

Unusual Sites of Metastatic and Benign I 131 Uptake in Patients with Differentiated Thyroid Carcinoma

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Abstract

Introduction: Differentiated thyroid carcinoma (DTC) is the most common pathological type of thyroid carcinoma, which includes papillary and follicular subtypes. DTC is usually indolent, characterized by good prognosis, and long-term survival. Total thyroidectomy is the mainstay of treatment in DTC which is followed by diagnostic whole body ^{131}I (WBI) scan. Like other primary malignancies of the head and neck, DTC follows a consistent pattern of spread in the cervical LNs. The central compartment, level VI and VII, is the first sentinel node followed by spread to the lateral compartments levels II–V, followed by the contralateral side. In spite of nodal involvement, DTC usually have a favourable outcome. Presence of extrapulmonary distant metastases could predict a poor prognosis for high-dose ^{131}I therapy. However, distant metastasis occurs often as a grave event and mortality rates vary depending on metastatic sites. **Aim and Objectives:** A range of rare ^{131}I concentrating DTC deposits in sella, orbit, choroid, skeletal muscles, liver, skin, costochondral soft tissue, pancreas and kidney, and a few benign ^{131}I concentrating sites are being depicted. **Materials and Methods:** Metastatic sites from DTC can be easily identified by performing a whole body ^{131}I (WBI) scan along with a stimulated thyroglobulin (Tg) estimation (TSH >30 uIU/ml). Apart from thyroid and thyroid-related diseases, certain benign non-thyroidal pathologies can concentrate radioiodine (^{131}I). From 13,000 of our patients who underwent radioiodine scan for thyroid cancer, we have selected a few cases of ^{131}I concentrating benign and malignant lesions for illustration. **Results:** Out of 13000 DTC patients who underwent whole body ^{131}I scintigraphy in our department from Jan 2007 till Mar 2018, 25 patients revealed benign sites of ^{131}I uptake. 61 % patients had residual thyroid tissue with or without associated nodal involvement. Remaining patients had distant metastases. Rare sites of functioning thyroid metastases and benign sites of I 131 uptake have been selected for illustration. **Conclusion:** Apart from the WBI (two-dimensional, planar) images, single-photon emission computed tomography-computed tomography (SPECT-CT) has been incremental in localizing benign lesions which greatly depends on their location. This pictorial review highlights the need to create an awareness to detect metastatic deposits of DTC at unexpected sites. Otherwise patients will need further investigation to rule out unsuspected sites of functioning distant metastases.

Keywords: Benign pathologies, differentiated thyroid carcinoma, metastatic sites, radio iodine, TENIS syndrome, whole body ^{131}I scan

INTRODUCTION

For many years, ^{131}I has played a central role in evaluating thyroid diseases and has an established role in the follow-up and management of differentiated thyroid carcinoma (DTC). Although DTC have a good prognosis, the main metastatic pattern is lymph nodal (LN) metastasis. It has been reported that up to 36% of cases of papillary thyroid carcinoma and 17% of cases of follicular thyroid carcinoma are accompanied with cervical LN metastasis^[1] and nodal metastasis is strongly related to higher incidence of recurrence.^[2] Appropriate range of cervical lymph node dissection can effectively reduce the local recurrence and improve the prognosis of DTC. Current guidelines^[3] and literature recommend performing

prophylactic central LN dissection and therapeutic lateral LN dissection in surgical treatment of DTC. The presence of distant metastases from DTC decreases the 10-year survival of patients by 50%. Metastases to the brain, breast, liver, kidney, muscle, skin, and other sites are relatively rare.^[4] Recognizing these rare sites of metastases from DTC has a significant impact on the clinical decision making and prognostication.^[5] Total thyroidectomy is the mainstay of

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treatment in DTC which is followed by diagnostic whole body ^{131}I (WBI) scan. Patients undergoing ^{131}I diagnostic scan or high-dose ^{131}I ablation/metastatic therapy are weaned off (for 3–4 weeks) stable iodine-containing foods such as seafood, iodised salt, drugs (cough expectorants, povidone iodine, amiodarone), and iodinated contrast agents 3–6 months prior to the procedure. It is mandatory to stop tablet thyroxine for 3–4 weeks prior to ^{131}I imaging or therapy so as to increase the endogenous thyroid stimulating hormone (TSH) level >30 $\mu\text{IU/ml}$ (micro International unit/milliliter). These salient instructions facilitate the uptake of ^{131}I by thyrocytes so that a higher therapeutic benefit is derived by the patient. Diagnostic WBI scan is usually performed 48–72 h after oral radioiodine administration using high-energy collimators on a Gamma camera. Radioiodine concentration in normal and affected thyrocytes is based on sodium iodide symporter (NIS) uptake mechanism. NIS is known to exist and has an active role also in other tissues as shown in Table 1. Many organs including the liver do not exhibit the NIS expression.

