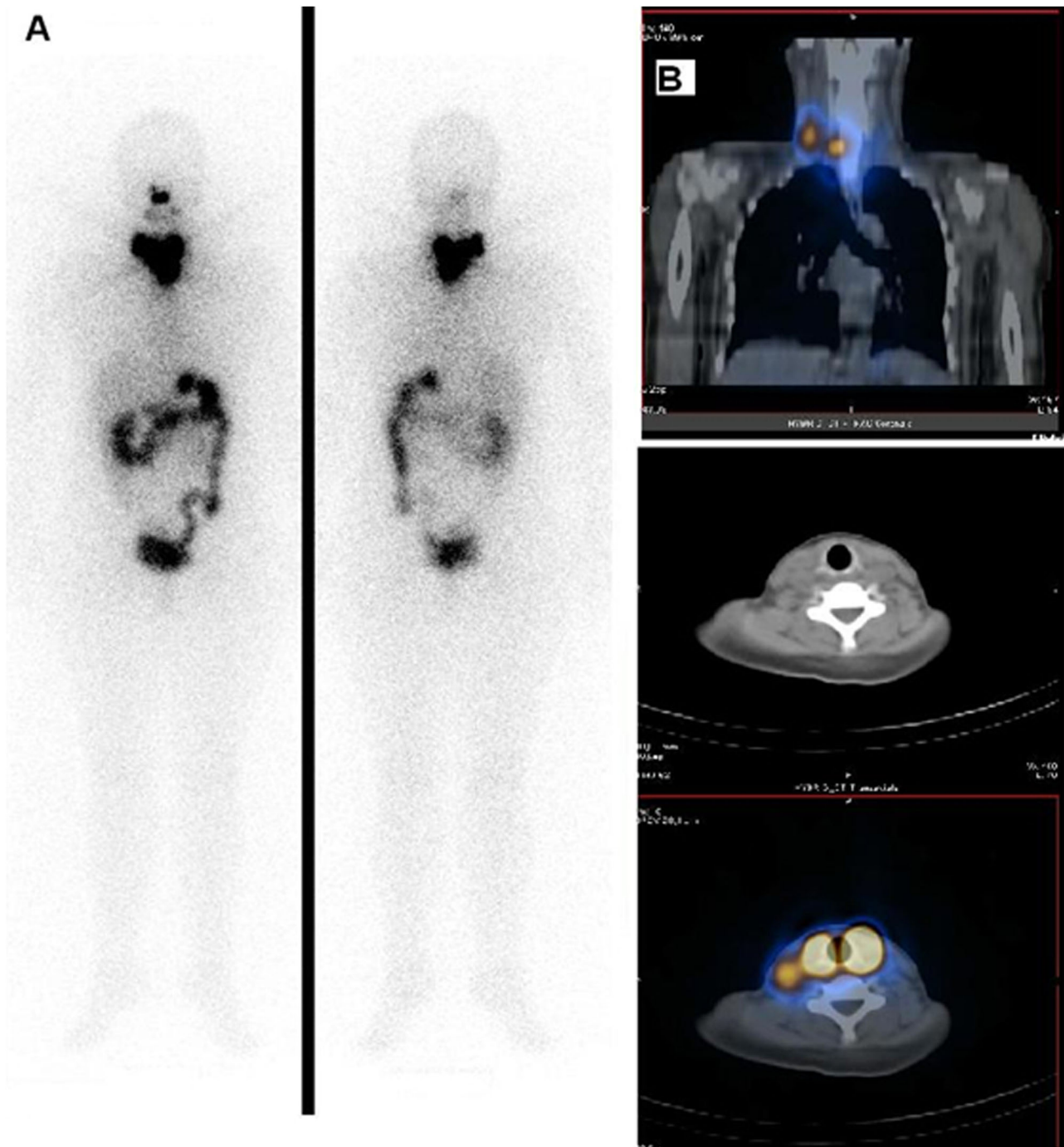


Fig. 1 Planar post therapy ^{131}I scan **a** in a 45-years-old female, after thyroidectomy, demonstrating a large amount of activity in the neck. SPECT/TC images; **b** show laterocervical right sided uptake, at level IV, indicating metastasis in a lymphatic node

diagnosed each year [1]. The primary treatment of DTC is total or nearly total thyroidectomy with or without LN dissection [20]. Papillary and follicular carcinomas account for the majority of DTC and these histological variants show iodine uptake in the majority of patients due to a presence of the sodium-iodine symporter in the cancer cells [21].

