

Rare metastases of differentiated thyroid carcinoma: pictorial review

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Abstract

Differentiated thyroid cancer (DTC) is usually indolent with good prognosis and long-term survival. However, DTC distant metastasis is often a grave event and accounts for most of its disease-specific mortality. The major sites of distant metastases are the lung and bone. Metastases to the brain, breast, liver, kidney, muscle, and skin are rare or relatively rare. Nevertheless, recognizing rare metastases from DTC has a significant impact on the clinical decision making and prognosis of patients. ¹³¹I single photon emission computed tomography/computed tomography (¹³¹I-SPECT/CT) can provide both metabolic and anatomic information about a lesion; therefore, it can better localize and define the ¹³¹I-WBS findings in DTC patients. In this pictorial review, the imaging features of a range of rare metastases from DTC are demonstrated, with a particular emphasis on the ¹³¹I-SPECT/CT diagnostic aspect.

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Introduction

Papillary and follicular carcinomas of the thyroid gland often referred to together as differentiated thyroid cancer (DTC), are characterized by a slowly progressive course, and a 10-year survival rate as high as 80–95% (Schlumberger 1998). It usually remains localized to the thyroid gland. Distant metastases are seen in a minority of patients and the reported rates of occurrence range from 4 to 15% (Hoie *et al.* 1988, Casara *et al.* 1993, Shaha *et al.* 1997, Clark *et al.* 2005, Aggarwal *et al.* 2007). The most common site of distant metastases is the lung, followed by the bone (Mazzaferri & Massoll 2002). Other distant metastases are rare or relatively rare and involve the brain, breast, liver, kidney, muscle, and skin. The presence of distant metastases is the most significant poor prognostic factor for survival, with only 50% metastatic patients surviving after 10 years (Elisei *et al.* 2010). Among the factors responsible for distant metastases and increased mortality in patients with DTC are age over 45 years and the involvement of multiple organs, both are independently associated with cancer mortality (Ruegemer *et al.* 1988). The common distant metastasis sites (lung and bone) from DTC usually draw significant concern and

are well known to us. However, rare metastases, due to their extremely low incidence, are usually not taken into account or are ignored in the clinical setting. Nevertheless, recognizing the patterns of rare metastases from DTC has a significant impact on the clinical decision making and prognosis of patients.

Because of its high sensitivity and specificity, post-therapeutic ¹³¹I-WBS and ¹³¹I single photon emission computed tomography/computed tomography (¹³¹I-SPECT/CT) currently remain indispensable for the management of patients with DTC. ¹³¹I-SPECT/CT is of incremental value over ¹³¹I-WBS at increasing diagnostic accuracy, reducing pitfalls, and modifying therapeutic strategies (Spanu *et al.* 2009). Owing to the use of ¹³¹I-SPECT/CT imaging fusion techniques, rare metastasis in DTC is increasingly becoming an incidental finding (Chen *et al.* 2008, Qiu *et al.* 2011). This pictorial review highlights the diagnostic aspects of ¹³¹I-SPECT/CT for the localization and definition of rare metastases in DTC patients.

Brain metastasis

Brain metastases are extremely rare, reportedly occurring in roughly 0.15–1.3% of thyroid carcinomas