The role of 18-Fluorodeoxyglucose positron emission computed tomography-computed tomography (18F FDG PET/CT) in thyroid cancer remains in evolution. There is no role for FDG PET/CT in the initial evaluation of DTC. However, FDG PET/CT is a well-established imaging modality in the evaluation of patients with TENIS syndrome (thyroglobulin elevated negative iodine scan) to look for occult disease. The use of FDG PET/CT in the initial staging and response evaluation of aggressive and poorly DTCs is also well known.

Prognosis of ^{131}I negative DTC metastasis (TENIS), the so-called non-functioning metastasis (I 131 non concentrating), is significantly worse. In these patients, an early diagnosis of non-functioning metastasis and their surgical extirpation remains to be the optimal therapeutic approach. At this stage there is an activation of cellular glucose metabolism, enabling FDG uptake in these dedifferentiated cells. By virtue of their increased growth rate and subsequent increased utilization of glucose, these lesions then become detectable by the FDG PET/CT imaging.

This pattern of differential radiotracer (^{131}I negative but FDG positive) uptake is called “flip-flop phenomenon.” The WBI and the FDG PET/CT scans are, therefore, complementary in this clinical scenario. Most often, a lesion will take up either only radioiodine or FDG, although a patient can have both the

radioiodine and FDG avid lesions depending on varying grades of differentiation among various lesions. Poorly differentiated or progressively dedifferentiated thyroid cancer do not express NIS gene and thereby exhibit negative WBI scan indicating a grave prognosis. These are usually refractory to high-dose ^{131}I therapy and may need advanced redifferentiation therapies and tyrosine kinase inhibitors. Feine *et al.* have shown that there can be a flip-flop in scan uptake patterns in thyroid cancers, first being ^{131}I positive, FDG negative, and with disease progression and dedifferentiation becoming FDG positive, iodine negative.^[6] It is these latter tumors, those that are iodine negative, in which FDG PET appears to be most potentially beneficial. Here, we illustrate rare sites of solitary ^{131}I concentrating distant metastases and a few sites of benign ^{131}I uptake.

MATERIALS AND METHODS

We retrospectively analyzed 13,000 patients who underwent WBI in the Nuclear Medicine Department of Amrita Institute of Medical Sciences, Cochin from 2007 onwards. Lymph nodes, lungs, and bones are the common sites of distant metastases in DTC that can be managed palliatively with multiple doses of high-dose ^{131}I therapy. In this pictorial review, a range of rare ^{131}I concentrating DTC metastatic deposits in sella, orbit, choroid, skeletal muscles, liver, skin, costochondral soft tissue, pancreas and kidney, and a few benign ^{131}I concentrating sites are being illustrated. A few of these patients also underwent whole body FDG PET/CT imaging as part of their workup which is also being depicted here.

Brain metastasis

A 49-year-old male, diagnosed case of follicular carcinoma of thyroid and cervical lymph nodal metastases, underwent total thyroidectomy. Patient received high-dose ^{131}I therapy on three occasions with a cumulative dosage of 349 mCi. Later he developed recurrent headache and progressively worsening double vision for 2 weeks [Figure 1]. Follow-up WBI scan showed no abnormal ^{131}I uptake in anterior neck, sella region, or elsewhere but stimulated Tg was elevated (167 ng/ml, normal is <2 ng/ml). Patient was thus categorised as a case of TENIS syndrome. Brain magnetic resonance imaging (MRI) T1 contrast coronal image showed an enhancing metastatic deposit in sella with suprasellar extension. Solitary brain metastases from DTC are extremely rare i.e. approximately 1% of all DTC. It typically affects older patients with aggressive thyroid cancer, with a reported incidence of 0.15–1.3%.^[4] The reported median survival of patients diagnosed with brain metastasis varies between 4 months to 33 months.^[4] Because of its rarity, the impact of brain metastasis on the survival of patients with DTC is unknown, and there are no clear guidelines for their management. For brain metastasis in general, although treatment guidelines can differ based on the prognosis of the patients and its extent, surgery remains the preferred treatment modality.^[7] Brain metastasis is associated with very poor prognosis even with combined treatment using high-dose ^{131}I therapy, external radiotherapy, and chemotherapy.

