Clin Transl Imaging (2014) 2:459–475
DOI 10.1007/s40336-014-0085-8

REVIEW ARTICLE

SPET–CT in thyroid cancer: a systematic review

Ka Kit Wong · Daniel J. Wale · Lorraine M. Fig · Milton D. Gross

Received: 4 June 2014 / Accepted: 1 October 2014 / Published online: 16 October 2014

Abstract The purpose of this study was to systematically review the utility of single-photon emission tomography–computed tomography (SPET–CT) fusion imaging in the investigation of thyroid cancer. We performed a systematic search of the world literature on radionuclide SPET–CT imaging of thyroid cancer using the medical databases Medline (OVID) and PubMed. The following search terms were used to identify relevant studies: (a) *thyroid*, combined with (b) *SPECT/CT* or *SPECT–CT* or *SPET/CT* or *SPET–CT*. The electronic searches returned citations for 1,189 potentially eligible articles and 98 abstracts were reviewed for relevance by two co-authors. Thirty-one peer-reviewed full articles reporting the utility, value and diagnostic performance of radioiodine SPET–CT for the imaging of well-differentiated thyroid cancer were selected. The quality of these studies was assessed using the quality assessment of diagnostic accuracy studies-2 tool. As there was heterogeneity in the studies, a systematic review analysis was conducted as our chosen research synthesis method. A total of 31 studies published between 2003 and 2014 report the utility of radioiodine SPET–CT. These studies uniformly found incremental diagnostic value of I-123 and I-131 SPET–CT over SPET and/or planar imaging. SPET–CT allows accurate characterization of radioiodine uptake in the neck and at distant sites, clarifies equivocal foci of radioactivity, improves specificity for disease, and evaluates benign physiological etiologies. Additional pilot uses of SPET–CT have been reported, e.g., for thyroid nodule evaluation, medullary thyroid cancer work-up, and investigation of lingual thyroid. Radioiodine SPET–CT fusion imaging of thyroid cancer has incremental utility, improving image interpretation as compared to planar and SPET imaging. It is likely to see more widespread application in the future.

Keywords SPECT–CT · SPECT/CT · Radioiodine · Well-differentiated thyroid cancer · Medullary thyroid cancer

Electronic supplementary material The online version of this article (doi:10.1007/s40336-014-0085-8) contains supplementary material, which is available to authorized users.

Color figures online at http://link.springer.com/article/10.1007/s40336-014-0085-8

K. K. Wong · D. J. Wale · M. D. Gross
Division of Nuclear Medicine, Department of Radiology, University of Michigan Hospital, Ann Arbor, MI 48109, USA

K. K. Wong · L. M. Fig · M. D. Gross
Department of Veterans Affairs Health System, Nuclear Medicine Service, Ann Arbor, MI 48105, USA

K. K. Wong (✉)
Division of Nuclear Medicine, Department of Radiology, University of Michigan Health System, B1G505 University Hospital SPC 5028, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5028, USA
e-mail: kakit41@gmail.com

Introduction

The avidity of thyroid tissue for radioiodine and the various applications of radioiodine in the evaluation of thyroid disease have served as the prototype for numerous subsequent functional imaging procedures in nuclear medicine. Since the earliest attempts to depict the distribution of radioiodine with rectilinear scanners, thyroid imaging, like other nuclear medicine examinations, has undergone a significant evolution, progressing from planar scans (first presented on paper) to three-dimensional single-photon emission tomography (SPET) and, most recently, to

simultaneously acquired SPET and computed tomography (CT), i.e., SPET–CT, with images viewed on high-resolution digital computers. Although advancing technology has markedly improved the efficacy of nuclear imaging, the fundamental information provided by the patterns of radioiodine uptake has not changed from the early beginnings of this approach. The accumulation of radioiodine by the thyroid sodium-iodide symporter (NIS) is the molecular basis for its clinical utility [1–3] and today, seven decades since its introduction, radioiodine continues to be a cornerstone in the management and treatment of well-differentiated thyroid cancer (WDTC) [4]. The incidence of WDTC is increasing both in adults and in the pediatric population largely because of earlier detection and diagnosis at a smaller tumor size, although unidentified environmental factors probably play a role too [5]. Because microcarcinoma (size $\leq$1 cm) accounts for an increasing proportion of newly diagnosed thyroid cancers [6, 7], the role of radioiodine in the management of WDTC is under scrutiny in low-risk patients, who do not show extrathyroidal extension or high-risk histopathology features [8]. WDTC has an excellent prognosis, with a ten-year survival rate of 85 % in follicular thyroid cancer and greater than 90 % in papillary thyroid cancer. Factors related to mortality from WDTC include age, gender, tumor characteristics (type, grade, size, and invasiveness) and clinical stage at diagnosis [9–11]. There is currently a movement away from the staging of thyroid cancer using classification systems that provide information on mortality, e.g., American Joint Committee on Cancer, Tumor Node Metastasis (AJCC TNM), in favor of a risk stratification design that predicts recurrence risk and allows more informative management decisions [4, 12]. Although the literature supports the use of I-131 in the treatment of local and distant metastases of WDTC [9, 10], there is no compelling evidence that it decreases recurrence or increases survival in low-risk, stage I patients [9–11, 13, 14]. Concurrently, exploration of lower dosages of I-131 for thyroid remnant ablation has provided convincing evidence for efficacy of this approach from doses as low as 1.1 GBq (30 mCi) of I-131. Furthermore, recombinant human thyrotropin (rhTSH: Thyrogen®) stimulation has been accepted as an alternative to thyroid hormone withdrawal for diagnostic radioiodine imaging and for performing thyroid remnant ablation [15, 16]. However, the use of this approach, compared with endogenous hypothyroidism, for the treatment of iodine-avid metastases remains to be validated. Around one-third of patients with WDTC will have recurrences in their lifetime, most of which will be non-iodine-avid; for these patients, multikinase inhibitor treatment offers promise for disease stabilization.

These innovations in the management of WDTC have been accompanied by technological advances in nuclear medicine image acquisition. Planar gamma camera images have been augmented with three-dimensional SPET allowing improved localization of metastatic disease and its differentiation from physiological anatomical variants. More recently, a further significant increase in interpretative accuracy and localization has been achieved with the introduction of simultaneously acquired radioiodine SPET–CT.

Our aim was to systematically review the utility of hybrid SPET–CT imaging for the investigation of thyroid cancer, focusing in particular on radioiodine imaging in WDTC as this makes up the bulk of the current literature.

Materials and methods

Literature search to identify studies

On March 1st, 2014, we performed a literature search for articles reporting the diagnostic utility of SPET–CT for the imaging of thyroid cancer focusing in particular on its use in WDTC. The bibliographic databases searched were Medline (OVID) and PubMed. The initial search strategy proved to be very effective. It was performed using the search words: (a) *thyroid*, and (b) *SPECT/CT* or *SPECT–CT* or *SPET/CT* or *SPET–CT* or *hybrid* or *fusion,* combined in the search engine in Medline (OVID) from 1946 to February, 2014. The list of citations obtained was then restricted to the period from 2003 onwards as this is the year of the first report of SPET–CT applied in a cohort with WDTC. The Medline search was augmented with a population index comparator outcome (PICO) search strategy which returned only one additional article for consideration. Individual searches were performed on each PICO parameter as relevant to the review topic, then the returned citations/hits were variously combined using the search engine functionality (e.g., PI, PIC, PICO) to include as many relevant articles as possible. Finally, a PubMed search was performed using the term *radioiodine SPECT–CT* which found an additional 18 articles for consideration. The list of articles was extended by cross-checking of all reference lists of retrieved articles. This revealed three extra articles for consideration. Details of the search strategy are summarized in Fig. 1. A complete list of search terms and strategy is provided in ESM Appendix 1.

Selection criteria

Two reviewers (K.K.W. and D.J.W.) independently performed the searches. Inclusion criteria were peer-reviewed articles describing original research pertaining to radioiodine SPET–CT evaluation of WDTC and other indications associated with thyroid cancer. Exclusion criteria included non-English language or literature and studies not using the SPET–CT technique.

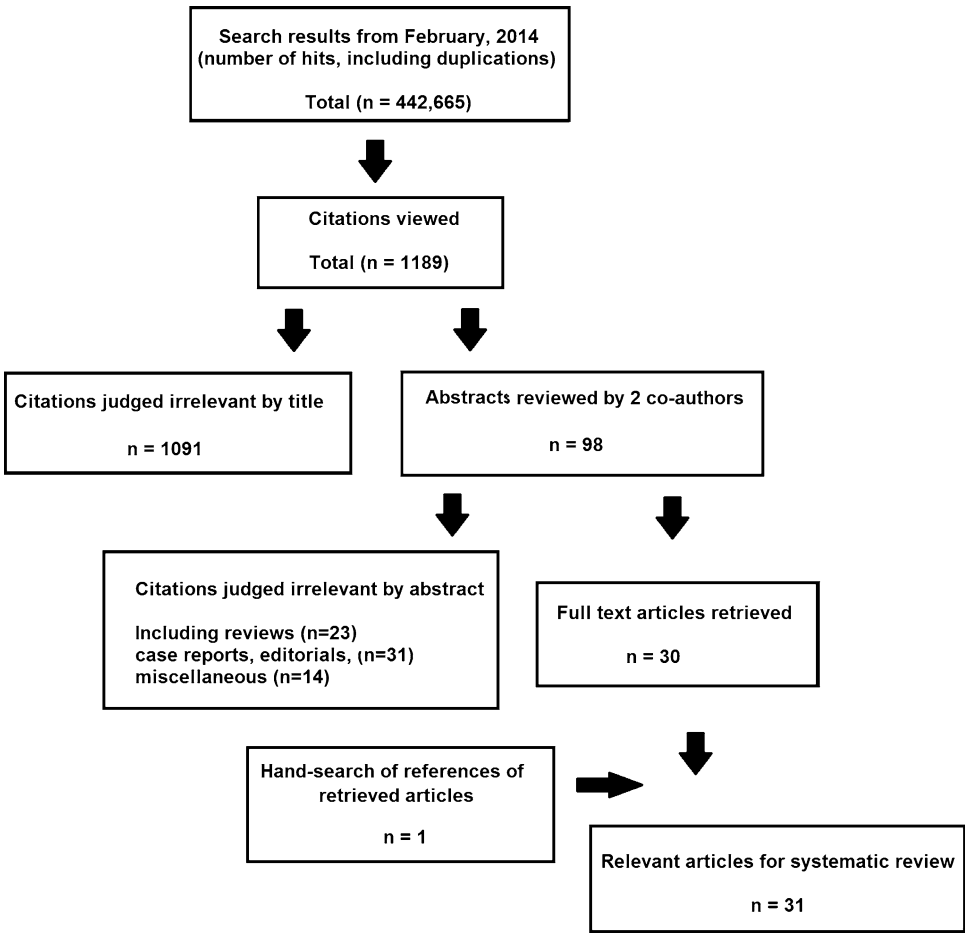

Fig. 1 Flow chart of the systematic search of world literature

Data extraction

Using the quality assessment of diagnostic accuracy studies-2 (QUADAS-2) tool relevant retrieved articles were reviewed for quality, applicability and risk of bias [17]. Due to significant heterogeneity arising from variability in patient cohorts, study design, imaging protocols and techniques, result reporting, and gold standard for follow-up, a systematic review analysis was conducted rather than using meta-analytical methods.