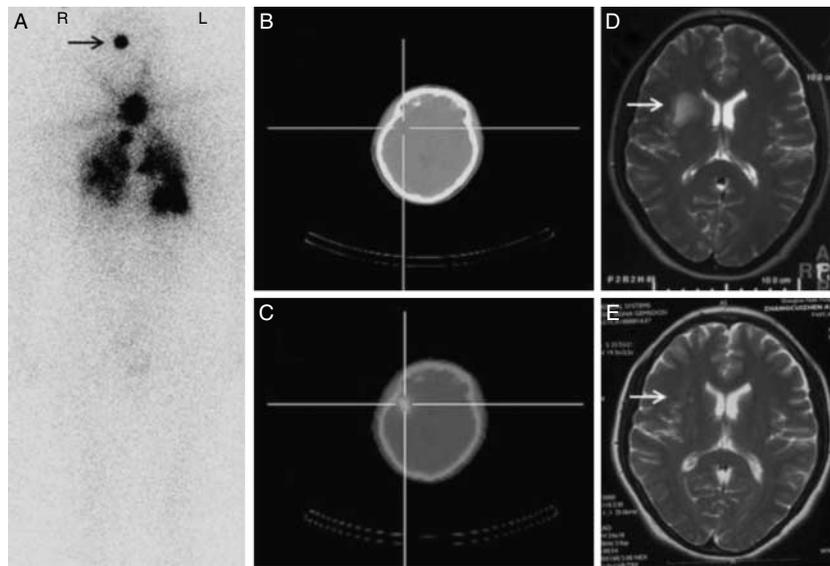


Figure 1 ¹³¹I-WBS, ¹³¹I-SPECT/CT, and magnetic resonance imaging (MRI) from a patient with brain metastases of papillary thyroid microcarcinoma. She was treated with 3.7 GBq of ¹³¹I for ablation of the post-surgical thyroid remnant and treatment of the lung metastases. Post-therapy ¹³¹I-WBS revealed a single cephalic uptake (A) of ¹³¹I in addition to the cervical and pulmonary uptake. ¹³¹I-SPECT/CT fusion images showed cephalic foci located in the right side of the cerebrum (B and C). Further examination with MRI revealed a solitary metastatic lesion in the area of the right internal capsule of the cerebrum, with marked peritumoral edema extending from the tumor margin (D). MRI scan images obtained 3 months after the radiosurgery showed that the peritumoral edema had nearly disappeared along with almost complete response of the lesion (E). Reproduced, with permission, from Xu et al. (2011a).

(Parker et al. 1986). However, in all rare metastases, the brain was the most frequent locus of secondary metastasis from DTC in a study of a large cohort of patients (Dinneen et al. 1995). Dinneen et al. (1995)

noted that ~18% of patients with distant metastases from PTC developed brain metastases during their disease course. It occurs more frequently in the cerebral hemispheres (Fig. 1); other sites for

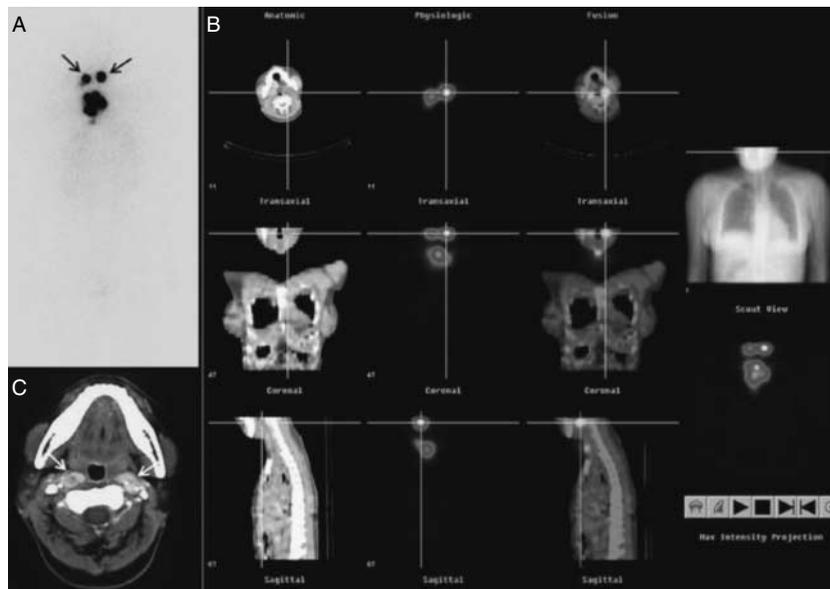


Figure 2 A 26-year-old female with papillary thyroid cancer after thyroidectomy was treated with 3.7 GBq of ¹³¹I for ablation of the post-surgical thyroid remnant. ¹³¹I-WBS and ¹³¹I-SPECT/CT were performed after ¹³¹I therapy. Anterior ¹³¹I-WBS imaging detected two abnormal ¹³¹I uptake foci in the pharyngeal region (A, black arrows). ¹³¹I-SPECT/CT provided metabolic and anatomic information that the two foci of ¹³¹I uptake were localized in the left and right parapharyngeal spaces (B). High-resolution contrast-enhanced CT scans indicated left and right parapharyngeal masses (C, white arrows). Reproduced, with permission, from Qiu et al. (2011).