Table 1: Sites of ^{131}I uptake unrelated to thyroid cancer

Choroid plexus, salivary glands, lacrimal glands, gastric mucosa, urinary tract
Contamination by physiological secretions
Ectopic gastric mucosa, other gastrointestinal abnormalities
Urinary tract abnormalities, mammary glands
Serous cavities and cysts
Inflammation and infection
Non-thyroidal neoplasms
Unexplained causes

Ocular (uveal) metastasis

A 56-year-old male with metastatic papillary carcinoma of thyroid s/p total thyroidectomy was referred for WBI scan. Scan showed extensive ¹³¹I concentrating skeletal metastases. He was treated twice with high-dose ¹³¹I therapy [Figure 2a]. Follow-up WBI scan after second dose showed abnormal focal ¹³¹I uptake corresponding to lesion in right orbit. After 2 weeks, patient developed sudden onset of diminished vision on the right side. Ophthalmic examination was performed [Figure 2b]. Ultrasound B scan showed two choroidal mass lesions in lower and posterior quadrants with homogenous internal opacity. Scan confirmed associated posterior uveal (choroidal) metastases on the right side. An urgent ophthalmic examination revealed a visual acuity of 6/24 of the right eye with right relative afferent papillary defect and choroidal lesions causing exudative retinal detachment on the right side. Ocular metastases secondary to thyroid cancer are extremely uncommon, typically affecting the orbit rather than the globe and uvea. Within the uveal structures, the choroid is more commonly involved than the iris and ciliary body. The literature review^[8,9] shows that posterior uvea (choroid) is most commonly involved (88%), followed by anterior uvea [i.e., iris (9%) and ciliary body (2%)].

Orbital metastases

A 58-year-old male with histologically proven papillary thyroid cancer s/p total thyroidectomy underwent high-dose ¹³¹I residual thyroid ablation. Patient later presented with swelling close to lateral aspect of the right eye. MRI of orbit showed enhancing soft tissue mass measuring 3.2 × 2 cm along the superolateral aspect of right orbit, abutting lateral rectus

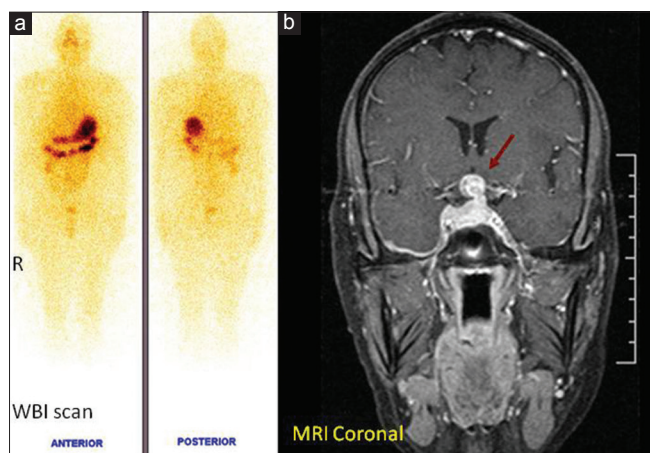


Figure 1: Follicular carcinoma of thyroid and cervical lymph nodal metastases s/p total thyroidectomy. Patient has been treated three times with radioiodine (cumulative dosage 349 mCi). Later patient developed recurrent headaches and progressively worsening double vision for 2 weeks. (a) Follow-up whole body ¹³¹I (WBI) scan was negative, stimulated thyroglobulin was high (167ng/ml), diagnosed as TENIS syndrome, thyroglobulin elevated negative iodine scan. (b) MRI T1 contrast coronal image showed an enhancing metastatic deposit in sella with suprasellar extension (Red arrow)

