

REVIEW

Editorial Process: Submission:07/27/2017 Acceptance:01/06/2018

Hybrid SPECT/CT Imaging in the Management of Differentiated Thyroid Carcinoma

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Abstract

Differentiated thyroid cancer (DTC) has a good prognosis overall; however, lifelong follow-up is required for many cases. Radioiodine planar imaging with iodine-123 (I-123) or radioiodine-131 (I-131) remains the standard in the follow-up after initial surgery and ablation of residual thyroid tissue using I-131 therapy. Radioiodine imaging is also used in risk-stratifying and for staging of thyroid cancer, and in long-term follow-up. Unfortunately, the lack of anatomical detail on planar gamma camera imaging and superimposition of areas presenting with increased radioiodine uptake can make accurate diagnosis and localization of radioiodine-avid metastatic disease challenging, leading to false positive results and potentially to over-treatment of patients. Hybrid SPECT/CT allows precise anatomical localization and superior characterization of foci of increased tracer uptake when compared to planar imaging. This, in turn, allows the differentiation of pathological and physiological uptake, increasing the accuracy of image interpretation and ultimately improving the accuracy of DTC staging and subsequent patient management. In this review, we look at the unique and emerging role that SPECT/CT plays in the management of DTC, illustrated by examples from our own clinical practice.

Keywords: Differentiated thyroid cancer- hybrid imaging-SPECT/CT

Asian Pac J Cancer Prev, **19** (2), 303-308

Introduction

Thyroid cancer is the most common type of endocrine-related cancer, with 64,300 estimated new cases in the USA in 2016, representing 3.8% of all new cancer cases (National Cancer Institute, no date). Differentiated thyroid cancer (DTC), which includes papillary and follicular cancer, comprises the vast majority (>90%) of all thyroid cancers (Enewold et al., 2009). Patients with DTC have an overall good prognosis; however, lifelong follow-up is required for many cases, since potentially curable local recurrences and distant metastases may occur even decades later (DeGroot et al., 1990). Patients with localized thyroid cancer, defined as “low risk” (TNM Stage I), have a cancer-specific mortality of 1% at 20 years, but this increases to between 25% and 45% at 10 years after diagnosis for “high-risk” (TNM Stage III/IV) patients (Jonklaas et al., 2006).

Radioiodine planar imaging with radioactive iodine-123 (I-123) or radioiodine-131 (I-131) plays a major role and remains the gold standard in follow-up after initial surgery. For example, following total surgical thyroidectomy, I-131 is used for the detection and ablation of residual thyroid carcinoma. Unfortunately, interpretation of radioiodine uptake on planar imaging can be challenging, leading

to misinterpretation and false-positive scans. The lack of anatomical detail on planar gamma camera imaging and superimposition of areas presenting with increased radioiodine uptake can make accurate diagnosis and localization of radioiodine-avid metastatic disease challenging. In addition, there is radioiodine uptake in normal structures and tissues, so it can be difficult to distinguish physiological radioiodine activity from metastatic disease. These issues are of particular importance in the neck and thorax where differentiation between physiological radioiodine accumulation, remnant thyroid tissue, and residual or recurrent thyroid cancer may be difficult. Therefore, accurate characterization and localization of malignant radioiodine uptake to lung, bone, or lymph nodes can be challenging. Leitha et al. revealed diagnostic pitfalls leading to additional imaging or diagnostic procedures in 59% of studies (Leitha and Staudenherz, 2003).

Single-photon emission computed tomography (SPECT) with integrated computed tomography (CT) is a novel technology that is increasingly being used with radioiodine scintigraphy to evaluate patients with thyroid cancer. This technique shows promise for improving imaging specificity. SPECT/CT enables co-registration of structural and functional data and provides accurate

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patient-specific attenuation correction of tracer distribution (Seo et al., 2008). This allows precise anatomical spatial localization and improved characterization of foci of increased tracer uptake when compared to planar imaging. This can effectively extricate benign disease and physiological uptake, ultimately improving the accuracy of DTC staging and subsequent patient management (Patton and Turkington, 2008).

In this review, we will discuss the emerging role of radioiodine scintigraphy with SPECT/CT imaging in the evaluation of postoperative residual thyroid tissue, regional and distant metastases, and the resolution of diagnostic challenges due to benign and false positive uptake. We will then evaluate the overall impact of this technology on the diagnosis and ongoing management of DTC and illustrate with some examples from our own clinical practice.