Study characteristics, test parameters and endpoints

The following parameters were extracted: (1) first author and year of publication; (2) study design; (3) description of patients; (4) radioiodine isotope and dose; (5) indication for SPET–CT; (6) type of hybrid SPET–CT camera and imaging parameters of the CT component; voltage and current; and (7) main findings. This present review summarizes the content of 31 original articles reporting the utility and diagnostic performance of SPET–CT for the investigation of WDTC. The systematic review was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [18].

Results

Study selection and characteristics analysis

The electronic searches returned citations for 1,189 potentially eligible articles and two reviewers viewed the titles independently to determine their relevance. There were 98 potentially relevant articles including reviews and pictorial essays ($n = 23$), case reports, editorials, and letters ($n = 31$), and miscellaneous articles reporting investigative uses of SPET–CT for thyroid cancer, including use in medullary thyroid cancer ($n = 14$). After review of the abstracts of these articles, a total of 30 articles were retrieved in full pertaining to SPET–CT imaging of WDTC. After cross-checking of all reference lists, one additional article of relevance was retrieved, resulting in a total of 31 original articles.

Table 1 QUADAS-2 assessment of the quality of studies of radioiodine SPET/CT for imaging of well-differentiated thyroid cancer

First author	Year	Risk of bias				Applicability concerns		
		Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference test
Barber	2014	Low	Low	Low	Low	Low	Low	Low
Gallichio	2013	Unclear[c]	Low	Low	Unclear	Low	Unclear	Low
Burlison	2013	Low	Low	Low	Low	Low	Low	Low
Savas	2013	Low	Low	Low	Low	Low	Low	Low
de Pont	2013	Low	Low	Low	Low	Low	Low	Low
Robenshtok	2013	Unclear[c]	Low	Low	Low	Low	Low	Low
Avram	2013	Low	Low	Low	Low	Low	Low	Low
Maruoka	2012	Low	Low	Low	Low	Low	Low	Low
Menges	2012	Low	Low	Unclear[a]	Low	Low	Low	Low
Qiu	2012	Low	Low	Low	Low	Low	Low	Low
Kim	2011	Low	Low	Low	Low	Low	Low	Low
Ciappuccini	2011	Low[b]	Low	Low	Low	Low	Low	Low
Oh	2011	Low	Low	Unclear[a]	Low	Low	Low	Low
Blum	2011	Low	Low	Low	Low	Low	Low	Low
Wakabayashi	2011	Low	Low	Low	Low	Low	Low	Low
Qiu	2010	Low	Low	Low	Low	Low	Low	Low
Grewal	2010	Unclear[c]	Low	Low	Low	Low	Low	Low
Wong	2010	Low[b]	Low	Low	Low	Low	Low	Low
Mustafa	2010	Low[b]	Low	Low	Low	Low	Low	Low
Barwick	2010	Low	Low	Unclear[a]	Low	Low	Low	Low
Schmidt	2010	Low[b]	Low	Low	Low	Low	Low	Low
Aide	2009	Low	Low	Low	Low	Low	Low	Low
Kohlfuerst	2009	Low	Low	Low	Low	Low	Low	Low
Wang	2009	Low	Low	Low	Low	Low	Low	Low
Schmidt	2009	Low	Low	Low	Low	Low	Low	Low
Spanu	2009	Low	Low	Low	Low	Low	Low	Low
Chen	2008	Low	Low	Low	Low	Low	Low	Low
Wong	2008	Low	Low	Low	Low	Low	Low	Low
Tharp	2004	Low	Low	Low	Low	Low	Low	Low
Ruf	2004	Low	Low	Low	Low	Low	Low	Low
Yamamoto	2003	Low	Low	Low	Low	Low	Low	Low

[a] These studies report sensitivity and specificity yet lack histopathologic correlation of imaging findings. However, all studies in the literature suffer from similar lack of biopsy proof as gold standard, with inclusion of the SPET–CT as the standard

[b] These studies contain patients who were previously reported as a smaller cohort, although risk of bias is still low

[c] Patient selection was based on ATA risk stratification (intermediate and high) and low-risk patients were excluded from the index test

Quality assessment of diagnostic accuracy studies

Using the QUADAS-2 tool, the studies were evaluated in four domains for risk of bias and applicability (see Table 1). It was noted that a few of the 31 studies had cohorts that overlapped with previously published reports. However, as the study designs focused on different questions, this was unlikely to affect the conclusions drawn. For example, some patients included in studies investigating incremental diagnostic value were subsequently included in studies investigating impact on cancer staging. Two studies were at high risk for selection bias due to the use of SPET–CT solely in intermediate and high-risk patients, with low-risk patients excluded from receiving the index test. Other studies had a potential bias based on the selective use of the index test; however, the risk was again considered low. Most studies lacked histopathological findings, instead relying on clinical follow-up and correlative imaging.

Study characteristics and protocols for SPET–CT

The identified I-131 and I-123 SPET–CT studies concerned patients prepared with either endogenous hypothyroidism or exogenous recombinant human TSH stimulation, and they used diagnostic imaging doses ranging from 37 to 430 MBq (1–11 mCi) [19–24] and post-therapy imaging doses ranging from 1.1 to 9.7+ GBq (30–260+ mCi) [20, 25–40]. Radioiodine SPET–CT was used for surveillance for thyroid cancer recurrence, before I-131 therapy [19, 20, 27, 41, 42],

in the post-surgical setting for radioiodine ablation of normal thyroid remnants, [21, 22, 24], or in post-therapy imaging [25–30, 32, 33, 36, 37, 39, 40, 43–45].

The study characteristics and summary findings are presented in Tables 2 and 3.

Discussion

Radioiodine SPET–CT imaging of well-differentiated thyroid cancer

Planar and SPET gamma camera imaging with I-131 suffers from inherent poor spatial resolution and septal penetration artifacts that arise from the high energy 364 keV gamma emissions [46–49]. Despite its high spatial resolution and fine anatomical detail, CT has been used sparingly in thyroid cancer because of the effects of iodinated contrast on thyroid function; indeed, it results in decreased subsequent radioiodine uptake and, therefore, impairs I-131 treatment intent. In addition, metastases may occur in lymph nodes that are anatomically normal in size and morphology, resulting in false-negative CT evaluations. Many of the drawbacks with thyroid cancer imaging using separate radioiodine scintigraphy and CT have been mitigated by hybrid SPET–CT scanners, where simultaneous SPET and CT (usually non-contrast-enhanced) information can be directly combined [19–23, 25–45, 50–53].

I-131 SPET–CT was first reported by Even-Sapir and colleagues in four cases of thyroid cancer included in a larger group of endocrine neoplasms [54]. Other investigators later found that SPET–CT improved diagnostic evaluation compared to SPET alone in 15/17 (88 %) thyroid cancer patients [38]. Tharp and colleagues reported increased diagnostic value of SPET–CT versus planar imaging in 41/71 (57 %) patients, noting that the anatomical information from low-resolution (non-diagnostic) CT better differentiated equivocal neck lesions encountered on planar images [20]. Furthermore, in 36 patients with extrathyroidal disease, SPET–CT distinguished I-131 foci of uptake as benign in nine patients, and confirmed bone metastases in 12 patients and lung metastases in five patients, changing the subsequent management plans. These early observations of the potential utility of radioiodine SPET–CT have since been confirmed in larger published studies.

SPET–CT diagnostic interpretation

SPET–CT allows precise localization and easier differentiation of benign radioiodine uptake in remnant thyroid tissues from malignant radioiodine accumulation in metastatic cervical lymph nodes or distant metastases (Fig. 2). It is widely accepted that I-131 SPET–CT reduces the equivocal findings frequently encountered on planar imaging. Maruoka and colleagues, in 147 patients, compared post-therapy I-131 SPET–CT scans to whole-body planar radioiodine scans and reported that SPET–CT clarified 25 equivocal interpretations on planar imaging as either metastatic regional lymph nodes or thyroid remnant tissues. SPET–CT further characterized 21 out of 52 (40 %) foci of I-131 uptake, differentiating metastases from benign, physiological mimics of disease [28]. In a similar fashion, diagnostic I-131 SPET–CT performed before thyroid remnant ablation accurately characterized central neck and distant distributions of I-131 activity, correctly classifying equivocal planar imaging findings as benign or malignant [22, 23]. The incremental value of SPET–CT over planar imaging was reported in 53 out of 130 (41 %) foci, with confident identification of thyroglossal duct and thyroid bed remnants [22, 23]. Others have confirmed that indeterminate neck lesions on planar scans, when restudied with SPET–CT, can be re-classified as thyroid remnants, lymph node metastases (Fig. 3), radioiodine contaminated oropharyngeal secretions, or other physiological variants (86, 89) (Fig. 4).

I-131 planar imaging has a reported sensitivity of 45 to 75 % and specificity of 90 to 100 %, depending on the administered dosage [19, 20, 46]. Barwick and colleagues reported that I-123 SPET–CT imaging for thyroid cancer recurrence had higher sensitivity (50 %), specificity (100 %) and accuracy (87 %) values compared to SPET alone (sensitivity 45 %, specificity 89 % and accuracy 78 %) and planar imaging (sensitivity 41 %, specificity 68 % and accuracy 61 %). They concluded that the main value of I-123 SPET–CT was that it offered increased imaging specificity [41]. Another benefit of the CT component reported by Menges and colleagues is its ability to identify non-iodine-avid tumor, resulting in sensitivity increasing from 62 to 74 %, with unchanged high specificity of 98 % (Fig. 5) [29]. Confirming this, other authors found that I-131 SPET–CT depicted additional non-iodine-avid disease in 32 out of 148 (21.6 %) patients with an intermediate-to-high risk of thyroid cancer recurrence [40]. The detection of non-iodine-avid disease, shown by loss of NIS expression (seen in 20–30 % of patients with WDTC), signifies that radioiodine treatments will no longer be effective. Current data in the literature show that SPET–CT reduces the number of equivocal findings, improves imaging specificity, and can detect metastatic disease without radioiodine concentration in some patients.

Metastatic thyroid cancer and SPET–CT

I-131 SPET–CT is useful for whole-body screening for distant metastatic disease [19, 21, 22, 27–29, 37, 39, 41].