muscle and lacrimal gland, displacing the globe medially. Lesion erodes the posterolateral wall of orbit, extends to lateral aspect of middle cranial fossa with no involvement of neuroparenchyma. Plain CT of paranasal sinuses revealed lesion in the posterolateral aspect of right orbit with wall erosion. Patient also showed associated frontal, left maxillary, and anterior ethmoidal sinusitis [Figure 3]. WBI scan showed functioning metastases at superolateral aspect of right orbit corresponding to the CT-detected lesion. Stimulated Tg was 1670 ng/ml. Patient received three sittings of high-dose ¹³¹I therapy. Recent WBI scan showed complete resolution of right orbital soft tissue mass with no new functioning metastases elsewhere. Orbit and globe are not common sites of thyroid cancer metastases. Ocular symptoms usually arise in patients with long-standing thyroid cancer or those with widely disseminated disease. It is more common in patients with Follicular Ca thyroid and indicates a hematogenous spread of the malignancy.

Breast metastasis

A 47-year-old woman with multifocal papillary thyroid carcinoma, underwent total thyroidectomy. WBI scan was performed and patient was orally ablated with 70 mCi of ¹³¹I sodium iodide solution. Post-therapy WBI scan showed a focal site of abnormal ¹³¹I uptake in the right lower chest [Figure 4]. SPECT-CT thorax localized the lesion

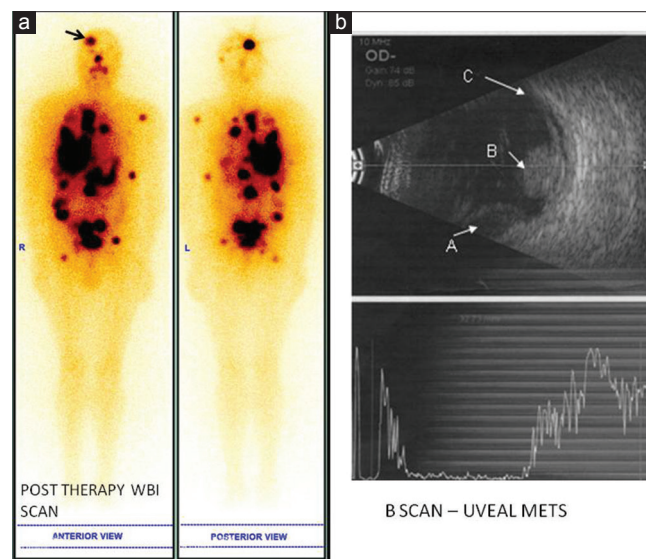


Figure 2: A 56-year-old male patient with metastatic papillary carcinoma of thyroid underwent total thyroidectomy. WBI scan showed extensive ¹³¹I concentrating skeletal metastases. He was treated twice with high-dose ¹³¹I therapy. (a) Post therapy WBI scan after second dose of ¹³¹I therapy showed extensive functioning distant metastases (arrow showing right frontal & Right supraorbital metastases). After 2 weeks, patient developed sudden onset of diminished vision on the right eye. Ophthalmic examination was performed. (b) Ultrasound B scan showed two choroidal mass lesions in lower and posterior quadrants with homogenous internal opacity (A and B denote the two choroidal mass lesions, C denotes retinal detachment). Scan confirmed associated uveal metastases on the right side

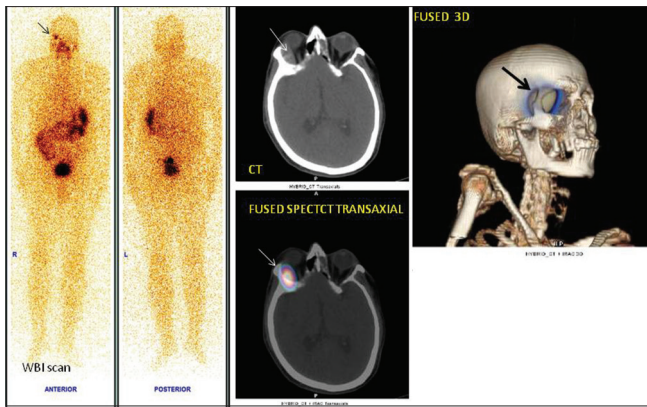


Figure 3: A 58-year-old male with papillary thyroid cancer s/p total thyroidectomy and high-dose ¹³¹I residual thyroid ablation with the right eye swelling. MRI of orbit was done which showed enhancing soft tissue mass measuring 3.2 × 2 cm along the superolateral aspect of right orbit. WBI scan showed functioning metastases at superolateral aspect of right orbit (Arrow depicting lesion). SPECTCT showed lesion abutting the lateral rectus muscle and lacrimal gland, displacing the globe medially. Stimulated Tg was 1670 ng/ml