SPECT/CT

SPECT/CT systems have the same gamma camera component generally used for planar and tomographic imaging of single photon emitting radiotracers. This is complemented by a separate CT device which may use common or adjacent mechanical gantries, and share the same scanning table, with the patient moving in the axial direction. The SPECT/CT workstation is responsible for system control, data acquisition, image reconstruction, and display, as well as data processing and analysis. CT data are calibrated in order to obtain attenuation correction maps for the SPECT images.

The first commercial SPECT/CT system was only introduced in 1999. This system combined a low-power x-ray tube with separate gamma and x-ray detectors mounted on the same slip ring gantry, allowing sequential acquisition of SPECT and CT images as the detectors rotated around the patient. Over the last decade, there has been a large expansion of SPECT/CT technology worldwide. Following the commercial success of PET/CT systems that employ multi-slice CT scanners, new hybrid systems using advanced spiral CT scanners of up to 64-slice with dual-head gamma cameras have further improved image quality and reduced acquisition time. Some of these systems are equipped with an ultra-high resolution SPECT/CT imaging system, with a new digital detector powered by cadmium zinc telluride (CZT) technology, allowing direct conversion of gamma radiation to an electrical signal (Seo et al., 2008).

Radioiodine SPECT/CT in Thyroid Cancer

I-131 is often used for the detection and treatment of residual thyroid carcinoma following surgical thyroidectomy. Ingested iodides are rapidly and nearly completely absorbed (>90%) from the duodenum into the bloodstream and most of the iodides are excreted by the kidneys. Iodides are actively taken up in the thyroid follicular cells, a process which is mediated by a transmembrane glycoprotein, Sodium Iodide Symporter (NIS). I-131 is only poorly concentrated by most extrathyroidal tissues. However, the salivary glands, stomach, intestines, urinary bladder and lactating mammary glands are the most notable exception to this

rule. NIS is also detectable and active in these tissues, although less expressed than in follicular cells, allowing these tissues to take up iodide by the action of the NIS (Kogai and Brent, 2012).

The therapeutic effect of I-131 is provided by its beta-emission. In addition, this iodine isotope emits 364 keV gamma rays that can be detected by gamma cameras (Green et al., 1990). I-131 is therefore also used as a diagnostic agent since most, but not all, metastases of thyroid carcinoma have retained the normal ability of the thyroid parenchyma to take up and accumulate iodine (Kogai and Brent, 2012).

The biodistribution of I-131 is usually sufficiently defined by planar scintigraphy. SPECT alone is rarely used for this purpose, as the image quality of I-131 -SPECT is hampered by the high energy of the gamma radiation emitted. However, images of I-131 distribution in the human body obtained with a gamma camera lack anatomical detail, as no clear reference landmarks can be recognized. This renders localization of radioiodine foci difficult and iodine-avid metastases can be small. Furthermore, they may occur in regions exhibiting distorted anatomy due to previous surgery. Their localization using CT or MRI alone may therefore also not be possible.

Advantages of SPECT/CT include accurate anatomic localization and characterization of radioiodine foci as benign or malignant for example in relation to cervical nodal metastases (Figure 1) which can be difficult to co-localise without the aid of CT. In addition interval assessment of the size, location and iodine avidity of metastatic lesions are better assessed with SPECT and CT, providing a better assessment of response to I-131 therapy and guiding further management decisions.

Several studies have focused on the role and clinical benefit of I-131 SPECT-CT. Tharp et al., (2004) found that SPECT-CT had an incremental diagnostic value in 57% (41 of 71) of patients compared with planar imaging, with a substantial impact on patient clinical management.

Of particular note is the ability of iodine SPECT/CT to substantially reduce the number of diagnostically equivocal foci of radioiodine uptake at planar imaging (Figure 2). Chen et al., (2008) reported that SPECT/CT accurately characterized 85% of foci considered inconclusive on planar imaging, resulting in altered management for 47% of patients. Aide et al., (2009) reported that findings at planar imaging were indeterminate for disease in 29% (16 patients) - a rate that decreased to 7% after a review of SPECT/CT images.

Post-Therapy Radioiodine SPECT/CT

Post-therapy whole-body scanning (with or without SPECT-CT) is recommended after radioactive iodine (RAI) remnant ablation or treatment, to inform disease staging and document the iodine-avidity of any morphologically visible disease (Haugen et al., 2016). The potential role of the combination of RAI scanning in conjunction with SPECT-CT has been examined in multiple studies.