Table 2 Summary of study characteristics of SPET–CT for well-differentiated thyroid cancer

First author	Year	Pts/scans	Design	Indication	Dose	Camera	CT settings
Diagnostic I-123 or I-131 SPET–CT							
Savas	2013	216/216	Retro	Diagnostic pre-ablation	131-I 37 MBq	Symbia T6	140 kV, 100 mAs
Avram	2013	320/320	Pros	Diagnostic pre-ablation	131-I 37 MBq	Symbia T6	140 kV, 100 mAs
Menges	2012	123/139	Retro	Follow-up and post-ablation	131-I 407 MBq	Symbia T2, T6	140 kV, 40 mAs
Kim	2011	13/20	Retro	Pre-ablation and follow-up diagnostic 123-I	131-I 59–85 MBq	Symbia T2 Millennium Hawkeye	CT dose 0.33 mSv
Blum	2011	38/40	Retro	Pre-ablation and follow-up	131-I 17–81 MBq	Symbia T6	Caredose 4D
Wong	2010	48/48	Retro	Diagnostic pre-ablation	131-I 37 MBq	Symbia T6	140 kV, 100 mAs
Barwick	2010	79/85	Retro	Follow-up	123-I 350–400 MBq	Millennium Hawkeye	140 kV, 2.5 mAs
Spanu	2009	117/117	Pros	Follow-up and post-ablation	123-I 185 MBq	Millennium Hawkeye Infinia Hawkeye	140 kV, 2.5 mAs
Wong	2008	53/56	Retro	Pre-ablation and follow-up	131-I 37–150 MBq	Symbia T6	140 kV, 100 mAs
Post-therapy I-131 SPET–CT							
Barber	2014	83/83	Retro	Post-ablation	1.1–4.2 GBq	Discovery 670	120 kV, 40–110 mAs
Gallichio	2013	91/30	Retro	Post-ablation	3.7–4.4 GBq	Infinia Hawkeye	140 kV, 2.5 mAs
Burlison	2013	58/58	Retro	Post-ablation	2.7–7.7 GBq	Symbia T2	Not specified
de Pont	2013	20/20	Retro	Post-ablation	2.7–5.5 GBq	Phillips Precedence 6-slice	120 kV, 30 mAs
Robenshtok	2013	290/290	Retro	Post-ablation	Not specified	Precedence	120 kV, adjusted mAs/kg
Maruoka	2012	147/147	Retro	Post-ablation	3.8–6.7 GBq	Symbia T6	130 kV, 30 mAs
Qiu	2012	80/80	Retro	Suspected bone metastases	7.4 GBq	Not specified	120 kV
Ciappuccini	2011	170/170	Pros	Post-ablation	0.9–4.8 GBq	Symbia T2	Not specified, 60 mAs
Oh	2011	140/140	Retro	Post-ablation	3.6–9.3 GBq	Infinia Hawkeye	140 kV, 5 mAs
Wakabayashi	2011	42/42	Retro	Post-ablation	3.7–7.4 GBq	Software co-registration	130 kV, 40 mAs
Qiu	2010	561/561	Pros	Post-ablation and retreatment	3.7–7.4 GBq	Millennium Hawkeye	140 kV, 2.5 mAs
Grewal	2010	148/148	Retro	Post-ablation and retreatment	1.7–8 GBq	Precedence	120 kV, adjusted mAs/kg
Mustafa	2010	151/151	Pros	Post-ablation	1.8–5.3 GBq	Symbia T2, T6	140 kV, 20-40 mAs
Schmidt	2010	81/81	Retro	Post-ablation	1.5–5.3 GBq	Symbia T2, T6	140 kV, 40 mAs
Aide	2009	55/55	Pros	Post-ablation	2.9–4.0 GBq	Symbia T2	Not specified, 60 mAs
Kohlfuerst	2009	41/53	Pros	Post-ablation and retreatment	2.9–7.5 GBq	Symbia T	130 kV, 25mAs
Wang	2009	94/94	Retro	Post-ablation	3.7–7.4 GBq	Infinia Hawkeye	140 kV, 2.5 mAs
Schmidt	2009	57/57	Retro	Post-ablation	1.5–5.3 GBq	Symbia T2, T6	140 kV, 40 mAs
Chen	2008	66/66	Pros	Post-ablation	3.7–7.4 GBq	Millennium Hawkeye	140 kV, 2.5 mAs
Tharp	2004	71/71	Retro	Post-ablation and retreatment	1.4–9.7 GBq	Millennium Hawkeye	140 kV, 2.5 mAs
Ruf	2004	25/25	Pros	Post-ablation	3.7 GBq	Millennium Hawkeye	140 kV, 2.5 mAs
Yamamoto	2003	17/17	Retro	Post-ablation	3.7–7.4 GBq	Aquilon CT, Picker Prism	Not specified

Retro retrospective, *Pros* prospective

Table 3 Summary of study findings SPET–CT for well-differentiated thyroid cancer

First author	Year	Site of radioactivity	Findings/comments
Diagnostic I-123 or I-131 SPET–CT			
Savas	2013	Oral cavity	Oral activity occurred in 57 % of 123 patients
			Of these patients 95/111 (86 %) demonstrated focal binding of radioiodine to high-density dental materials
Avram	2013	Neck/distant	SPET–CT changed staging in 4 % of younger and 35 % of older patients
			It identified regional disease in 35 % and unsuspected distant disease in 8 % of patients
Menges	2012	Neck/distant	SPET–CT sensitivity 62 %, specificity 98 %, for iodine-avid disease
			SPET–CT sensitivity 78 %, specificity 98 %, for non-iodine-avid disease
			Planar sensitivity 62 %, specificity 78 % for iodine-avid disease
Kim	2011	Neck/distant	All foci were localized with SPET–CT distinguishing benign uptake
			SPET–CT supported decision not to treat with 131-I in 2 patients
			SPET–CT did not contribute in 3 of 13 patients
Blum	2011	Neck/distant	SPET–CT confirmed cryptic findings of thyroid origin ($n = 10$)
			SPET–CT confirmed cryptic findings of non-thyroid origin ($n = 39$)
			This led to 32 cases whereby radioiodine treatment was avoided
Wong	2010	Neck/distant	SPET–CT changed TNM stage in 10/48 (21 %) patients
			SPET–CT changed proposed 131-I dose selection in 28/48 (58 %) patients
			SPET–CT identified unsuspected metastases in 4/8 patients with M1
Barwick	2010	Neck/distant	Planar: sensitivity 41 %, specificity 68 %, accuracy 61 %
			SPET: sensitivity 45 %, specificity 89 %, accuracy 78 %
			SPET–CT: sensitivity 50 %, specificity 100 %, accuracy 87 %
			SPET–CT provided additional information in 42 % pts and 70 % of foci
Spanu	2009	Neck/distant	SPET–CT had incremental value over planar scan in 67.8 % patients
			SPET–CT changed treatment in 35.6 % of patients with disease
			SPET–CT led to avoidance of 131-I therapy in 20 % of patients without disease
			SPET–CT identified 158 foci compared to only 116 foci on planar scans
Wong	2008	Neck/distant	Diagnostic value SPET–CT > planar scans in 53/130 (41 %) neck foci
			Diagnostic value SPET–CT > planar scans in 17/17 (100 %) distant foci
			SPET–CT using diagnostic 131-I activities allows adjustment of prescribed radioiodine activity
Post-therapy I-131 SPET–CT			
Barber	2014	Neck	SPET–CT characterized thyroglossal tract tissue in 39/83 (47 %) patients
			Benign remnant tissue in the thyroglossal tract accounted for a significant amount of the total radioiodine therapy administered
Gallichio	2013	Neck	Rate of regional metastases was 35/85 patients with thyroid microcarcinoma, with SPET–CT confirming nodal metastatic disease in 26/30 patients
Burlison	2013	Oral cavity	45/57 (78 %) patients had high-density dental restorations on SPET–CT
			Of these 45 patients, 91 % demonstrated focal binding of radioiodine to the high-density dental materials
de Pont	2013	Neck/distant	124-I PET found 57/62 (92 %), SPET–CT 50/62 (81 %) and planar scans only 63 % of foci
			5/20 patients had a change in stage, in 3 cases due to findings only on PET
Robenshtok	2013	Neck/distant	SPET–CT found lymph node uptake in 46/290 (16 %) and lung uptake in 4/290 (1.4 %), even in cases where Tg was undetectable
Maruoka	2012	Neck	SPET–CT clarified all 25 equivocals as remnant or regional metastases
			Distant: SPET–CT clarified all 20 equivocal distant foci
			SPET–CT improved interpretation in 21 of 52 (40 %) distant foci
Qiu	2012	Neck/distant	131-I SPET–CT sensitivity 93 %, specificity 97 %
			FDG PET/CT sensitivity 86 %, specificity 94 %
			Bone scintigraphy sensitivity 73 %, specificity 74 %

Table 3 continued

First author	Year	Site of radioactivity	Findings/comments
Ciappuccini	2011	Neck/distant	Follow-up: median, 29 months, range 1.5–4.5 years
			Prognostic value SPET–CT for recurrence in follow-up evaluation
			32 (19 %) patients had disease: 18 nodal metastases, 8 distant metastases and 6 both
			SPET–CT negative or equivocal in all patients free of disease
			Post-ablation scintigraphy 78 % sensitivity, 100 % specificity for predicting recurrent disease
Oh	2011	Neck/distant	131-I SPET–CT sensitivity 65 %, specificity 95 %
			131-I planar sensitivity 65 %, specificity 55 %
			FDG PET/CT sensitivity 61 %, specificity 94 %
Wakabayashi	2011	Neck/distant	SPET–CT and delayed-phase (7 day) post-therapy imaging
			Interobserver agreement and reader confidence improved
Qiu	2010	Neck	SPET–CT identified parapharyngeal metastases in 14/561 (2.5 %) patients
			Parapharyngeal metastases were associated with regional and/or distant metastases
Grewal	2010	Neck/distant	SPET–CT changed N in 15 % of post-surgical patients and in 21 % of recurrence patients
			SPET–CT changed ATA risk classification in 7/109 (6.4 %) patients
			SPET–CT identified non-iodine-avid metastases in 32/148 (22 %) patients
			Size of nodal metastases was measured on CT component of SPET–CT
			SPET–CT avoided additional imaging in 48 % of patients
Mustafa	2010	Neck	Accuracy SPET–CT > planar scans in 24.5 % of patients
			SPET–CT revised N score in 24.5 % of patients
			Lymph nodal metastases occur in 26 % of patients with T1 and 22 % of patients with microcarcinoma ($\leq$1 cm)
Schmidt	2010	Neck	0/61 patients with negative SPET–CT were disease free at 5 months
			17/20 patients with positive SPET–CT were disease free at 5 months
			Metastasis size <0.9 ml predicted treatment success
Aide	2009	Neck	SPET–CT clarified diagnosis in 16 patients with indeterminate planar scans
			9/9 patients without disease had negative SPET–CT
			4/5 pts with disease had positive SPET–CT
Kohlfuerst	2009	Neck/distant	SPET–CT had an impact in 21/33 (63.6 %) patients, changed N score in 12/33 (36.4 %)
			SPET–CT had an impact in 14/19 (73.7 %) pts, changed M score 4/19 (21.1 %)
			SPET–CT changed treatment in 10/41 (24.4 %) patients: 8/33 (24.2 %) changed treatment due to N score, 2/19 (10.5 %) changed treatment due to M score
Wang	2009	Neck/distant	Accuracy SPET–CT > planar scans in 20/94 (21 %) patients.
			Changed treatment in 22/94 (23 %) patients
			SPET–CT identified unsuspected metastases in 7/94 (7 %) patients
Schmidt	2009	Neck	SPET–CT completed N staging
			SPET–CT changed N score in 20/57 (35 %) patients
			SPET–CT changed risk stratification in 14/57 (25 %) patients
Chen	2008	Neck/distant	Incremental diagnostic value SPET–CT > planar in 17/23 (74 %) patients,
			SPET–CT clarified 69/81 (85 %) inconclusive planar foci
			SPET–CT changed treatment in 8/17 (47 %) patients
Tharp	2004	Neck/distant	Incremental value SPET–CT > planar in 41/71 (57 %) patients
			Dx SPET–CT changed treatment in 7/17 (41 %) patients
Ruf	2004	Neck/distant	SPET–CT had an impact in 17/39 (44 %) foci
			Changed treatment in 6/24 (25 %) patients
Yamamoto	2003	Neck/distant	Accuracy SPET–CT > SPET 15/17 (88 %) patients