to lower outer quadrant of right mammary gland raising the suspicion of a co-existing primary breast malignancy or a metastatic deposit from DTC. An ultrasound-guided fine-needle aspiration cytology (FNAC) confirmed metastases from DTC. Isolated breast metastasis from DTC are extremely rare. ¹³¹I uptake in both lactating and non-lactating breasts has been described. In the lactating breast, as well as in the thyroid gland, NIS mediates iodine uptake.^[10] Radioiodine uptake in benign breast pathologies can be seen with gynecomastia, supernumerary breasts, and lactational duct cyst or galactocele. Increased ¹³¹I uptake is also associated with hyperprolactinemia.^[11] To date, only 11 cases of breast metastases arising from DTC have been described in the literature, but these are invariably associated with other sites of DTC metastasis.

Cutaneous metastasis

A 45-year-old male presented with multinodular goiter. FNAC from thyroid was reported as a follicular neoplasm. He underwent total thyroidectomy and right neck dissection. Histopathology revealed a papillary thyroid carcinoma – conventional type (pT3N1bMx). WBI scan showed ¹³¹I concentrating residual thyroid tissue with suspicious cervical nodal metastases. Patient was ablated with 120 mCi of ¹³¹I orally. Four months later patient developed small painless, purple-colored skin nodules [Figure 5]. Tg while on T4 was found to be elevated. Whole body FDG PET/CT off T4 for 3 weeks (TSH >30 uIU/ml) was suggested. Images showed focal FDG avidity in multiple intramuscular deposits (left 6th intercostal space, left gluteus intermedius, paravertebral muscle on left side at level of L4/L5, right pectoralis major anterior to 3rd rib, right psoas muscle, left longissimus colli, and bilateral latissimus dorsi). Stimulated Tg was also performed which was significantly elevated (845 ng/ml). Cutaneous and intramuscular nodules

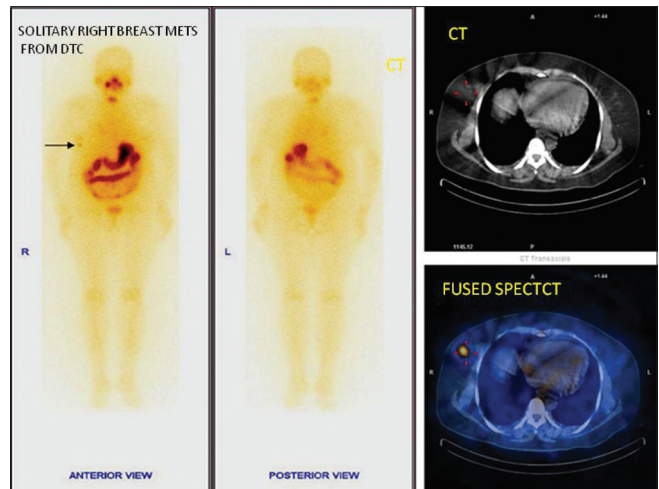


Figure 4: A 47-year-old woman with multifocal papillary thyroid carcinoma, underwent total thyroidectomy and high-dose ¹³¹I residual thyroid ablation. Post-therapy WBI scan showed a focal site of abnormal ¹³¹I uptake in the right lower chest (Arrow indicating ¹³¹I uptake in right breast lesion). SPECT-CT thorax localized the lesion to lower outer quadrant of right mammary gland raising the suspicion of a co-existing primary breast malignancy or a metastatic deposit from DTC. Ultrasound guided FNAC confirmed breast lesion to be metastases from DTC

cytopathology was positive for metastatic papillary thyroid carcinoma. In view of extensive cutaneous and intramuscular nodular metastases, patient was treated with 170 mCi of ¹³¹I. On review, patient had further deterioration of the disease clinically and based on the thyroid tumor board decision, patient was started on tyrosine kinase inhibitors. Presentation of cutaneous metastases is associated with advanced disease. Dahl *et al.*^[12] reported that papillary thyroid carcinoma was most common (41%) followed by follicular (28%), anaplastic (15%), and medullary carcinomas (15%), respectively. The scalp was the most common site of metastasis in that series.