One study showed SPECT/CT improved diagnostic evaluation compared with SPECT alone in 15 of 17 patients (88%) (Yamamoto et al., 2003). In a series of

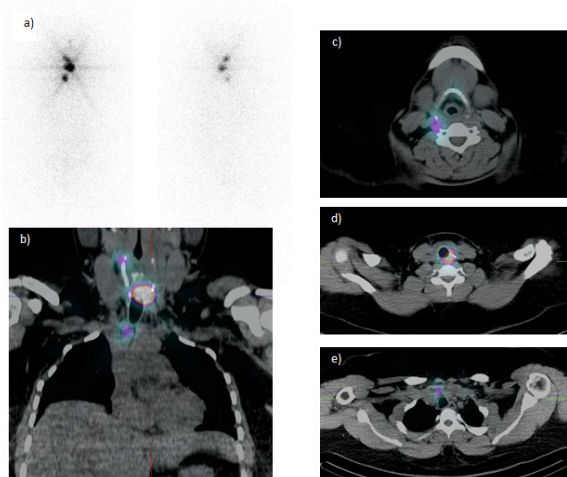


Figure 1. A case of papillary carcinoma in a 49 year old female who underwent total thyroidectomy (pT2N0Mx). Whole body scanning (WBS) was performed with 2.7mCi of I-131 under hormonal withdrawal a) Whole body images (WBI) show three foci of increased radiotracer uptake in the neck. b-e) SPECT-CT images demonstrates increased activity in left thyroid bed. There is also a focal area of increased tracer uptake in the right upper cervical region medial to the sternomastoid muscle (level II) and right supraclavicular region, findings consistent with nodal metastasis.

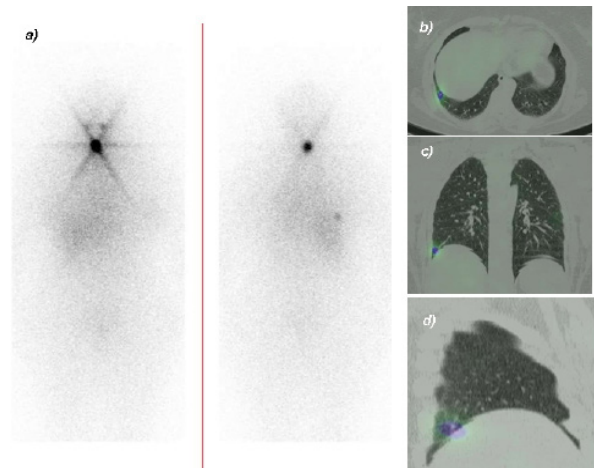


Figure 2. a) A known case of papillary carcinoma in a 40 year old male, status post thyroidectomy (pT3NxMx). Post ablation WBS was performed with 30mCi of I131. a) In addition to the thyroid bed activity, whole body images show faint increased tracer uptake which appear to be in the liver dome b-d) Fused SPECT-CT images that this co-localises to a I-131 avid pulmonary nodule at the base of the right lung. Findings, in this case, are consistent with solitary lung metastasis. Assessment with CT can be a key in correctly identifying the site of uptake, in particular, the lung bases.

25 patients with post-therapy I-131 scans, SPECT/CT improved diagnostic interpretation compared with planar images in 44% of radioactivity foci, resulting in a change in management in 25% of patients (Ruf et al., 2004). Ciappuccini and colleagues showed the combination of RAI post-therapy scanning and neck/thorax SPECT-CT was estimated to have a sensitivity of 78% (95% CI 60 – 90%), with a specificity of 100% (where negative or indeterminate scans were grouped as negative) for the outcome of resistant or recurrent disease (median study follow-up period of 29 months) (Ciappuccini et al., 2011). Wang et al., (2009) demonstrated that SPECT/CT improved anatomic localization of focal activity seen on planar post-therapy I-131 imaging in 21% of cases; in addition, SPECT/CT identified new metastatic foci unsuspected on planar imaging in 7% of patients. Most importantly, and similarly to the above single center study, the additional information obtained with SPECT/CT resulted in a reconsideration of therapeutic approach in 22 of 94 patients (23%). The incremental value of SPECT/CT in influencing therapeutic planning appears to be greatest in studies where its use was reserved for situations of post-therapy scan diagnostic uncertainty (impacted management in 24.4% [8 of 33] of cases, all of which went on to surgery) (Kohlfuerst et al., 2009), or when disease is advanced and whole body scan is inconclusive (impacted management in 35% [8 of 23] of such patients in another study) (Chen et al., 2008).