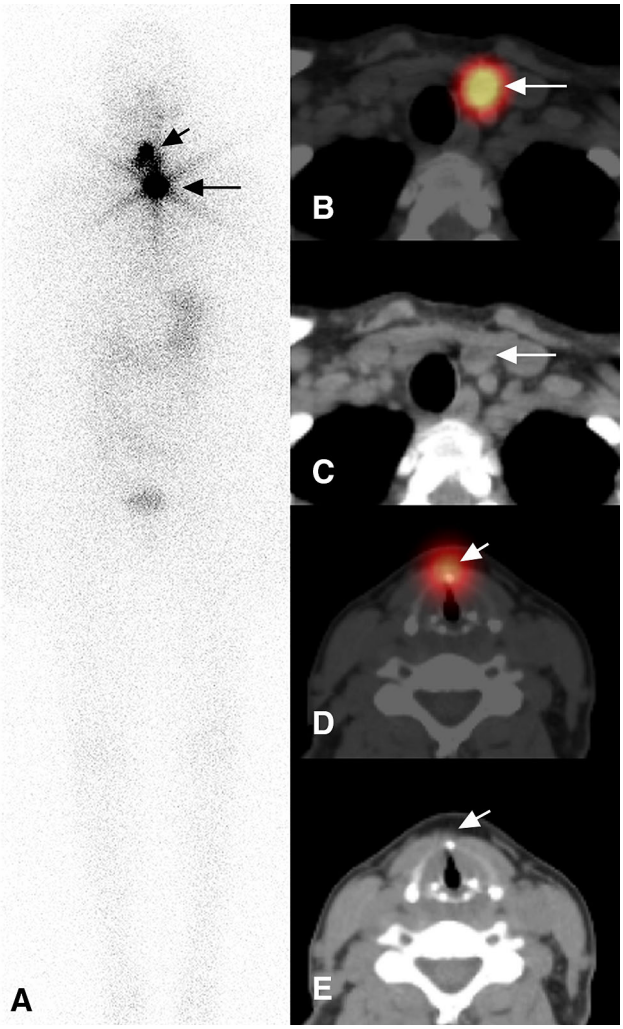

Fig. 2 Thyroglossal duct remnant and nodal metastases. Pre-ablation I-131 SPET–CT scan in a 59-year-old woman with multifocal papillary thyroid cancer, the largest lesion measuring 1.4 cm in the left lobe, without capsular or vascular invasion, no extrathyroidal extension and negative surgical margins; 0/2 central lymph nodes were negative for metastatic disease. Post-surgical thyroglobulin was 44 ng/mL with a TSH of 57 mIU/L. She was pT1b N0 Mx, stage 1, initially classified as low risk not requiring radioiodine ablation. Planar scan (**a**) depicts two foci of neck activity with the inferior focus (*long arrow*) corresponding on SPET–CT (**b**, **c**) to a small iodine-avid cervical level VII lymph node with central necrosis. The superior focus (*short arrow*) corresponds on SPET–CT (**d**, **e**) to the tip of the hyoid bone (*short arrows*) compatible with thyroglossal duct remnant tissue. After imaging, the patient was restaged as T1a N1b M0, stage 4A, and re-classified as intermediate ATA risk with a recommendation for medium dose I-131 treatment (color figure online)

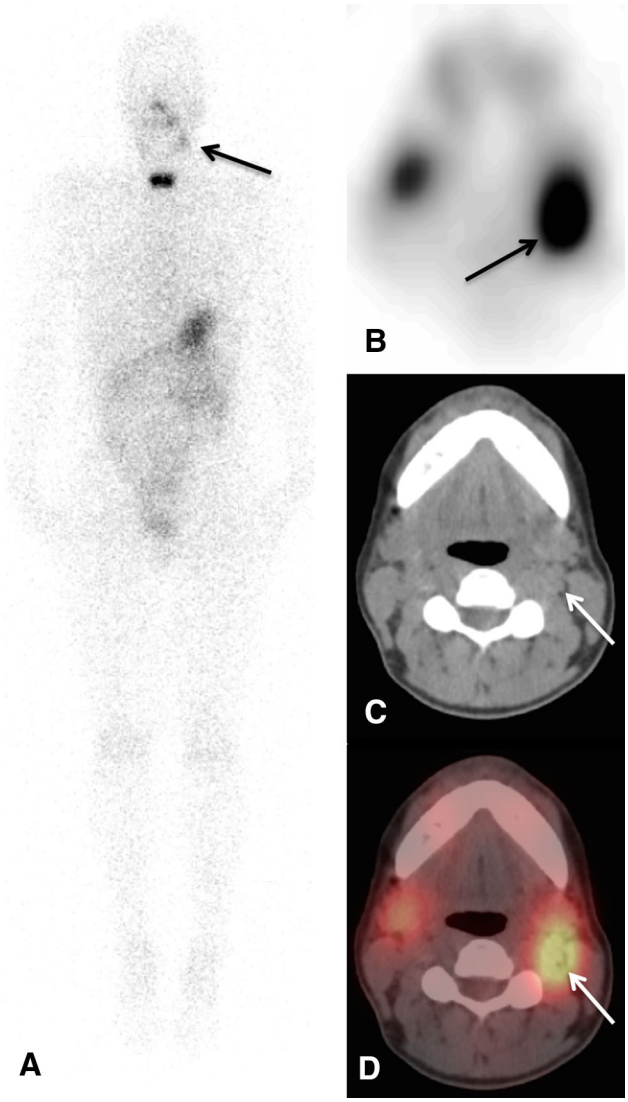

Fig. 3 Left neck Level 2 nodal metastases diagnosed only on SPET–CT. Pre-ablation I-131 whole-body planar and SPET–CT scan in a 46-year-old woman with papillary thyroid cancer. Planar scan (**a**) shows subtle asymmetric radioiodine uptake in what was initially thought to be the left submandibular gland (*arrow*). Axial SPET (**b**), unenhanced CT (**c**), and fused SPET–CT (**d**) demonstrate radioiodine-avid left cervical lymph nodes posterior to the left submandibular gland (*arrows*) consistent with nodal metastases. This case shows the limitation of planar imaging due to its inherent overlapping nature as well as the added diagnostic benefit of SPET–CT over planar imaging by providing anatomical localization (color figure online)

I-131 SPET–CT can be used to localize early skeletal metastases (prior to radiographic abnormality) as well as metastases in the lungs and mediastinal lymph nodes (Fig. 6). Qiu and colleagues reported that I-131 SPET–CT exhibited significantly higher sensitivity than ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) bone scans in depicting thyroid cancer metastases to bone [44]. Song and colleagues described distant metastatic disease depicted on I-131 SPET–CT, including some unusual sites [34, 35]. Additional reports have confirmed the value of I-131 SPET–CT in localizing unanticipated metastases of thyroid cancer to the trachea, muscle, liver and kidneys [53, 55–63]. Furthermore, I-131 SPET–CT accurately identifies cervical nodal metastases that may be present in anatomically normal lymph nodes and not readily identified on post-thyroidectomy neck ultrasound [52]. SPET–CT can

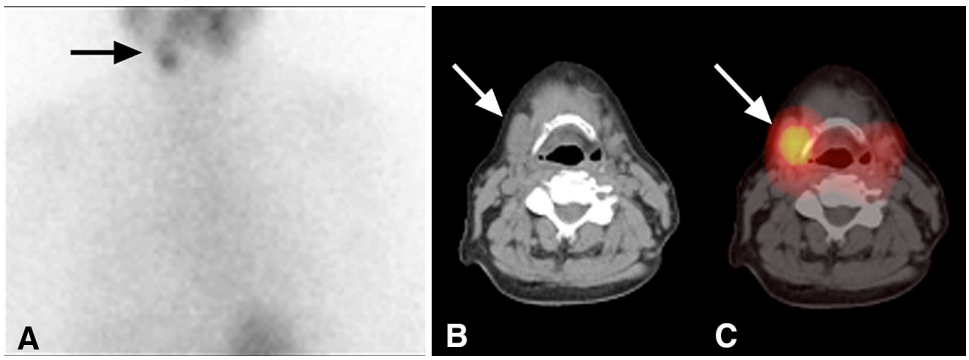

Fig. 4 Benign salivary gland activity found in a 78-year-old woman post-total thyroidectomy for papillary thyroid cancer. Diagnostic 4 mCi I-131 planar image (**a**) demonstrates focal uptake in the right side of the neck suspicious for lymph node metastasis (*arrow*). Axial CT (**b**) and SPET–CT (C) localize the neck activity to the salivary glands with more intense radioiodine uptake seen in the right gland which is larger than the left gland (*arrow*). This asymmetric salivary gland physiological uptake may occur following radioiodine administration (color figure online)

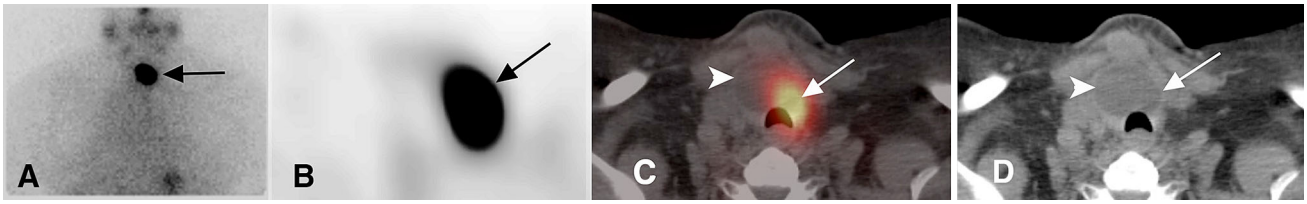

Fig. 5 Non-iodine-avid disease. Pre-ablation I-131 SPET–CT imaging in a 60-year-old woman with a 6.8-cm anaplastic thyroid cancer, with capsular and vascular invasion, extrathyroidal extension present and positive surgical margins (2+/4 resected central nodes had metastatic disease); pT4A N1a Mx, Stage 4B. Post-surgical thyroglobulin was 0.5 ng/mL with a TSH of 51 mIU/L. She was classified as high risk requiring medium dose of I-131. Planar anterior (**a**) image depicts focal neck activity (*long arrow*) corresponding on SPET–CT (**b**–**d**) to soft tissue in the left thyroid bed compatible with remnant thyroid tissue. However, adjacent to this, there is a low-attenuation necrotic pretracheal mass that does not accumulate radioiodine activity compatibly with non-iodine-avid disease (*arrowheads*). There was no iodine uptake demonstrated within metastatic disease in the mediastinum, liver, bone and abdomen detected with FDG PET/CT imaging. After imaging, the patient was restaged as T4a N1b M1, stage 4C, classified as high ATA risk. Recommendation was for high-dose I-131 treatment and referral for external beam radiation therapy (color figure online)

identify metastatic disease in the neck and at distant sites, improving image interpretation and reducing the need for correlative diagnostic CT or MRI.