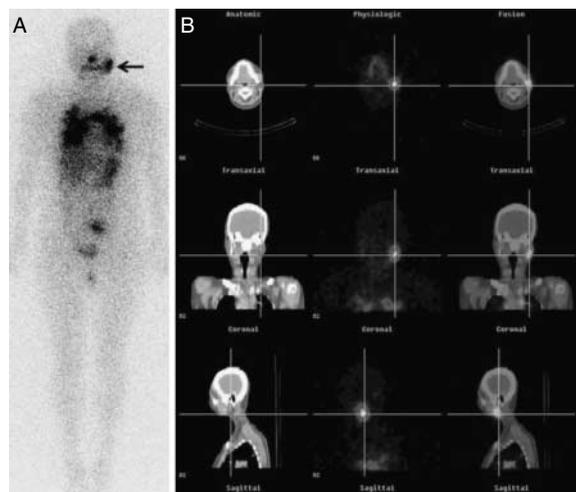


Figure 3 A 55-year-old woman who had a 4-year history of follicular thyroid cancer received ^{131}I therapy for the treatment of lung metastases. Post-therapeutic ^{131}I -WBS incidentally detected abnormal foci of ^{131}I uptake in the left facial region (A, black arrow). ^{131}I -SPECT/CT localized the lesion of ^{131}I uptake in the left parotid gland, which was suspected of being metastasis because of the asymmetric ^{131}I uptake in the bilateral parotids (B). Surgical pathology confirmed the diagnosis of the left parotid metastasis.

intracranial metastases are the cerebellum (Pazaitou-Panayiotou *et al.* 2005, Al-Dhahri *et al.* 2009) and pituitary (Chrisoulidou *et al.* 2004, Yilmazlar *et al.* 2004). Brain metastases are usually asymptomatic, and only a few have suggestive symptoms, including headache, visual disturbances, or ocular motor weakness. There is a general consensus in the literature that brain metastasis is associated with poor prognosis with a tendency for recurrence (Al-Dhahri *et al.* 2009).

Parapharyngeal metastasis

Parapharyngeal metastasis from DTC is quite rare, accounting for only 0.5% of all head and neck tumors (Pang *et al.* 2002). Totally, two relatively large numbers of DTC cases with parapharyngeal metastases have been described, suggesting that the incidence rate of parapharyngeal metastasis is extremely low (Desuter *et al.* 2004). Parapharyngeal mass is often nonspecific or asymptomatic when the tumor does not exceed 3.0 cm in size (Tomoda *et al.* 2005). Frequently, patients complain of a mass in the neck or oropharynx that causes dysphagia. Most parapharyngeal metastases are unilateral, whereas some rare cases are bilateral (Fig. 2). Integrated ^{131}I -SPECT/CT is a useful tool for the screening of parapharyngeal metastasis in patients

with DTC, especially earlier parapharyngeal metastasis (Qiu *et al.* 2011). Parapharyngeal metastasis should be included in the differential diagnosis of parapharyngeal masses.

Parotid metastasis

Involvement of the parotid gland from DTC is extremely rare and is mostly detected at autopsy (Alzaraa *et al.* 2008). In an analysis of 108 cases, three cases of a metastatic thyroid cancer metastasizing to the parotid were reported, with secondary metastases to the salivary glands (Seifert *et al.* 1986). Typically, it is an incidental finding in the clinical setting (Fig. 3).

Breast metastasis

Metastasis to the breast from DTC is extremely rare. To date, only 11 cases have been described in the