Liver metastasis

A 40-year-old man, with papillary carcinoma of thyroid with cervical lymph nodal metastases post-total thyroidectomy, central compartmental neck dissection, and radioiodine ablation, presented to our department with rising Tg. Follow-up WBI scan was negative. He was orally ablated with 184 mCi of ¹³¹I [Figure 6]. Post-¹³¹I therapy WB scan showed a solitary functioning right lobe of liver metastasis (confirmed with SPECT-CT) and histopathology. Liver metastasis from DTC is a rare event, with a reported frequency of 0.5%.^[13] Only 10 cases have been documented in the literature so far.

Pancreas and kidney metastases

A 60-year-old female patient with follicular carcinoma of thyroid and lymph nodal metastases underwent total thyroidectomy. About 3 weeks later WBI scan was done which was negative [Figure 7a]. Stimulated Tg was >1000 ng/ml with TSH of only 1.2 uIU/ml. Recombinant human TSH (rhTSH) assisted whole body FDG PET/CT was performed (TSH >100 uIU/

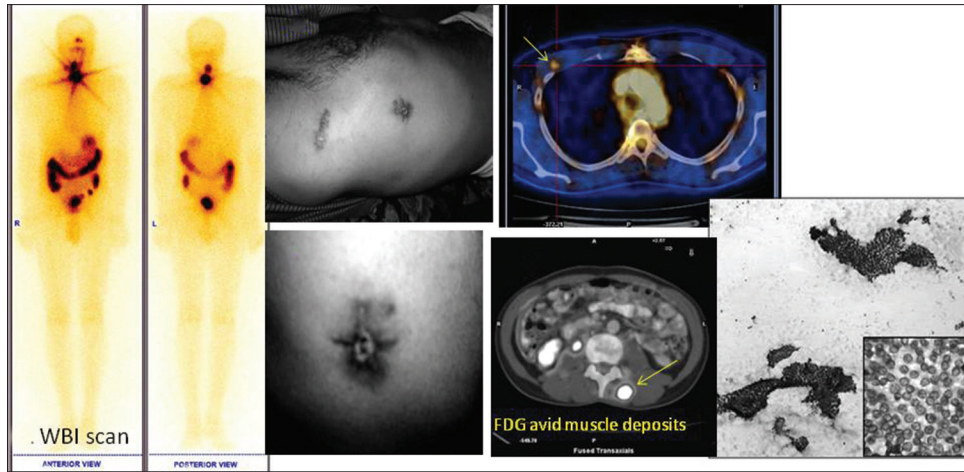


Figure 5: A 45-year-old male with multinodular goiter s/p total thyroidectomy and right neck dissection. Histopathology was reported as papillary thyroid carcinoma – conventional type treated with 120 mCi of ¹³¹I. Four months later developed small painless, purple-colored skin nodules. Whole body FDG PET/CT was suggested. Images showed focal FDG avidity in multiple intramuscular deposits (left 6th intercostal space, left gluteus intermedius, paravertebral muscle on left side at level of L4/L5, right pectoralis major anterior to 3rd rib, right psoas muscle, left longissimus colli, and bilateral latissimus dorsi). Stimulated Tg was 845 ng/ml. (c) FDG PETCT scan - arrow showing FDG positive cutaneous and muscle deposits, (d) Biopsy of Right psoas muscle deposit - shows infiltrating neoplasm composed of cells arranged in a papillary pattern, separated by fibrinous stroma. Each cell has round to oval clear nuclei, with nuclear overlapping, moderate eosinophilic cytoplasm. Neoplastic cells are CK 7 and thyroglobulin positive and negative for CK 20.