Benign remnant thyroid tissues and physiological variants evaluated with SPET–CT

Numerous physiological variants and potential disease mimics are recognized and well described on radioiodine scintigraphy [64–66]. In addition to thyroid cells, NIS activity can be found in salivary glands, gastric mucosa, and lactating and non-lactating breasts [67]. Radioiodine uptake has also been identified in lacrimal glands, choroid plexus, the ciliary body of the eye, skin, placenta, and thymus [1, 67–71]. It is estimated that at least 22 % of radioiodine scans will have cryptic findings including benign mimics of disease [42]. Although the majority of these normal variants are correctly identified on planar imaging, SPET–CT helps to resolve diagnostic uncertainty, increasing interpretation confidence and accuracy [72, 73]. Multiple case reports confirm this utility of SPET–CT in distinguishing an increasing list of benign mimics of disease that include obstructed nasolacrimal duct(s), lingual thyroid(s), thymus, struma ovarii, ovarian teratomas, menstruating uterus and renal cysts [53, 55–63, 74–78] (Fig. 7). Two papers independently reported the utility of SPET–CT for investigation of a physiological mechanism of radioiodine uptake not previously described in the literature. Savas and colleagues reviewed 216 SPET–CT scans and found that oral radioiodine uptake was present on 123 (57 %) [79] and postulated an affinity of radioiodine for metals via a semi-permanent chemical reaction. Others studied 58 post-therapy patients with SPET–CT and confirmed that 91 % showed focal radioiodine localizing to dental restorations [80].

Investigators from Australia retrospectively evaluated post-therapy SPET–CT in 83 consecutive patients paying particular attention to the presence of remnant thyroid tissue located along the thyroglossal tract [81], i.e., thyroid tissue remaining along the embryological path of thyroid

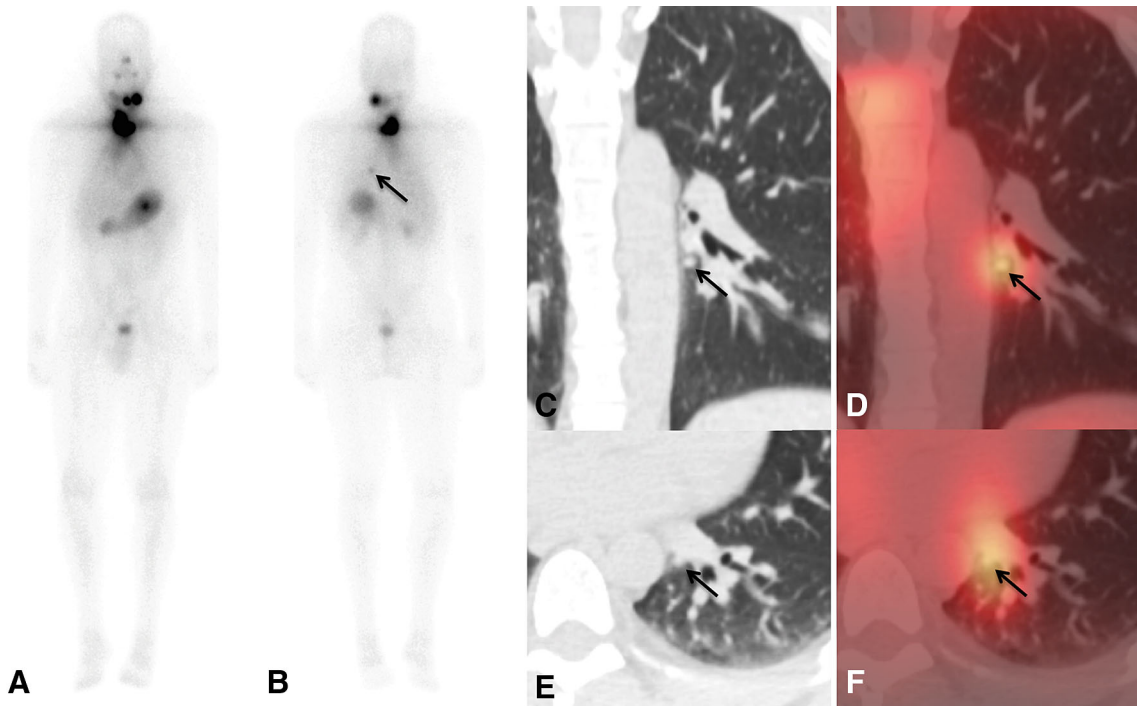

Fig. 6 Distant metastases: Radioiodine-avid lung metastases. Post-ablation I-131 whole-body planar and SPET–CT scan in a 36-year-old male with papillary thyroid cancer. Anterior (**a**) and posterior (**b**) whole-body planar images demonstrate a subtle focus of activity in the left thorax (*arrow*), which is better visualized on the posterior image. Coronal unenhanced CT (**c**), coronal SPET–CT (**d**), axial unenhanced CT (**e**), and axial SPET–CT (**f**) show a small 6-mm radioiodine-avid nodule in the left lower lobe (*arrows*). By localizing the scintigraphic findings to the nodule present on CT, the overall confidence in the diagnosis of lung metastases is increased (color figure online)

descent from the foramen cecum (near the tongue) to the thyroid bed. This tissue is not usually removed with total thyroidectomy and can create diagnostic uncertainty on post-surgical TSH-stimulated planar radioiodine scans [22, 23]. This thyroglossal tract thyroid tissue was reported to be present in 39/83 (47 %) patients and could be accurately characterized on SPET–CT. The investigators observed that some of the total dosage of radioiodine was administered with the aim of ablating these otherwise benign post-surgical findings in these patients. SPET–CT can confidently confirm that uptake in the neck and elsewhere in the body is benign in nature, preventing misinterpretation of findings as metastatic disease.

Comparison with other imaging modalities in thyroid cancer

Qiu and colleagues compared the diagnostic performance of ^{99m}Tc-MDP bone scans, I-131 SPET–CT and ^{18}F-FDG PET in patients with suspected bone metastases. I-131 SPET–CT had a sensitivity of 92 % and a specificity of 98 %, which were values similar to those recorded for ^{18}F-FDG PET (sensitivity of 85 %, specificity of 88 %). Both these modalities were superior to ^{99m}Tc-MDP bone scans, which had a sensitivity of 73 % and a specificity of 74 % [44]. In a retrospective study of 140 patients suspected of having metastatic disease based on imaging and serum thyroglobulin, Oh and colleagues reported a sensitivity of 65 % and a specificity of 95 % for I-131 SPET–CT, similar to the values for ^{18}F-FDG PET and higher than those of whole-body I-131 planar scans [43]. In this investigation, I-131 SPET–CT outperformed ^{18}F-FDG PET after a single I-131 treatment, while the sensitivity of ^{18}F-FDG PET was better than that of I-131 SPET–CT in patients after multiple radioiodine treatments [43]. Imaging with I-131 SPET–CT and ^{18}F-FDG PET provides complementary diagnostic information that assists in the management of patients with WDTC and should be ordered on the basis of the specific clinical situation.

Preliminary data suggest that the sensitivity of I-124 PET/CT is higher than that of post-therapy I-131 SPET–CT for the detection of radioiodine lesions (remnants or metastases). de Pont and colleagues reported a study that compared pretreatment I-124 PET/CT with post-therapy I-131 SPET–CT in 20 patients. I-124 PET/CT performed best, identifying 92 % of total foci, whereas radioiodine SPET–CT identified 81 % and planar imaging only 63 %. Staging and management were changed in 25 % of patients, three of whom were detected only with PET/CT [82].

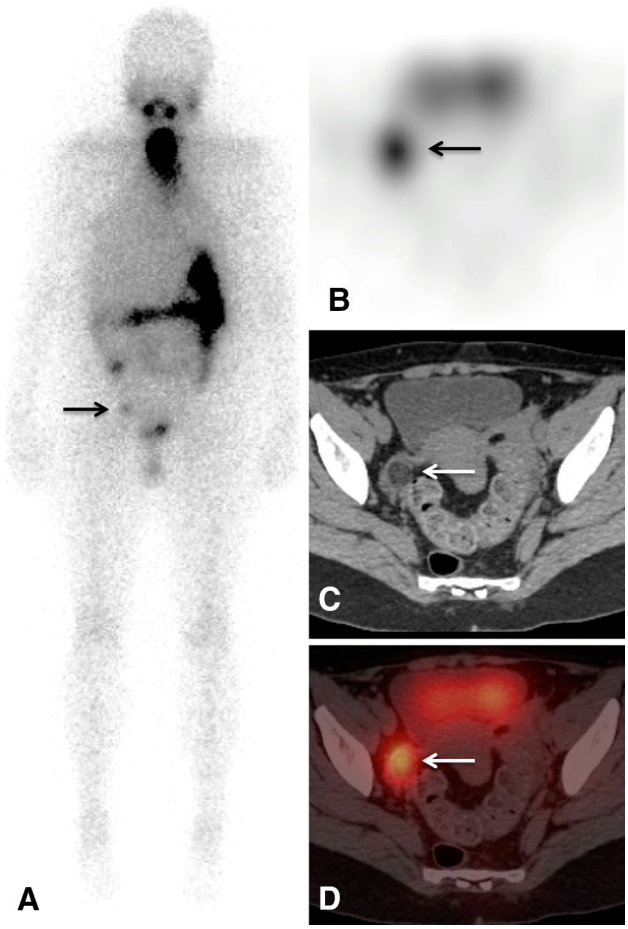

Fig. 7 Benign mimic of distant metastases found in a 48-year-old woman post-total thyroidectomy for papillary thyroid cancer. Post-therapy scan obtained several days after 100 mCi I-131. Anterior planar image (**a**) demonstrates focal uptake in the right side of the pelvis that was not present on the diagnostic scan (*arrow*). Axial SPECT (**b**) confirms the presence of focal activity in the right pelvis (*arrow*). Axial unenhanced CT (**c**) and fused SPET–CT (**d**) localize the activity to a benign cystic teratoma (dermoid) of the right ovary (*arrows*). SPECT–CT accurately characterized this lesion as benign mimic of malignancy and avoided the misdiagnosis of distant metastases (color figure online)

Impact of SPET–CT on thyroid cancer staging, management and prognosis

Accurate staging and risk stratification are critical considerations in the management of thyroid cancer. Post-therapy I-131 SPET–CT studies [20, 25, 26, 30, 33, 37, 40] and follow-up diagnostic scans after thyroid remnant ablation [19, 41] have demonstrated improved characterization of nodal (N) and distant metastases (M) status on TNM staging schema. At the first radioablation therapy, post-therapy SPET–CT was found to restage the cervical N status in 20/57 (35 %) patients [33]. Similarly, Kohlfuerst and colleagues noted that SPET–CT changed the N score in 12/33 (36.4 %) and M score in 4/19 (21.4 %) of patients with inconclusive post-therapy planar scans, resulting in changes in management in 10/41 (24.4 %) patients [27].