Planar ^{131}I WBS is the standard method for identifying thyroid remnants or metastatic disease [22]. It boasts good sensitivity and high specificity, but anatomical localization of the lesions and the differentiation of neoplastic from normal iodine-avid tissue is frequently critical [23]. The high activity contained in the thyroid residue may hamper

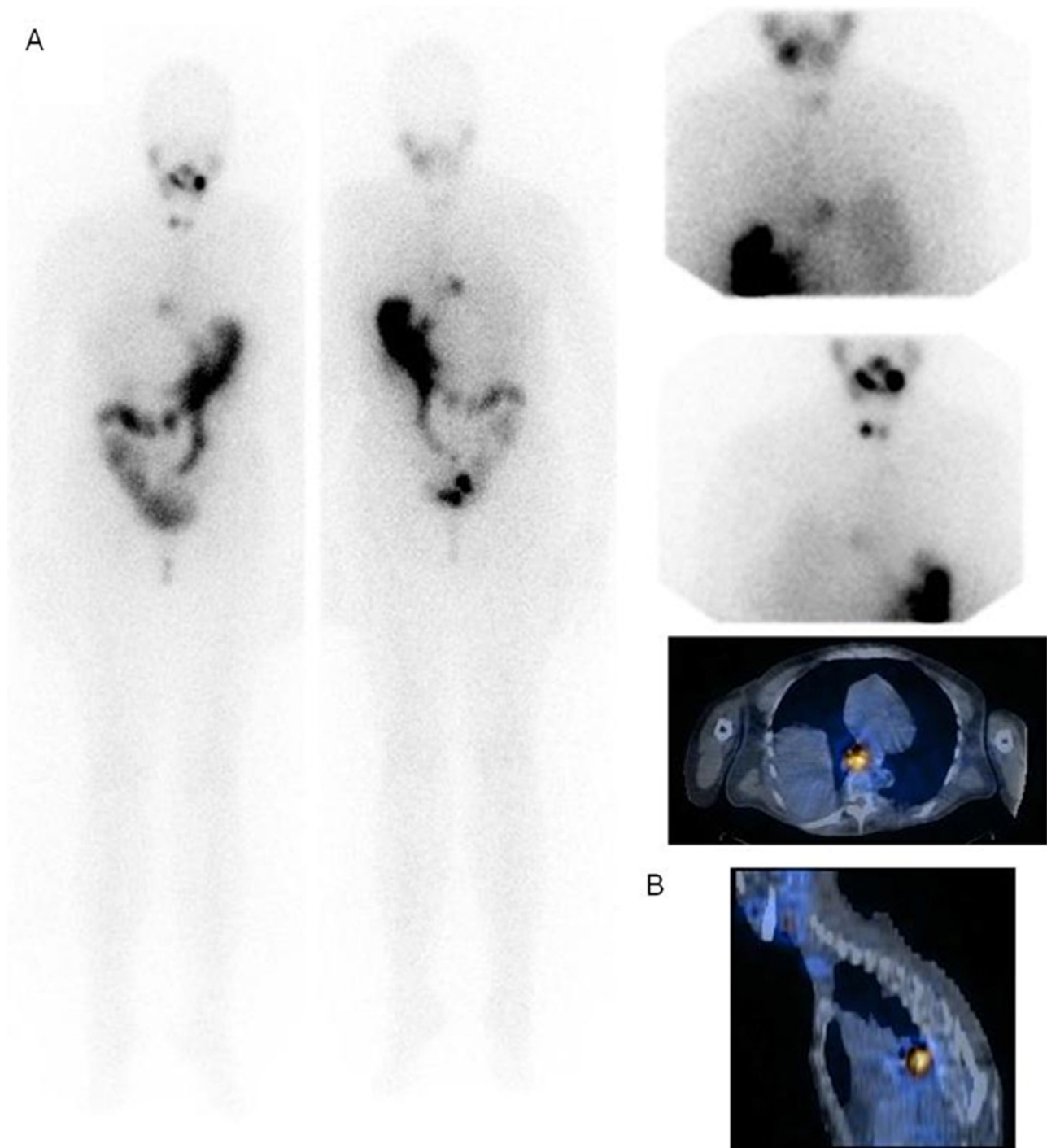


Fig. 2 Planar post therapy ^{131}I scan **a** in a 58-years-old female, after thyroidectomy, demonstrating a mediastinal focal uptake, confirmed in two acquisitions performed at the third and fourth day post therapy.