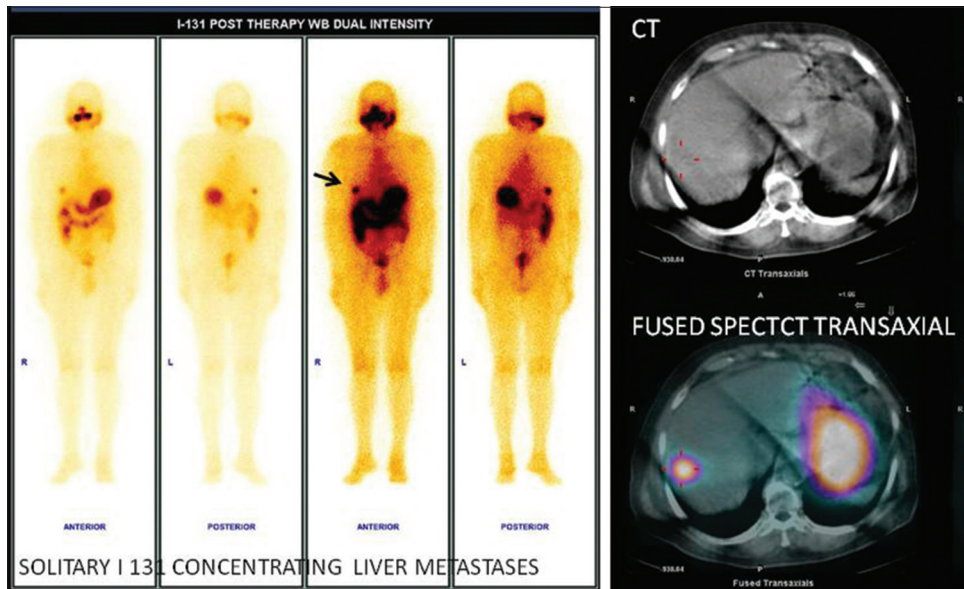


Figure 6: Papillary carcinoma of thyroid and cervical lymph nodal metastases post-total thyroidectomy and central compartmental neck dissection, presented with rising Tg. Follow-up WBI scan was negative. Post-¹³¹I therapy WB scan showed a solitary site of abnormal ¹³¹I uptake in right lobe of liver as confirmed with SPECT-CT (Arrow depicting the lesion on planar whole body image & cross hair on SPECTCT).

ml). Images showed FDG avid metastatic deposits in the pancreas [Figure 7b], and the right kidney [Figure 7c]. Patient was treated with 182 mCi of ¹³¹I. Clinical detection of DTC metastasis of the kidney is infrequent.^[14] Both the kidney and pancreatic involvement are unusual and extremely rare without any nodal or other sites of distant metastases. To the best of our knowledge, only 25 cases have been reported in the literature.

Muscle (deltoid) metastasis

A 66-year-old male, a case of multinodular goiter underwent total thyroidectomy. Histopathology revealed

completely intrathyroidal widely invasive follicular thyroid carcinoma (3.3 × 2.5 × 2 cm) in the left upper lobe with micropapillary carcinoma in the right lobe. Diagnostic WBI scan was done and patient was treated with 70 mCi of ¹³¹I [Figure 8a]. Six months later WBI scan showed no abnormal ¹³¹I uptake in anterior neck and rest of whole body but stimulated Tg was high (124 ng/ml). Whole body FDG PET/CT (non-contrast study) was suggested to look for any occult site of metastases. Figure 8b 18-F FDG PET/CT showed no local recurrence but an isolated FDG avid lesion