It is obvious that identification of the presence of loco-regional and/or distant metastatic disease prior to thyroid remnant ablation alters subsequent patient management. Pre-ablation SPET–CT altered TNM staging in 10/48 (21 %) patients, resulting in reconsideration of the proposed I-131 therapeutic dose in 28/48 (58 %), with lower administered radioiodine, 1.1 GBq (30 mCi), in low-risk patients with the goal of performing remnant ablation only, and higher doses 3.7–7.7+ GBq (100–200+ mCi) when the intention was to treat persistent iodine-avid thyroid cancer [21]. The effect of I-131 SPET–CT on N and M scores and TNM stage was assessed in 320 patients evaluated at the time of planned thyroid remnant ablation. In 138 patients <45 years old unanticipated distant metastases were identified in five (4 %) and nodal metastases in 61 patients (44 %), while in 182 patients older than 45 years distant metastases were found in 18 (10 %) and nodal metastases in 51 patients (28 %). With the additional information obtained from I-131 SPET–CT scanning, TNM staging was changed in 4 % of patients aged under 45 years, and in 25 % of those over the age of 45 [24].

In a cohort of 290 patients at intermediate risk, as established by the American Thyroid Association (ATA) thyroid cancer guidelines risk assessment [4], who had undergone radioiodine treatment, retrospectively selected on the basis of negative or low thyroglobulin, SPET–CT was found to disclose unsuspected disease in the neck and the lungs even in patients with undetectable post-surgical thyroglobulin levels [83].

SPET–CT has been used to study the incidence of nodal metastases in T1 tumors. In a study of 151 patients using a combination of pN1 (nodal disease found on the pathology specimen from surgical neck dissection) and sN1 (nodal disease detected on SPET–CT imaging), lymph node metastases were identified in 26 % of T1 stage (≤2.0 cm) tumors and in 22 % of small primary tumors (≤1.0 cm), with obvious implications for risk stratification and management [30]. Another study using diagnostic SPET–CT found that T1a tumors were associated with nodal metastases in 28/49 (57 %); unsuspected distant metastases were found in 2/49 cases (4 %) [24]. In a study of thyroid microcarcinoma, SPET–CT on post-therapy imaging was used to confirm a significant proportion (26/30 patients) as having regional nodal metastatic disease: the proportion of patients with N1 disease was 30/85 (35 %) [84].

The results of radioiodine SPET–CT imaging lead to changes in clinical management that include subsequent use of therapeutic radioiodine, modification of the extent of surgery, the use of external beam radiation therapy, and the inclusion of alternative imaging procedures (e.g., ^{18}F-FDG PET). SPET–CT with either I-123 or I-131 accurately

localized all neck foci including benign etiologies in 13 children with WDTC, depicted additional foci of I-131 accumulation not identified on planar imaging in two, and changed the clinical decision (ruling out I-131 therapy) in two others [51]. It is, in fact, important to avoid unnecessary radiation exposure where residual and/or metastatic disease has been excluded [85, 86]. SPET–CT can characterize focal I-131 central neck uptake as benign thyroid remnants, thereby reducing the dose requirements or even eliminating the need for radioiodine therapy in some patients [87].

Important prognostic information regarding the success of radioiodine treatment is provided by I-131 SPET–CT imaging. In a short-term follow-up study, Schmidt and colleagues [32] reported that an involved neck nodal volume of <0.9 ml, estimated using SPET–CT, was highly likely to respond to I-131 therapy without surgical intervention. Other authors found that the presence (or absence) of I-131 uptake on post-therapy SPET–CT can be used to better predict short-term outcome and failure of I-131 therapy compared with planar imaging alone [25]. Ciappuccini and colleagues performed post-therapy SPET–CT imaging in 170 patients to identify prognostic factors predicting treatment failure at 2 years. In this study, TNM staging, macroscopic cervical lymph node disease, and positivity of planar and SPET–CT imaging were identified as significant predictive factors, with SPET–CT as the only independent prognostic indicator [26]. Radioiodine SPET–CT assists risk stratification of WDTC, can predict failure of radioiodine treatments, and gives insight into the prognosis of patients with WDTC.

SPET–CT derived tumor dosimetry

Radioiodine SPET–CT imaging can be used to identify patients with unsuspected metastatic disease and thus to define targets for I-131 therapy, rather than relying on blind empiric treatments. The information obtained from imaging can be used to determine tumor dosimetry, particularly when high-dose I-131 therapy is being considered [21, 88]. It is well established that absorbed doses of >7,800 cGy are necessary to ablate residual carcinomas [89, 90]. While the general goal of initial I-131 therapy is to ablate as much tumor as possible, most therapies are planned with standard doses of radioiodine, limiting the role of tumor dosimetry, the best predictor of therapeutic success, to more complicated patients. Until recently, calculation of absorbed radiation dose in affected lymph nodes was problematic in the absence of accurate measurement of tumor volume. SPET–CT can be used to better define the volume of metastatic disease and thereby provide more accurate tumor dosimetry. Its use to deliver tailored doses of radiation to the tumor has been reported in a patient with a large metastasis to the skull [91] and in a case of diffuse bone metastases [92].

Limitations of SPET–CT

The spatial resolution of SPET–CT is limited in small lesions by partial volume averaging that excludes delineation of small lymph node metastases. Accurate tumor staging, therefore, requires knowledge of the histopathological status of extrathyroidal extension and the presence or absence of disease at surgical margins for T staging and the status of central lymph nodes for N staging. Misregistration of radioiodine and CT datasets, either as a result of patient motion or normal physiology (e.g., respiratory motion) may complicate image fusion and scan interpretation.

SPET–CT for imaging medullary thyroid cancer

Medullary thyroid cancers (MTCs) are derived from parafollicular (C cells) of neural crest origin, and they account for 3–12 % of all thyroid cancers. MTC is an indolent disease and after surgery up to 40 % of patients will have residual or recurrent disease, as indicated by elevated serum calcitonin or carcinoembryonic antigen tumor biomarkers [93]. Molecular imaging agents for MTC have limited sensitivities: ^{99m}Tc(V)DMSA (50–80 %), ^{201}Tl-thallium (19 %), ^{99m}Tc-sestamibi (47 %), $^{123/131}$I-MIBG (25–30 %), ^{111}In-octreotide (50–75 %) [94] and recently ^{99m}Tc-EDDA/HYNIC-TOC (80 %) [95]. ^{111}In-octreotide SPET–CT was able to depict a paratracheal MTC recurrence [96], while another report described a MEN2B patient with ^{99m}Tc-(V)DMSA SPET–CT imaging of bone metastases [97]. To our knowledge, due to the rarity of MTCs, no dedicated cohorts have been studied with SPET–CT, although some utility is reported [98, 99].

SPET–CT for miscellaneous uses related to thyroid cancer

SPET imaging with CT has also been fused with MRI for the investigation of thyroid cancer metastases [50]. It has been used to guide aspiration biopsy, when the ultrasound fine-needle aspiration biopsy is negative, but the lymph node aspirate is positive for thyroglobulin [100, 101]. A novel use is to predict nodal metastatic status with ^{99m}Tc-sestamibi [102]. Future use of these novel applications of SPET–CT remains to be elucidated.

Conclusion

SPET–CT imaging has improved our ability to localize disease and distinguish benign and otherwise normal

anatomical variants from thyroid cancer in the neck and elsewhere. The addition of anatomical maps that can be directly combined with the distribution of radioiodine in multi-planar orthogonal projections has changed the approach to diagnosis, staging, therapy and prognostic assessment of well-differentiated thyroid cancer.

Conflict of interest The authors Ka Kit Wong, Daniel J. Wale, Lorraine M. Fig and Milton D. Gross declare no conflict of interest for preparation of this manuscript.

Human and animal studies This systematic review was conducted with the approval of the Internal Review Board.