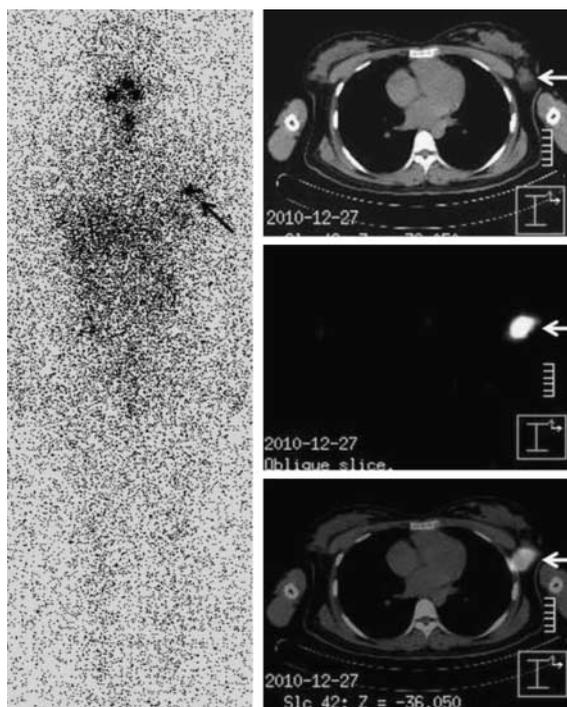


Figure 4 A 28-year-old woman with papillary thyroid cancer was treated with ^{131}I for ablation of a post-surgical thyroid remnant. An unexpected focus of abnormal ^{131}I uptake in the superficial left chest wall was observed on the post-ablation ^{131}I -WBS (A, shown by arrow), and it was difficult to decide whether it was a real lesion or a site of ^{131}I contamination on the skin based on the planar images alone. Therefore, ^{131}I -SPECT/CT was performed to accurately localize the foci of ^{131}I uptake. The images clearly showed that the abnormal ^{131}I uptake in the left chest wall was located in the left vice-mammary gland (B, C, and D). Finally, ultrasound-guided fine needle aspiration (FNA) demonstrated that the lesion was metastasis from papillary thyroid cancer.

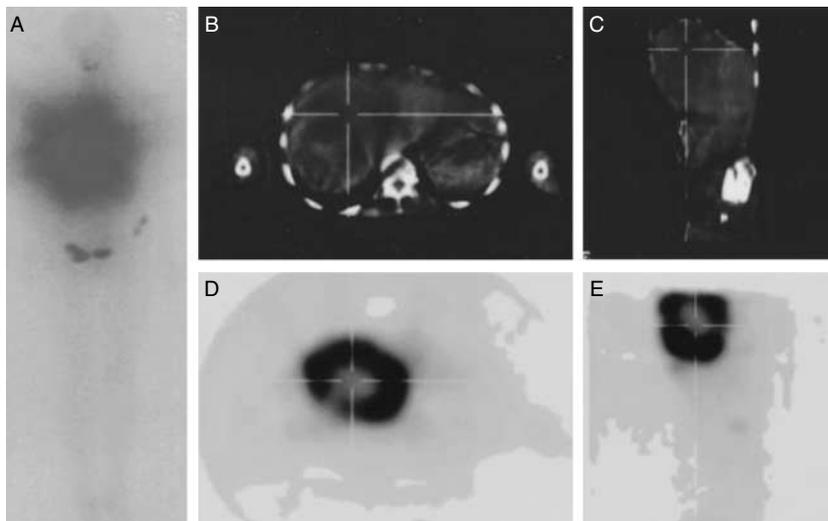


Figure 5 ^{131}I -WBS and ^{131}I -SPECT/CT fusion images from a patient who received a thyroidectomy for follicular thyroid cancer. After 25 years, she was treated with 7.4 GBq of ^{131}I for bone metastases in the pelvis. Post-therapeutic ^{131}I -WBS demonstrated a star, irregular, and intense radioactivity signature in the right upper part of the abdomen in addition to the pelvic uptake. (A). To accurately locate the ^{131}I uptake lesion, ^{131}I -SPECT/CT was performed and the ^{131}I uptake was localized in a large liver mass (B, C, D, and E). Fine needle aspiration confirmed the diagnosis of liver metastasis from follicular thyroid cancer.

literature (Chisholm *et al.* 1980, Tan *et al.* 1991, Cristallini *et al.* 1994, Loureiro *et al.* 1997, Fiche *et al.* 1998, Al-Abed *et al.* 2008, Angeles-Angeles *et al.* 2009). All of the patients were female, with four papillary and three follicular types in the primary tumor. Vice-mammary gland metastasis from DTC is even rare (Fig. 4) and has not been reported to date. Breast metastasis usually occurs in the setting of disseminating metastases. However, Loureiro *et al.* (1997) reported a unique case of a follicular variant of papillary thyroid carcinoma, with three cutaneous and one breast metastases in the absence of other sites of dissemination. It seems that metastatic disease to the breast tends to be superficial and usually located at the upper outer quadrant. Metastases to the breast are associated with poor prognosis.