In thyroid cancer, imaging assessment of the post-surgical neck is of particular interest. Surgeons often have to leave residual thyroid tissue to avoid complications such as damage to the laryngeal nerve or the parathyroid glands. Determining whether the cancer is still present in the remaining tissue and local neck lymph

nodes becomes important for staging the disease. In one study I-131 post-therapy scanning in conjunction with SPECT-spiral CT of the neck, only 1 of the 61 patients with negative cervical scintigraphy / SPECT/CT had evidence of abnormal cervical scintigraphy 5 months later, whereas 3 (15%) of the 20 patients (3 patients) with positive or indeterminate cervical post-therapy scintigraphy/SPECT-CT had abnormal cervical scintigraphy 5 months later (Schmidt et al., 2010). In 2009, Schmidt et al., (2009) found that post-therapy SPECT/CT determines lymph nodal status in the neck more accurately than planar imaging, reporting on nodal staging in 57 patients who underwent planar imaging and SPECT/CT after a first radioablation. They found that 6 out of 11 lesions considered nodal metastases on planar imaging were reclassified as benign on SPECT/CT, and 11 of 15 lesions considered indeterminate on planar imaging were reclassified as nodal metastases on SPECT/CT. SPECT/CT allowed clarification of the nodal status in 20 of 57 patients (35%), which resulted in a change in risk stratification in 25% of patients. Mustafa et al., (2010) reported that nodal metastases occurred in 26% of T1 thyroid tumors and in 22% of microcarcinomas (T1a tumors, less than 1.0 cm). Regarding nodal staging, SPECT/CT was more accurate than planar imaging in 24.5% of patients. Qiu et al., (2011) found that the use of SPECT/CT permitted the identification of parapharyngeal metastases in 14 of 561 patients (2.5%); in these patients, parapharyngeal metastases were also associated with regional or distant metastases.

SPECT-CT is sometimes used in conjunction with post-therapy scanning to identify non-iodine-avid lesions using the CT portion. Grewal et al. found that SPECT/CT data provided information that reduced

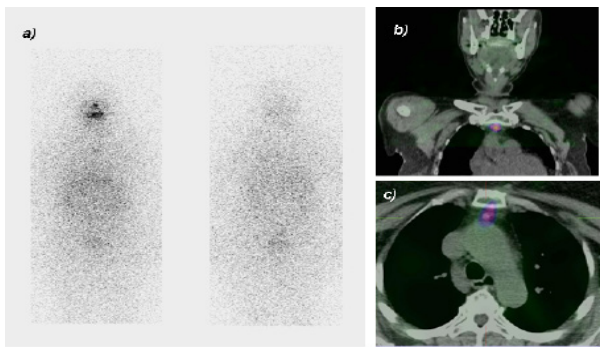


Figure 3. A known case of a follicular variant of papillary carcinoma in a 62-year old female. Total thyroidectomy was performed with 0/4 lymph node. (pT2N0Mx). WBS was performed with 2.7mCi of I-131 under hormonal withdrawal. Whole body images show tracer uptake in the neck line and very faint uptake in the chest in the midline. b-c) Fused SPECT CT images localize the neck uptake at the right upper thyroid bed and the faint activity is seen in an anterior mediastinal node consistent with locoregional lymph node metastasis.

the need for additional cross-sectional imaging in 29 patients (20%) and significantly altered the initial risk of recurrence estimates in 7 of 109 patients (6.4%), thereby altering patient management recommendations with regard to frequency and intensity of follow-up studies (Grewal et al., 2010). The additional advantage of morphological assessment with CT is of particular importance in some body parts for example at the lung-diaphragm-liver interface where respiratory motion can lead to misregistration as well as underestimation of tracer avidity particularly of smaller foci (Figure2).