References

1. Chung JK (2002) Sodium iodide symporter: its role in nuclear medicine. J Nucl Med 43:1188–1200
2. Dai G, Levy O, Carrasco N (1996) Cloning and characterization of the thyroid iodide transporter. Nature 379:458–460
3. Smanik PA, Liu Q, Furminger TL, Ryu K, Xing S, Mazzaferri EL, Jhiang SM (1996) Cloning of the human sodium iodide symporter. Biochem Biophys Res Commun 226:339–345
4. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM (2009) Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 19:1167–1214
5. Siegel R, Naishadham D, Jemal A (2013) Cancer statistics, 2013. CA Cancer J Clin 63:11–30
6. Davies L, Welch HG (2006) Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA 295:2164–2167
7. Chen AY, Jemal A, Ward EM (2009) Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. Cancer 115:3801–3807
8. Hay ID, McDougall IR, Sisson JC (2009) A proposition for the use of radioiodine in WDTC Management. J Nucl Med 50:328–329 author reply 329-330
9. Hay ID, McConahey WM, Goellner JR (2002) Managing patients with papillary thyroid carcinoma: insights gained from the Mayo Clinic's experience of treating 2,512 consecutive patients during 1940 through 2000. Trans Am Clin Climatol Assoc 113:241–260
10. Jonklaas J, Sarlis NJ, Litofsky D, Ain KB, Bigos ST, Brierley JD, Cooper DS, Haugen BR, Ladenson PW, Magner J, Robbins J, Ross DS, Skarulis M, Maxon HR, Sherman SI (2006) Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid 16:1229–1242
11. Mazzaferri EL, Jhiang SM (1994) Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 97:418–428
12. British Thyroid Association RCOP (2007) Guidelines for the management of thyroid cancer (2nd edn). http://www.british-thyroidassociationorg/Guidelines/. Accessed 24 Mar 2009
13. Hay ID (2007) Management of patients with low-risk papillary thyroid carcinoma. Endocr Pract 13:521–533
14. Mazzaferri EL (2007) Management of low-risk differentiated thyroid cancer. Endocr Pract 13:498–512
15. Mallick U, Harmer C, Yap B, Wadsley J, Clarke S, Moss L, Nicol A, Clark PM, Farnell K, McCready R, Smellie J, Franklyn JA, John R, Nutting CM, Newbold K, Lemon C, Gerrard G, Abdel-Hamid A, Hardman J, Macias E, Roques T, Whitaker S, Vijayan R, Alvarez P, Beare S, Forsyth S, Kadalayil L, Hackshaw A (2012) Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. N Engl J Med 366:1674–1685
16. Schlumberger M, Catargi B, Borget I, Deandreis D, Zerdoud S, Bridji B, Bardet S, Leenhardt L, Bastie D, Schvartz C, Vera P, Morel O, Benisvy D, Bournaud C, Bonichon F, Dejax C, Toubert ME, Leboulleux S, Ricard M, Benhamou E (2012) Strategies of radioiodine ablation in patients with low-risk thyroid cancer. N Engl J Med 366:1663–1673
17. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 155:529–536
18. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 62:1006–1012
19. Spanu A, Solinas ME, Chessa F, Sanna D, Nuvoli S, Madeddu G (2009) 131I SPECT/CT in the follow-up of differentiated thyroid carcinoma: incremental value versus planar imaging. J Nucl Med 50:184–190
20. Tharp K, Israel O, Hausmann J, Bettman L, Martin WH, Daitzchman M, Sandler MP, Delbeke D (2004) Impact of 131I-SPECT/CT images obtained with an integrated system in the follow-up of patients with thyroid carcinoma. Eur J Nucl Med Mol Imaging 31:1435–1442
21. Wong KK, Sisson JC, Koral KF, Frey KA, Avram AM (2010) Staging of differentiated thyroid carcinoma using diagnostic 131-I SPECT-CT. AJR Am J Roentgenol 195:730–736
22. Wong KK, Zarzhevsky N, Cahill JM, Frey KA, Avram AM (2008) Incremental value of diagnostic 131I SPECT/CT fusion imaging in the evaluation of differentiated thyroid carcinoma. AJR Am J Roentgenol 191:1785–1794
23. Wong KK, Zarzhevsky N, Cahill JM, Frey KA, Avram AM (2009) Hybrid SPECT-CT and PET-CT imaging of differentiated thyroid carcinoma. Br J Radiol 82:860–876
24. Avram AM, Fig LM, Frey KA, Gross MD, Wong KK (2013) Preablation 131-I Scans With SPECT/CT in Postoperative Thyroid Cancer Patients: what Is the Impact on Staging? J Clin Endocrinol Metab. doi:10.1210/jc.2012-363025
25. Aide N, Heutte N, Rame JP, Rousseau E, Loiseau C, Henry-Amar M, Bardet S (2009) Clinical relevance of single-photon emission computed tomography/computed tomography of the neck and thorax in postablation (131)I scintigraphy for thyroid cancer. J Clin Endocrinol Metab 94:2075–2084
26. Ciappuccini R, Heutte N, Trzepla G, Rame JP, Vaur D, Aide N, Bardet S (2011) Postablation (131)I scintigraphy with neck and thorax SPECT-CT and stimulated serum thyroglobulin level predict the outcome of patients with differentiated thyroid cancer. Eur J Endocrinol 164:961–969
27. Kohlfuerst S, Igerc I, Lobnig M, Gallowitsch HJ, Gomez-Segovia I, Matschnig S, Mayr J, Mikosch P, Beheshti M, Lind P (2009) Posttherapeutic (131)I SPECT-CT offers high diagnostic accuracy when the findings on conventional planar imaging are inconclusive and allows a tailored patient treatment regimen. Eur J Nucl Med Mol Imaging 36:886–893
28. Maruoka Y, Abe K, Baba S, Isoda T, Sawamoto H, Tanabe Y, Sasaki M, Honda H (2012) Incremental diagnostic value of SPECT/CT with 131I scintigraphy after radioiodine therapy in patients with well-differentiated thyroid carcinoma. Radiology 265:902–909
29. Menges M, Uder M, Kuwert T, Schmidt D (2012) 131I SPECT/CT in the follow-up of patients with differentiated thyroid carcinoma. Clin Nucl Med 37:555–560
30. Mustafa M, Kuwert T, Weber K, Knesewitsch P, Negele T, Haug A, Linke R, Bartenstein P, Schmidt D (2010) Regional

lymph node involvement in T1 papillary thyroid carcinoma: a bicentric prospective SPECT/CT study. Eur J Nucl Med Mol Imaging 37:1462–1466
31. Ruf J, Lehmkuhl L, Bertram H, Sandrock D, Amthauer H, Humplik B, Ludwig Munz D, Felix R (2004) Impact of SPECT and integrated low-dose CT after radioiodine therapy on the management of patients with thyroid carcinoma. Nucl Med Commun 25:1177–1182
32. Schmidt D, Linke R, Uder M, Kuwert T (2010) Five months' follow-up of patients with and without iodine-positive lymph node metastases of thyroid carcinoma as disclosed by (131)I-SPECT/CT at the first radioablation. Eur J Nucl Med Mol Imaging 37:699–705
33. Schmidt D, Szikszai A, Linke R, Bautz W, Kuwert T (2009) Impact of 131I SPECT/spiral CT on nodal staging of differentiated thyroid carcinoma at the first radioablation. J Nucl Med 50:18–23
34. Song HJ, Xue YL, Qiu ZL, Luo QY (2012) Uncommon metastases from differentiated thyroid carcinoma. Hell J Nucl Med 15:233–240
35. Song HJ, Xue YL, Xu YH, Qiu ZL, Luo QY (2011) Rare metastases of differentiated thyroid carcinoma: pictorial review. Endocr Relat Cancer 18:R165–R174
36. Wakabayashi H, Nakajima K, Fukuoka M, Inaki A, Nakamura A, Kayano D, Kinuya S (2011) Double-phase (131)I whole body scan and (131)I SPECT-CT images in patients with differentiated thyroid cancer: their effectiveness for accurate identification. Ann Nucl Med 25:609–615
37. Wang H, Fu HL, Li JN, Zou RJ, Gu ZH, Wu JC (2009) The role of single-photon emission computed tomography/computed tomography for precise localization of metastases in patients with differentiated thyroid cancer. Clin Imaging 33:49–54
38. Yamamoto Y, Nishiyama Y, Monden T, Matsumura Y, Satoh K, Ohkawa M (2003) Clinical usefulness of fusion of 131I SPECT and CT images in patients with differentiated thyroid carcinoma. J Nucl Med 44:1905–1910
39. Chen L, Luo Q, Shen Y, Yu Y, Yuan Z, Lu H, Zhu R (2008) Incremental value of 131I SPECT/CT in the management of patients with differentiated thyroid carcinoma. J Nucl Med 49:1952–1957
40. Grewal RK, Tuttle RM, Fox J, Borkar S, Chou JF, Gonen M, Strauss HW, Larson SM, Schoder H (2010) The effect of posttherapy 131I SPECT/CT on risk classification and management of patients with differentiated thyroid cancer. J Nucl Med 51:1361–1367
41. Barwick T, Murray I, Megadmi H, Drake W, Plowman PN, Akker S, Chew S, Grossman A, Avril N (2010) Single photon emission computed tomography (SPECT)/computed tomography using Iodine-123 in patients with differentiated thyroid cancer: additional value over whole body planar imaging and SPECT. Eur J Endocrinol 162:1131–1139
42. Blum M, Tiu S, Chu M, Goel S, Friedman K (2011) I-131 SPECT/CT elucidates cryptic findings on planar whole-body scans and can reduce needless therapy with I-131 in post-thyroidectomy thyroid cancer patients. Thyroid 21:1235–1247
43. Oh JR, Byun BH, Hong SP, Chong A, Kim J, Yoo SW, Kang SR, Kim DY, Song HC, Bom HS, Min JJ (2011) Comparison of ^{131}I whole-body imaging, ^{131}I SPECT/CT, and ^{18}F-FDG PET/CT in the detection of metastatic thyroid cancer. Eur J Nucl Med Mol Imaging 38:1459–1468
44. Qiu ZL, Xue YL, Song HJ, Luo QY (2012) Comparison of the diagnostic and prognostic values of ^{99}mTc-MDP-planar bone scintigraphy, ^{131}I -SPECT/CT and ^{18}F-FDG-PET/CT for the detection of bone metastases from differentiated thyroid cancer. Nucl Med Commun 33:1232–1242
45. Weber K, Berger F, Mustafa M, Reiser MF, Bartenstein P, Haug A (2012) SPECT/CT for staging and treatment monitoring in oncology. Applications in differentiated thyroid cancer and liver tumors. Radiologe 52:646–652
46. Delbeke D, Schoder H, Martin WH, Wahl RL (2009) Hybrid imaging (SPECT/CT and PET/CT): improving therapeutic decisions. Semin Nucl Med 39:308–340
47. Filesi M, Signore A, Ventroni G, Melacrinis FF, Ronga G (1998) Role of initial iodine-131 whole-body scan and serum thyroglobulin in differentiated thyroid carcinoma metastases. J Nucl Med 39:1542–1546
48. Lind P, Kohlfurst S (2006) Respective roles of thyroglobulin, radioiodine imaging, and positron emission tomography in the assessment of thyroid cancer. Semin Nucl Med 36:194–205
49. Xue Y, Qiu Z, Perotti G, Salvatori M, Luo Q (2013) 131I SPECT/CT: a one-station imaging modality in the management of differentiated thyroid cancer. Clin Transl Imaging 1(3):163–173
50. Aqueveque AC, Gonzalez EP, Gutierrez BD, Jaimovich FR, Diaz PJ, Csendes GP, Orellana PP, Lavados MH, Alliende GI, Araya LS (2007) Fusion of SPECT with computed tomography or magnetic resonance for the interpretation of abnormal tracer uptake. Rev Med Chil 135:725–734
51. Kim HY, Gelfand MJ, Sharp SE (2011) SPECT/CT imaging in children with papillary thyroid carcinoma. Pediatr Radiol 41:1008–1012
52. Qiu ZL, Xu YH, Song HJ, Luo QY (2011) Localization and identification of parapharyngeal metastases from differentiated thyroid carcinoma by ^{131}I-SPECT/CT. Head Neck 33:171–177
53. Wong KK, Avram AM (2008) Posttherapy I-131 thymic uptake demonstrated with SPECT/CT in a young girl with papillary thyroid carcinoma. Thyroid 18:919–920
54. Even-Sapir E, Keidar Z, Sachs J, Engel A, Bettman L, Gaitini D, Guralnik L, Werbin N, Iosilevsky G, Israel O (2001) The new technology of combined transmission and emission tomography in evaluation of endocrine neoplasms. J Nucl Med 42:998–1004
55. Agriantonis DJ, Hall L, Wilson MA (2009) Utility of SPECT/CT as an adjunct to planar whole body I-131 imaging: liver metastasis from papillary thyroid cancer. Clin Nucl Med 34:247–248
56. Aide N, Lehembre E, Gervais R, Bardet S (2007) Unusual intratracheal metastasis of differentiated thyroid cancer accurately depicted by SPECT/CT acquisition after radioiodine ablation. Thyroid 17:1305–1306
57. Dumcke CW, Madsen JL (2007) Usefulness of SPECT/CT in the diagnosis of intrathoracic goiter versus metastases from cancer of the breast. Clin Nucl Med 32:156–159
58. Macdonald W, Armstrong J (2007) Benign struma ovarii in a patient with invasive papillary thyroid cancer: detection with I-131 SPECT-CT. Clin Nucl Med 32:380–382
59. Qiu ZL, Luo QY (2009) Erector spinae metastases from differentiated thyroid cancer identified by I-131 SPECT/CT. Clin Nucl Med 34:137–140
60. Rachinsky I, Driedger A (2007) Iodine-131 uptake in a menstruating uterus: value of SPECT/CT in distinguishing benign and metastatic iodine-positive lesions. Thyroid 17:901–902
61. Thust S, Fernando R, Barwick T, Mohan H, Clarke SE (2009) SPECT/CT identification of post-radioactive iodine treatment false-positive uptake in a simple renal cyst. Thyroid 19:75–76
62. von Falck C, Beer G, Gratz KF, Galanski M (2007) Renal metastases from follicular thyroid cancer on SPECT/CT. Clin Nucl Med 32:751–752
63. Zhao LX, Li L, Li FL, Zhao Z (2010) Rectus abdominis muscle metastasis from papillary thyroid cancer identified by I-131 SPECT/CT. Clin Nucl Med 35:360–361