Liver metastasis

Liver metastasis from DTC is a rare event, with a reported frequency of 0.5% (Salvatori *et al.* 2004). Only ten cases have been documented in the literature; three were males and seven were females, with an average age of about 63 years (range from 32 to 85 years). Histologically, the primary tumor was identified as papillary in four patients, follicular in five patients, and Hurthle cell thyroid cancer in one patient. Liver masses can be detected by various imaging modalities, such as ultrasonography and CT, and are usually ^{131}I negative. ^{131}I -positive metastases are extremely rare (Fig. 5). DTC liver metastasis has a

poor prognosis. Surgical resection of liver lesions has been reported to offer the best chance for prolonged survival (Niederle *et al.* 1986).

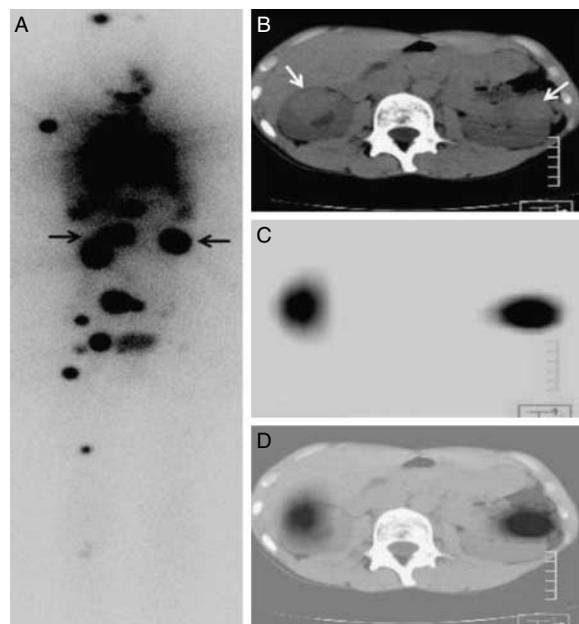


Figure 6 A 19-year-old patient who had a 8-year history of papillary thyroid cancer developed systemic multiple metastases. Post-therapeutic ^{131}I -WBS showed strong focal tracer uptake in the regions of the head, lung, abdomen, and limbs (A). The ^{131}I uptake in the abdominal region (A, shown by arrows) drew our attention. Subsequent ^{131}I -SPECT/CT of the abdomen revealed two separate lesions that were localized in the bilateral renal masses (B–D).

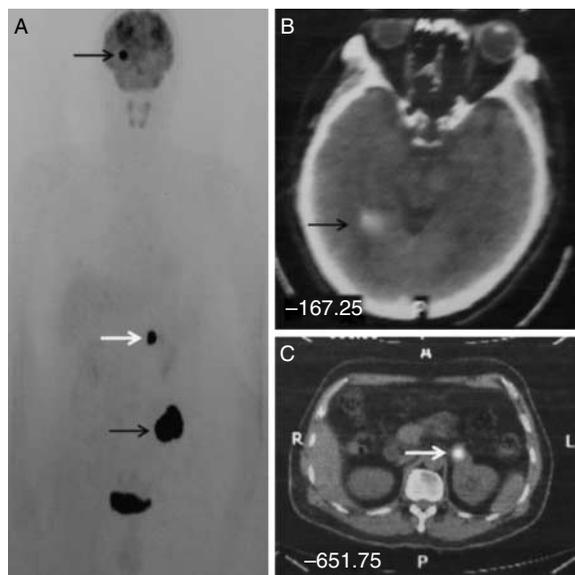


Figure 7 A patient was given ^{131}I treatment after total thyroidectomy. No abnormal ^{131}I uptake was found in the post-therapeutic ^{131}I -WBS; however, the serum thyroglobulin (Tg) was 2569 ng/ml. ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F FDG-PET/CT) was performed to search for potential metastatic lesions (A). Three ^{18}F FDG-positive lesions were found in the right cerebrum (B), left adrenal gland (C), and iliac bone. Negative ^{131}I -WBS but elevated Tg levels in DTC patients is indicative of metastatic disease. ^{18}F FDG-PET/CT can localize the source of Tg production and identify the metastases by their enhanced glucose metabolism. Reproduced, with permission, from Xu *et al.* (2011a).