Pre-Ablative SPECT/CT Whole Body scan

There remains an ongoing debate regarding the utility of postoperative RAI diagnostic scanning (with or without SPECT/CT) in guiding decision-making regarding the use of therapeutic RAI. Post-surgical RAI whole-body scans prior to initial radioiodine ablation may be useful when the extent of the thyroid remnant or residual disease cannot be accurately ascertained from the post-surgical report or neck ultrasonography, and when the results may affect the

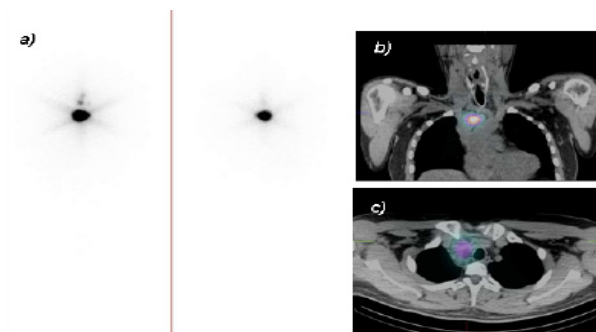


Figure 4. This 47 year old patient presented with a high Tg level, 11 years after been successfully treated with Total thyroidectomy and RAI. WBS was performed with 2.7mCi of I-131 under hormonal withdrawal. a) WBI show increased tracer uptake at the thoracic inlet. b,c) SPECT CT images localize the activity within soft tissue mass at the right upper paratracheal region consistent with locoregional nodal recurrent disease.

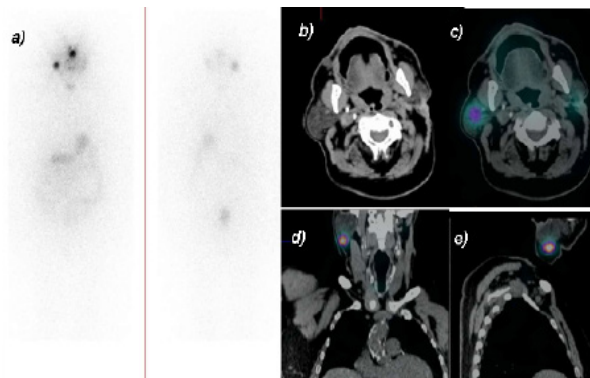


Figure 5. A known case of papillary thyroid cancer in a 46 year old female who underwent RAI done 4 years ago with a dose of 100mCi. Follow-up WBS with 2.2 mCi of Iodine 1-131 was performed under hormonal withdrawal. a) WBI shows a focus of increased radiotracer uptake in the right side of the neck. b-e) CT and Fused SPECT-CT images localize this uptake in the right parotid gland (asymmetrical physiological uptake) with no other pathological findings.

decision to provide further treatment or on the activity of RAI that is to be administered. It allows the prescription of appropriately higher activities at the first I-131 therapy for high-risk patients when the iodine-concentrating ability of the tumor is presumably highest and a reduction in activity administered for radioablation of thyroid remnants. Questions were raised about the potentially negative impact of such scans on the subsequent therapeutic efficacy of I-131 in successful remnant ablation (“stunning”). Therefore, pre-therapy diagnostic scans should utilize I-131 (1.5–3 mCi) or a low activity of I-131 (1–3 mCi), with the therapeutic activity optimally administered within 72 hours of the diagnostic activity and the use of SPECT/CT usually ensures that diagnostic efficacy in identifying Uptake foci is not compromised with some reduction in administered activity. uptake foci may be enhanced by concomitant SPECT/CT (Haugen et al., 2016) (Figure 3).

Wong et al., (2010) demonstrated that SPECT/CT using low diagnostic activities (37 MBq) of I-131 is

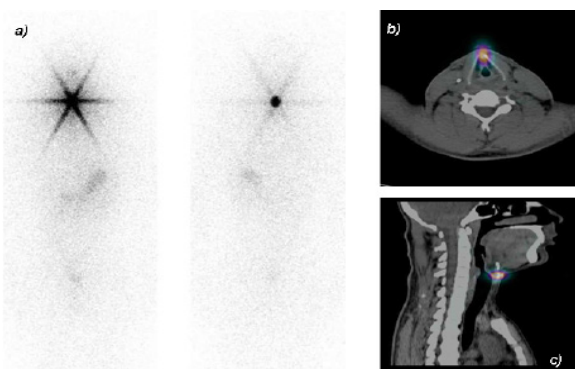


Figure 6. a) Whole body planar images obtained 48 hours after oral administration of 2.7 mCi of I-131 shows a focus of increased radiotracer uptake in the central neck. b,c) Fused SPECT/CT images co-localises this focus of radioactivity at the tip of the hyoid bone, consistent with a thyroglossal duct remnant.