64. Carlisle MR, Lu C, McDougall IR (2003) The interpretation of ^{131}I scans in the evaluation of thyroid cancer, with an emphasis on false positive findings. Nucl Med Commun 24:715–735
65. Mitchell G, Pratt BE, Vini L, McCready VR, Harmer CL (2000) False positive ^{131}I whole body scans in thyroid cancer. Br J Radiol 73:627–635
66. Shapiro B, Rufini V, Jarwan A, Geatti O, Kearfott KJ, Fig LM, Kirkwood ID, Gross MD (2000) Artifacts, anatomical and physiological variants, and unrelated diseases that might cause false-positive whole-body 131-I scans in patients with thyroid cancer. Semin Nucl Med 30:115–132
67. Bizhanova A, Kopp P (2009) Minireview: the sodium-iodide symporter NIS and pendrin in iodide homeostasis of the thyroid. Endocrinology 150:1084–1090
68. Carvalho DP, Ferreira AC (2007) The importance of sodium/iodide symporter (NIS) for thyroid cancer management. Arq Bras Endocrinol Metabol 51:672–682
69. Filetti S, Bidart JM, Arturi F, Caillou B, Russo D, Schlumberger M (1999) Sodium/iodide symporter: a key transport system in thyroid cancer cell metabolism. Eur J Endocrinol 141:443–457
70. Shen DH, Kloos RT, Mazzaferri EL, Jhian SM (2001) Sodium iodide symporter in health and disease. Thyroid 11:415–425
71. Dohan O, De la Vieja A, Paroder V, Riedel C, Artani M, Reed M, Ginter CS, Carrasco N (2003) The sodium/iodide symporter (NIS): characterization, regulation, and medical significance. Endocr Rev 24:48–77
72. Glazer DI, Brown RK, Wong KK, Savas H, Gross MD, Avram AM (2013) SPECT/CT evaluation of unusual physiologic radioiodine biodistributions: pearls and pitfalls in image interpretation. Radiographics 33:397–418
73. Oh JR, Ahn BC (2012) False-positive uptake on radioiodine whole-body scintigraphy: physiologic and pathologic variants unrelated to thyroid cancer. Am J Nucl Med Mol Imaging 2:362–385
74. Jammah AA, Driedger A, Rachinsky I (2011) Incidental finding of ovarian teratoma on post-therapy scan for papillary thyroid cancer and impact of SPECT/CT imaging. Arq Bras Endocrinol Metabol 55:490–493
75. Yuoness S, Rachinsky I, Driedger AA, Belhocine TZ (2011) Differentiated thyroid cancer with epiphora: detection of nasolacrimal duct obstruction on I-131 SPECT/CT. Clin Nucl Med 36:1149–1152
76. Vercellino L, Alaoui NI, Faugeron I, Berenger N, de Labriolle-Vaylet C, Hindie E, Toubert ME (2011) Lingual thyroid imaging with ^{123}I SPECT/CT. Eur J Nucl Med Mol Imaging 38:1173
77. Mebarki M, Menemani A, Medjahedi A, Boualou F, Slama A, Ouguirti S, Kherbouche FZ, Berber N (2012) Radioiodine accumulation in a giant ovarian cystadenofibroma detected incidentally by 131-I whole body scans. Case Rep Radiol 2012:295617
78. Sakahara H, Yamashita S, Suzuki K, Imai M, Kosugi T (2007) Visualization of nasolacrimal drainage system after radioiodine therapy in patients with thyroid cancer. Ann Nucl Med 2:525–527
79. Savas H, Wong KK, Saglik B, Hubers D, Ackermann RJ, Avram AM (2013) SPECT/CT characterization of oral activity on radioiodine scintigraphy. J Clin Endocrinol Metab 98:4410–4416
80. Burlison JS, Hartshorne MF, Voda AM, Cocks FH, Fair JR (2013) SPECT/CT localization of oral radioiodine activity: a retrospective study and in vitro assessment. Nucl Med Commun 34:1216–1222
81. Barber TW, Cherk MH, Topliss DJ, Serpell JW, Yap KS, Bailey M, Kalff V (2014) The prevalence of thyroglossal tract thyroid tissue on SPECT/CT following I-131 ablation therapy after total thyroidectomy for thyroid cancer. Clin Endocrinol (Oxf) 81:266–270
82. de Pont C, Halders S, Bucerius J, Mottaghy F, Brans B (2013) ^{124}I PET/CT in the pretherapeutic staging of differentiated thyroid carcinoma: comparison with posttherapy ^{131}I SPECT/CT. Eur J Nucl Med Mol Imaging 40:693–700
83. Robenshtok E, Grewal RK, Fish S, Sabra M, Tuttle RM (2013) A low postoperative nonstimulated serum thyroglobulin level does not exclude the presence of radioactive iodine avid metastatic foci in intermediate-risk differentiated thyroid cancer patients. Thyroid 23:436–442
84. Gallicchio R, Giacomobono S, Capacchione D, Nardelli A, Barbato F, Nappi A, Pellegrino T, Storto G (2013) Should patients with remnants from thyroid microcarcinoma really not be treated with iodine-131 ablation? Endocrine 44:426–433
85. Tuttle RM, Leboeuf R, Robbins RJ, Qualey R, Pentlow K, Larson SM, Chan CY (2006) Empiric radioactive iodine dosing regimens frequently exceed maximum tolerated activity levels in elderly patients with thyroid cancer. J Nucl Med 47:1587–1591
86. Kulkarni K, Van Nostrand D, Atkins F, Aiken M, Burman K, Wartofsky L (2006) The relative frequency in which empiric dosages of radioiodine would potentially overtreat or undertreat patients who have metastatic well-differentiated thyroid cancer. Thyroid 16:1019–1023
87. Avram AM (2012) Radioiodine scintigraphy with SPECT/CT: an important diagnostic tool for thyroid cancer staging and risk stratification. J Nucl Med 53:754–764
88. Van Nostrand D, Aiken M, Atkins F, Moreau S, Garcia C, Acio E, Burman K, Wartofsky L (2009) The utility of radioiodine scans prior to iodine 131 ablation in patients with well-differentiated thyroid cancer. Thyroid 19:849–855
89. Maxon HR, Thomas SR, Hertzberg VS, Kereiakes JG, Chen IW, Sperling MI, Saenger EL (1983) Relation between effective radiation dose and outcome of radioiodine therapy for thyroid cancer. N Engl J Med 309:937–941
90. Koral KF, Adler RS, Carey JE, Beierwaltes WH (1986) Iodine-131 treatment of thyroid cancer: absorbed dose calculated from post-therapy scans. J Nucl Med 27:1207–1211
91. Sisson JC, Dewaraja YK, Wizauer EJ, Giordano TJ, Avram AM (2009) Thyroid carcinoma metastasis to skull with infringement of brain: treatment with radioiodine. Thyroid 19:297–303
92. Song H, He B, Prideaux A, Du Y, Frey E, Kasecamp W, Ladenson PW, Wahl RL, Sgouros G (2006) Lung dosimetry for radioiodine treatment planning in the case of diffuse lung metastases. J Nucl Med 47:1985–1994
93. Rufini V, Castaldi P, Treglia G, Perotti G, Gross MD, Al-Nahhas A, Rubello D (2008) Nuclear medicine procedures in the diagnosis and therapy of medullary thyroid carcinoma. Biomed Pharmacother 62:139–146
94. Bozkurt MF, Ugur O, Banti E, Grassetto G, Rubello D (2008) Functional nuclear medicine imaging of medullary thyroid cancer. Nucl Med Commun 29:934–942
95. Czepczynski R, Parisella MG, Kosowicz J, Mikolajczak R, Ziemnicka K, Gryczynska M, Sowinski J, Signore A (2007) Somatostatin receptor scintigraphy using ^{99}mTc-EDDA/HYNIC-TOC in patients with medullary thyroid carcinoma. Eur J Nucl Med Mol Imaging 34:1635–1645
96. Fiore D, Rubello D, Casara D, Pelizzo MR, Franchi A, Muzzio PC (2004) Role of CT/^{111}In-octreotide SPECT digital fusion imaging in the localization of loco-regional recurrence of medullary thyroid carcinoma. Minerva Chir 59:295–299
97. De Bonilla-Damia A, Calvo-Moron C, De La Riva-Perez PA, Iglesias-Jerez R, Molina-Mora M, Castro-Montano J (2011) Detection by SPECT-CT scan with (^{99}m)Tc-(V) DMSA of bone metastases in patient with medullary thyroid cancer. Rev Esp Med Nucl 30:365–367

98. Chowdhury FU, Scarsbrook AF (2008) The role of hybrid SPECT-CT in oncology: current and emerging clinical applications. Clin Radiol 63:241–251
99. Patel CN, Chowdhury FU, Scarsbrook AF (2008) Clinical utility of hybrid SPECT-CT in endocrine neoplasia. AJR Am J Roentgenol 190:815–824
100. Giovanella L, Suriano S, Lunghi L, Bongiovanni M, Ceriani L (2013) Radioguided surgery of thyroid carcinoma recurrences: the role of preoperative (^{99}m)Tc-labeled human serum albumin macroaggregates-SPECT/CT mapping. Clin Nucl Med 38:e207–e209
101. Ahn BC (2013) Radioiodine SPET/CT guided needle aspiration as a useful technique for recurrence surveillance in a thyroidectomized differentiated thyroid cancer patient with negative US and serum Tg and positive Tg of the lymph node aspirate. Hell J Nucl Med 16:142–143
102. Tangjaturonrasme N, Vasavid P, Sombuntham P, Keelawat S (2013) Pre-operative prediction of cervical nodal metastasis in papillary thyroid cancer by ^{99}mTc-MIBI SPECT/CT; a pilot study. J Med Assoc Thai 96:696–702