Renal metastasis

Clinical detection of DTC metastasis to the kidney is infrequent. To the best of our knowledge, only 25 cases have been reported in the literature. Most of the subjects were females >45 years of age. Kidney metastasis usually appears in the setting of multifocal metastases in the body (Fig. 6). Liou *et al.* (2005) reported the first and only case of metastatic papillary thyroid microcarcinoma in the kidney with wide dissemination (including renal, pulmonary, and pelvic bony metastases). Renal metastasis can develop several years (occasionally decades) after removal of the primary thyroid cancer. This finding is consistent with the slow course of DTC. However, DTC renal metastasis presenting as a primary renal tumor has been reported by Graham & Roe (1995) and Ruggiero *et al.* (2005). Therefore, intense ^{131}I uptake in the abdomen by ^{131}I -WBS should not be assumed to simply be physiological gastrointestinal tract uptake or a false-positive finding (Langsteger *et al.* 1993, McDougall 1995, Brucker-Davis *et al.* 1996); the suspicion of a renal metastasis should be raised and effectively excluded.

Adrenal metastasis

Adrenal metastasis from DTC is generally asymptomatic and is often associated with lung or bone metastases. The first case of a patient with an adrenal metastasis secondary to Hurthle cell carcinoma has

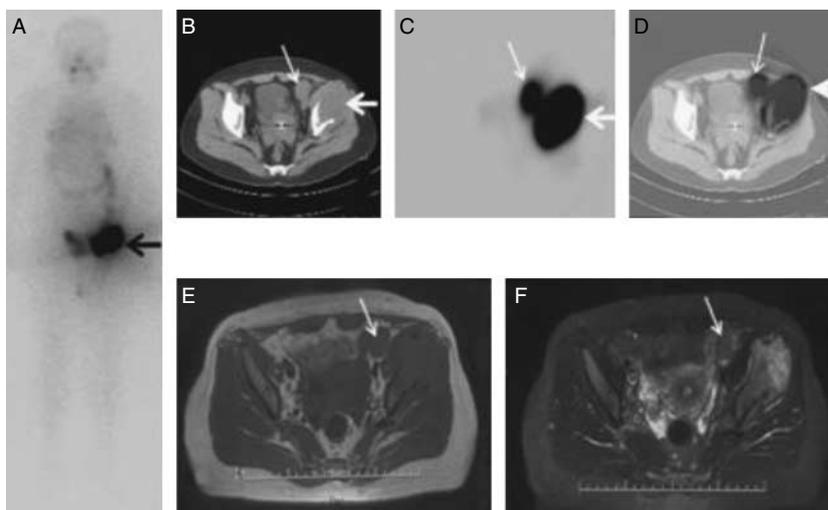


Figure 8 A 42-year-old woman was treated with ^{131}I for ilium metastasis from papillary thyroid cancer. Post-therapeutic ^{131}I -WBS showed intense ^{131}I uptake in the left pelvis (A, black arrow). ^{131}I -SPECT/CT fusion scans were performed to localize and identify the pelvic lesion. What surprised us was that the pelvic ^{131}I uptake was not only a pelvic ^{131}I uptake lesion in the left ilium (B, C, D, thick white arrow) but also a separate solid mass in the pelvic cavity (B, C, D, thin white arrow). MRI of the pelvis found that the mass in the pelvic cavity was most likely an ovarian lesion (E, F, thin white arrow). Finally, the mass was histologically confirmed to be an ovarian metastasis from papillary thyroid cancer. Reproduced, with permission, from Xu *et al.* (2011b).