SPECT/CT images **b** revealed uptake in right prevertebral region, indicating a hiatal hernia

the detection of radioiodine-positive cervical LN because of streak artifacts.

Compared with planar imaging, SPECT/CT more clearly localizes and better characterizes the nature of neck and distant radioactivity foci and allows clarification of

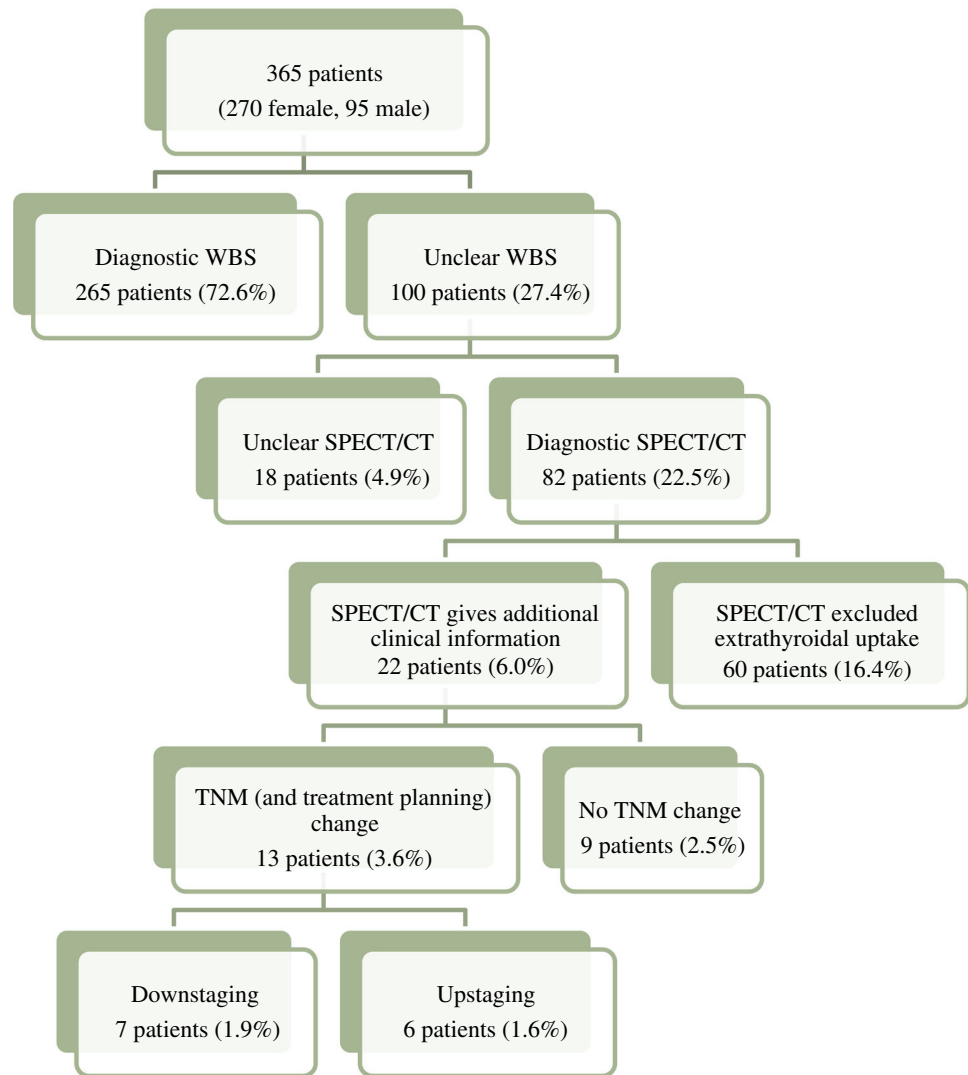
equivocal or inconclusive results on planar imaging, with subsequent impact on management [24].