feasible and can be used in addition to histopathological information to complete staging and risk stratification before radioablation. They found that SPECT/CT improved above and beyond the planar scan interpretation for 19 (40%) of 48 patients, detecting regional nodal metastases in four patients and clarifying equivocal focal neck uptake in 15 patients. Compared with histopathological analysis and chest radiograph data, planar images and SPECT/CT changed the post-surgical DTC stage for 10 (21%) of 48 patients. Information obtained from SPECT/CT affected the proposed I-131 therapeutic dose for 28 (58%) of 48 patients. Avram et al., (2015) found that detection of unsuspected nodal and distant metastases by pre-ablative diagnostic SPECT/CT and elevated stimulated thyroglobulin levels resulted in a change in the estimated risk of recurrence in 15% of patients and in the management of 31% of patients, as compared to initial risk stratification and management based on histopathology alone. In another study with pre-ablation I-131 scans, diagnostic pre-ablation I-131 planar and SPECT/CT scintigraphy detected regional nodal metastases in 22% and distant metastases in 8% of patients, leading to upstaging of 4% of young patients (<45 years old) and 25% of older patients (≥ 45 years old), as compared with pTNM staging based on surgical pathology alone (Avram et al., 2011).

Utility of Diagnostic SPECT/CT in Long Term Follow Up

Diagnostic RAI scans have the potential to impact staging and risk stratification and subsequently the decision regarding I-131 therapy, and long-term follow-up strategy. Together with thyroglobulin serum level assay and conventional radiologic procedures, diagnostic I-131 scintigraphy is now commonly accepted as a basic component of the management strategy in thyroidectomized patients with DTC during the follow-up period. SPECT/CT is usually performed during follow-up after the administration of a diagnostic I-131 dose. Spanu et al., (2009) demonstrated that SPECT/CT has incremental value over planar scanning in 67.8% of patients. They performed studies on 2 different hybrid dual-head gamma cameras; 108 patients underwent I-131 diagnostic imaging and SPECT/CT. SPECT/CT identified more foci of pathologic activity (158 foci on SPECT/CT compared with only 116 foci on planar imaging), changed the treatment approach in 35.6% of patients with disease, and led to avoidance of unnecessary I-131 therapy in 20% of patients without disease. The procedure was also able to differentiate between residual tissue in the thyroid bed and well-localized cervical lymph node metastases, permitting the choice of radioiodine therapy for the former and surgery for the latter. Although in a majority of their cases found to be true-positive for metastases on SPECT/CT had high thyroglobulin serum levels, in some patients SPECT/CT showed metastases when thyroglobulin levels were only slightly elevated or borderline. Based upon these findings the author suggested the use of SPECT/CT more widely in the follow-up of thyroidectomized DTC patients, particularly when planar I-131 whole-body imaging is not conclusive. However, they emphasized the need for a larger series of patient studies to better establish the

role of this procedure in the follow-up period (Figure 4).

SPECT/CT for Evaluation of Unusual/Physiologic Radioactivity Distributions

SPECT/CT RAI scans may accurately localize and help differentiate benign mimics of disease in particular physiological uptake. Given a fairly ubiquitous physiological distribution profile of radioiodine isotopes in the body, this can be of significant benefit. It has also emerged as a powerful tool for assessing unexpected concentrations of radioiodine resulting from benign uptake in organs with NIS expression, radioactive secretions or excretory products, inflammation, or other mechanisms of uptake (Wong et al., 2009). Several reports outline the usefulness of SPECT/CT in solving difficult diagnostic interpretations and revealing unusual radioiodine distribution to these locations such as the salivary glands, dental fillings, retrosternal goiter, esophageal or airway secretions, hiatus hernias and occasionally in synchronous pathology (Dümcke and Madsen, 2007; Wong and Avram, 2008). In this scenario, morphological assessment on CT plays a pivotal role in deciding whether further characterization is required or can this be ignored as physiological or benign focus (Figure 5). One particular example which is commonly seen in practice is intense focal uptake in the midline of the central neck that localizes to the tip of the hyoid bone, along the expected path of descent of the embryologic thyroid gland. This pattern has been termed thyroglossal duct remnant and represents small areas of thyroid tissue that concentrate radioiodine in the setting of elevated TSH levels and is much easier to assess on SPECT/CT (Figure 6).

In conclusion hybrid SPECT/CT imaging has developed an important role in the management of patients with DTC at various stages, both in the short-term for risk stratification and treatment planning as well as for long-term follow-up. Given the poor anatomical localization of radioactive foci on planar imaging, hybrid imaging with radioiodine is indeed a powerful tool in accurately identifying and helping to distinguish benign mimics of disease due to physiological or non-pathological uptake, with the potential to positively influence the management plan and avoid unnecessary treatment due to false-positive results.

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