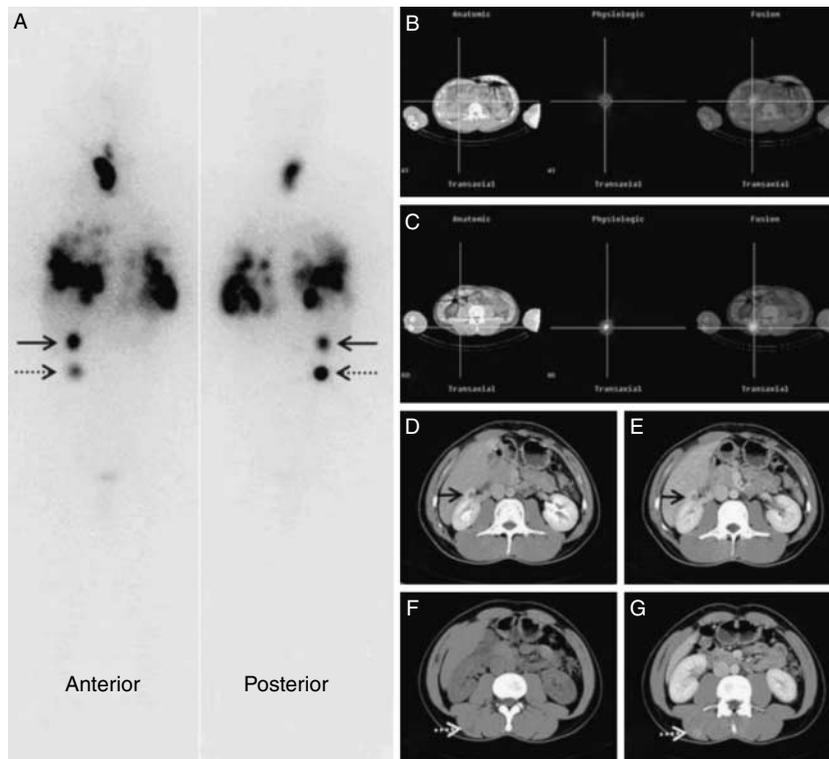


Figure 9 A 29-year-old patient presenting with locoregional lymph nodes and pulmonary metastases from papillary thyroid cancer was treated with ^{131}I . The post-therapeutic ^{131}I -WBS revealed two abdominal foci of ^{131}I uptake (A, solid line arrows and dashed line arrows) in addition to the cervical and pulmonary uptake. The ^{131}I -SPECT/CT fusion images identified abdominal foci located in the area of the right kidney (B) and lower back muscle (C). High-resolution CT further confirmed a solitary lesion on the upper pole of the right kidney (D, E, solid line arrow) and a solitary lesion in the right erector spinae (F, G, dashed line arrow). Reproduced, with permission, from Luo *et al.* (2008).

been reported by Orsolon *et al.* (1996). Although adrenal and renal metastases are closely related in terms of anatomy, concomitant adrenal and renal metastases from DTC are exceptional, as only two cases have been reported in the literature (Kumar *et al.* 2005, Malhotra *et al.* 2010). ^{131}I -avid adrenal metastasis is very rare. Koutkia & Safer (2001) described the first case of a solitary, functioning adrenal metastasis secondary to papillary thyroid carcinoma, and it was found by ^{131}I -WBS. The majority of adrenal metastases are detected by other medical imaging modalities (Fig. 7).

Ovarian metastasis

The rarity of ovarian metastasis from DTC is supported by a review of the literature, where only three cases have been reported (Young *et al.* 1994, Logani *et al.* 2001, Brogioni *et al.* 2007). It seems that ovarian metastasis tends to occur unilaterally rather than bilaterally (Fig. 8). Bilateral ovarian metastasis from papillary thyroid cancer has been reported by Brogioni *et al.* (2007). Ovarian metastasis from DTC

tends to occur many years after the primary tumor is discovered. Because of the long intervals, when there is a woman who presents with a cystic ovarian mass, the differential diagnoses to consider should include ovarian metastasis from DTC. Therefore, the patient history should be thoroughly investigated for evidence of a prior neoplasm in the thyroid gland.

Muscle metastasis

Although more than 40% of the total human weight comprises skeletal muscle, hematogenous metastasis to skeletal muscle is extremely rare. A hypothesis is that skeletal muscle is a hostile environment for the retention and proliferation of cancer cells, including muscle motion, unadapted muscle pH, and the muscle's ability to remove tumor-produced lactic acid (Seely 1980). A retrospective review of the literature revealed only ten reports of DTC muscle metastases. It seems that DTC is prone to metastasizing to the erector spinae, as three of the ten cases were erector spinae metastases (Luo *et al.* 2008, Qiu & Luo 2009). Muscle metastases are generally associated with other distant