In fact hybrid, SPECT/CT systems allow combination of scintigraphic functional imaging (SPECT) data with

Table 1 Clinical data of patients with additional information provided by 131I SPECT/CT

Gender	Age	Gender	Histology	Tg (ng/mL)	TgAb UI/ml	TSH mU/L	Region of body	Planar 131I- WBS	¹³¹ I SPECT/CT	Change of therapeutic strategy	TNM change
1	51	F	Papillary (follicular variant)	<1	3	77,04	Abdomen/pelvis	Equivocal	diverticulum	Yes	Downstaging
2	68	F	Papillary (follicular variant)	13,6	<1	44,73	Chest	Equivocal	Bone met	No	No change
3	65	F	Papillary (follicular variant)	842	<1	8,55	Chest	Equivocal for bone	Bone met	No	No change
4	53	M	Papillary	124	<1	81	Neck and Chest	Equivocal	Lung met and LN involvement	No	No change
5	67	F	Papillary (follicular variant)	<1	4	>100	Chest	Equivocal	Lung met	No	No change
6	81	F	Follicular or others	>1000	1,2	42	Chest/Abdomen/pelvis	Equivocal	Bone met and hepatic met	No	No change
7	75	F	Papillary (follicular variant)	8,9	30	>100	Neck	Equivocal for LN	Thyroid remnant	Yes	Downstaging
8	37	M	Papillary (other variant)	9,2	89,5	76	Neck	Equivocal for LN	Thyroid remnant	Yes	Downstaging
9	62	F	Papillary (follicular variant)	<1	1,6	61,49	Neck	Equivocal for LN	LN involvement	Yes	Upstaging
10	42	M	Follicular	37,8	4	59,95	Neck	Equivocal	LN involvement	Yes	Upstaging
11	66	M	Papillary (follicular variant)	2,1	<1	>100	Neck	Equivocal	LN involvement	Yes	Upstaging
12	65	F	Papillary (other variant)	1,8	<1	>100	Neck	Equivocal	LN involvement	Yes	Upstaging
13	48	F	Papillary	2	2	50	Neck	Equivocal for LN	Thyroid remnant	Yes	Downstaging
14	48	F	Papillary (follicular variants)	2,6	<1	56	Neck	Equivocal	LN involvement	Yes	Upstaging
15	58	F	Follicular	1,4	7	>100	Chest	Equivocal for LN or bone	Hiatal hernia	Yes	Downstaging
16	67	F	Papillary (follicular variants)	<1	3	>100	Neck	Equivocal	Salivary gland	Yes	Downstaging
17	52	F	Papillary (other variant)	<1	<1	>100	Neck	Equivocal	LN involvement	Yes	Upstaging
18	39	F	Papillary (follicular variants)	16,1	1,9	67	Neck	Equivocal for LN	Thyroid remnant	Yes	Downstaging
19	28	F	Papillary (other variant)	<1	<1	97	Neck	Equivocal	LN involvement	No	No change
20	42	M	Papillary	296	2,9	68,51	Neck	Equivocal for LN	Thyroid remnant	No	No change
21	58	M	Follicular or others	11,1	<1	38	Neck	Equivocal	LN involvement	No	No change
22	81	F	Follicular or others	<1	836	34	Neck	Equivocal	LN involvement	No	No change

Tg thyroglobulin, TgAb Thyroglobulin auto-antibody, TSH thyroid-stimulating hormone, LN neck lymph node, met metastasis or metastases

Fig. 3 Summary diagram of the study results

anatomical (CT) information in a single examination, improving the accuracy of the technique.

Several studies have demonstrated that ^{131}I SPECT/CT has incremental diagnostic value in the diagnosis, treatment, and management of DTC [13, 16, 17, 25–29].

Particularly, ^{131}I SPECT/CT was found to allow a gain in information on nodal staging in 35–36.4 % of patients and resulted in new risk stratification in 6.4–25 % [30, 31].

Disadvantages of SPECT/CT include additional imaging time and possible patient discomfort, claustrophobia from lying in a fixed position for 20 min in the tightly enclosed space of the SPECT/CT gantry and the additional radiation exposure from the CT component of the study (1 mSv for each acquisition).

Barwick and colleagues demonstrated that the use of ^{131}I SPECT/CT changes clinical management in significant numbers of patients with DTC, both when used routinely on

all consecutive patients and when used on selected patients with inconclusive planar images [32].

The most commonly used staging system in DTC is the TNM staging of the American Joint Committee on Cancer/International Union against Cancer, currently in the seventh edition [18]. Because this staging was developed to predict risk for death—not for recurrence—and does not take into account several independent prognostic variables, the ATA has developed a 3-level risk stratification for patients with DTC⁷.

Avram concluded that risk stratification and staging of patients should not be based solely on clinical and histopathological criteria, but should include specific imaging, in particular ^{131}I SPECT/CT imaging, to evaluate for the presence of regional and distant metastases [33].

Kohlfuerst et al. showed that SPECT/CT had a diagnostic effect in 21 (64 %) of 33 patients, and therapeutic

planning was changed in eight (24 %) of 33 patients [25]; Schmidt et al. reported that node status was changed with SPECT/CT in 20 (35 %) of 57 patients at the first radioablation [26].

In comparison to previously published studies, specific features of our study are:

- prospective evaluation of the largest cohort of patients affected by DTC prospectively enrolled for comparison between WBS and SPECT/CT [24];
- a hybrid SPECT/CT system was adopted in all patients, whereas in other studies fusion imaging was used;
- to our knowledge the first large cohort of patients evaluated after administration of therapeutic ^{131}I activities (1.1–4.2 GBq) by SPECT/CT equipped with high sensitivity 1'' Starbrite™ detector allowing higher sensitivity and better image contrast in comparison to 3/8 or 5/8 inch crystal.

The characteristics of this equipment may explain, at least partially, the very low equivocal studies found after SPECT/CT, 18/365 (4.9 %).

Depending on the location of the iodine uptake site, the findings of the ^{131}I SPECT/CT may change a treatment planning, the surveillance, and the need for additional imaging, laboratory tests or invasive procedures like biopsies [33].

Beyond the impact on staging, the utility of ^{131}I SPECT/CT is defined by its impact on clinical management, which may be changed in 23.5–25 % of patients, as reported by Xue et al. in their recent systematic review on the incremental value of ^{131}I SPECT/CT [30].

Our study results demonstrated that the interpretation of equivocal radioactive focal uptake at WBS was clarified by SPECT/CT in 82 (22.5 %) out of 365 patients.

In addition, clinical staging according to the TNM classification and therapeutic planning by addition of SPECT/CT findings were modified in 13 (3.6 %) out of 365 patients. A controversial issue is the selection criteria of patients for SPECT/CT imaging after ^{131}I therapy: all patients or only subjects with positive or equivocal studies. We think that our findings (upstaging in six patients and downstaging in seven, respectively, are sufficient to justify the need of SPECT/CT in the global population, especially in the era of defensive medicine. It is, however, our opinion that at least all patients with equivocal and/or positive findings for nodal or distant metastatic lesions should compulsorily undergo SPECT/CT after ^{131}I treatment.

Study limitations

The main limitation of this study is the use of a low-dose and low-resolution CT; it is, therefore not clear, if the use of

a high resolution CT scan might have limited the number of studies (18 patients) still equivocal after SPECT/CT. It should be, however underlined, that a combination of Starbrite™ crystals and high resolution CT is not currently offered by different vendors.

The results of the present study were obtained by a SPECT/CT with Starbrite™ Crystals and consequently they could not be reproduced by centers adopting SPECT/CT equipped with 3/8'' or 5/8'' crystals. PET/CT with ^{124}I could represent a competitive alternative, but its application is limited by the difficult supplying of this radiopharmaceutical.

Conclusion

In this study, SPECT/CT showed incremental value over WBS in increasing diagnostic accuracy, reducing pitfalls, and modifying the TNM classification and clinical management defined by planar imaging. SPECT/CT is a powerful diagnostic tool that allows accurate anatomical localization and characterization of radioiodine foci, and both patients and physicians will benefit from this technique in terms of diagnosis, proper staging, restaging, and treatment planning.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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