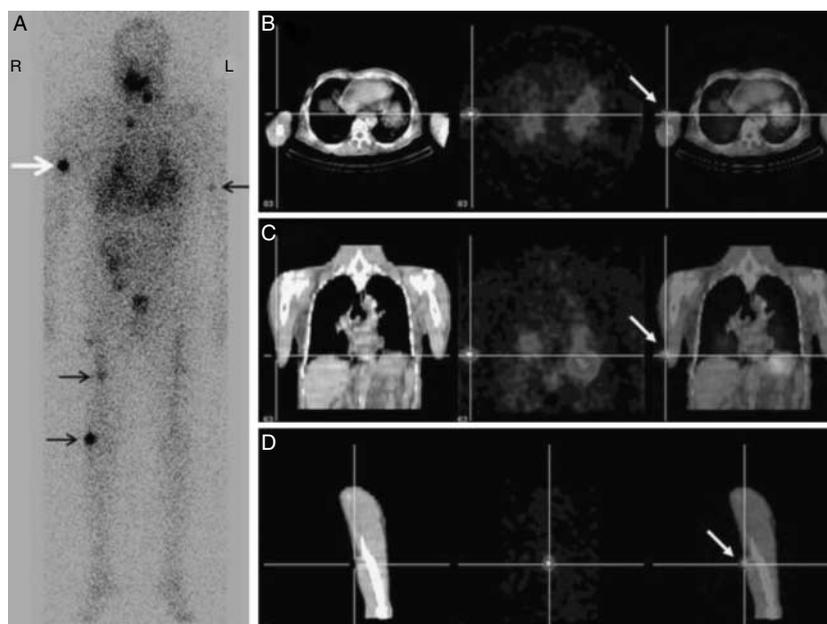


Figure 10 ^{131}I -WBS and ^{131}I -SPECT/CT fusion images of multiple subdermal metastases from papillary thyroid cancer. The post-therapeutic ^{131}I -WBS showed several rounded foci of ^{131}I uptake in the upper and lower limbs, which were thought to be skin contamination by ^{131}I (A). However, subsequent ^{131}I -SPECT/CT revealed lesions that were localized in the subdermal region (B, C, and D); these were found to correlate with the subdermal nodules. Finally, the subdermal nodules were histologically confirmed to be skin metastases from papillary thyroid cancer by FNA. Reproduced, with permission, from Luo *et al.* (2008).

metastases (Fig. 9). An elderly hyperthyroid patient presented with single metastasis in the right arm bicep without any other metastasis (Pucci *et al.* 2006). Most skeletal muscle metastases are neither painful nor palpable; therefore, muscle metastases tend to be an incidental finding in the clinical setting.

Skin metastasis

DTC skin metastasis typically presents as slowly growing erythematous or nodules, usually on the scalp, face, or neck. The scalp is the most common site, being involved in approximately two-thirds of cases (Dahl *et al.* 1997). This may relate to local vascular factors essential for the highly complex nature of metastasis (Avram *et al.* 2004). Cutaneous metastases in the genital area are less common. Shon *et al.* (2010) reported the first case of ulcerated skin nodules in the scrotum from Hurthle cell carcinoma of the thyroid. Limb skin metastasis is rare (Fig. 10). Skin lesions may be solitary or multiple and are almost always asymptomatic. Ulceration is uncommon. Varma *et al.* (2007) reported three clinically interesting cases of papillary cancer presenting with skin ulceration. Although the presence of cutaneous metastases in patients with thyroid cancer portends a poor prognosis, understanding the clinical manifestation determines the overall management of the patients.

Summary and conclusion

In conclusion, DTC, which ordinarily behaves in an indolent manner, can have unusual metastatic presentations and patterns. ^{131}I -WBS and ^{131}I -SPECT/CT play an important role in the management of patients with DTC. With the popularity of ^{131}I treatment and the emergence of ^{131}I -SPECT/CT fusion imaging techniques, rare metastases in DTC may not be as rare as we once thought and may be increasingly common. Increasing importance should be given to rare metastases in DTC patients. This review highlights the need for an awareness of the possibility of unique metastatic deposits of DTC at unexpected sites. Care should be taken to determine whether ^{131}I uptake found at an unexpected site is DTC metastasis or false-positive uptake.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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