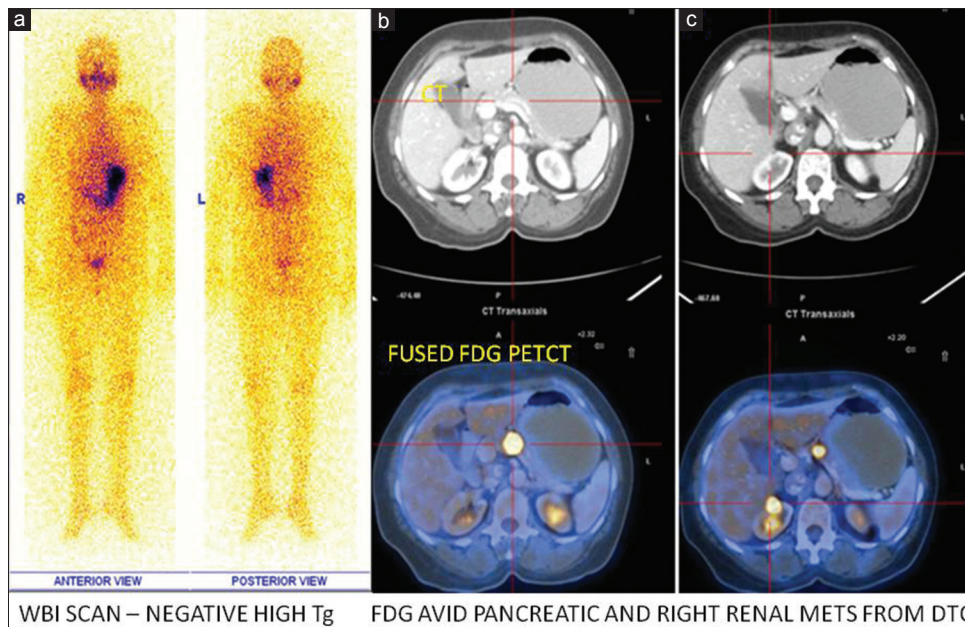


Figure 7: A 60-year-old female patient with follicular carcinoma of thyroid with lymph nodal metastases underwent total thyroidectomy. Three weeks later (a) WBI scan was done which was negative stimulated serum thyroglobulin was > 1000 ng/ml with TSH of only 1.2 uIU/ml. Recombinant human TSH (rhTSH) assisted whole body FDG PET/CT was performed (TSH was >100 uIU/ml after two intramuscular rhTSH injections). Images showed FDG avid metastatic deposits in the pancreas (b), and the right kidney (c) Cross hair shows FDG avid pancreatic and renal metastatic deposit

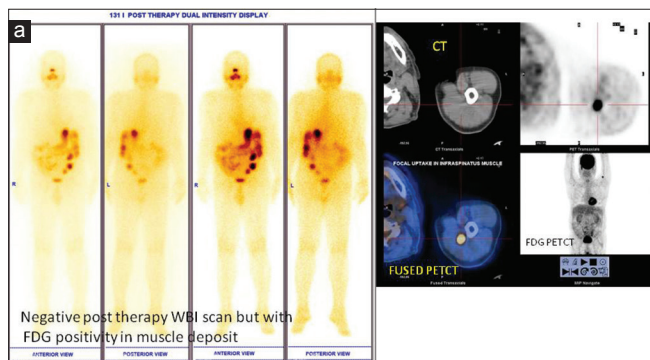


Figure 8: A 66-year-old male, a case of multinodular goiter underwent total thyroidectomy – case of completely intrathyroidal widely invasive follicular carcinoma. WBI scan was done and patient was administered 70 mCi of ¹³¹I [(a), post-therapy WBI scan]. Six months later follow-up WBI scan was negative with stimulated Tg of 124 ng/ml. FDG PET/CT (b) showed no local recurrence but an isolated FDG avid lesion in left deltoid muscle suggestive of a metastatic deposit

in left deltoid muscle suggestive of a metastatic deposit. Ultrasound examination of the lesion showed an echogenic nodule measuring 12.8 mm in the deltoid muscle anteriorly. Excision biopsy revealed a neoplasm of follicular and papillary patterns amidst skeletal muscle fibers with nuclear clearing and many intranuclear pseudoinclusions. Neoplasm showed diffuse positivity for cytokeratin 19 (CK19), TTF-1, and Tg on immunohistochemistry (IHC). The literature review shows that hematogenous metastasis from DTC to skeletal muscle is extremely rare.^[15] A retrospective review of the literature revealed only 10 reports of DTC muscle metastases.

Costochondral and soft tissue metastases

A 62-year-old patient with follicular Ca thyroid s/p total thyroidectomy and high-dose ¹³¹I therapy presented with swelling in chest region of 2 months duration. WBI scan was negative [Figure 9a] with stimulated Tg of 346 ng/ml. Whole body FDG PET/CT [Figure 9b] off T4 showed a large FDG avid lesion in left 1st costal cartilage (SUV Max 40.9) (b) anterior to left 4th costal cartilage (SUV Max 29.0), and a small subcutaneous deposit in anterior chest wall at parasternal region toward left side [Figure 9c]. No other FDG avid lesions seen in thyroid bed and elsewhere. Patient was treated empirically with 150 mCi of ¹³¹I. Patient is lost to follow-up.

Although occasionally soft tissue metastases may present themselves as painful masses, they are usually asymptomatic. Therefore, they may be an unexpected finding in imaging studies. Besides the possibility of underdiagnosis, several factors have been implicated in the rare occurrence of soft tissue metastases, such as muscle motion, mechanical tumor destruction, muscle ability to remove tumor-produced lactic acid, changes in pH, accumulation of metabolites, and local temperature of the soft tissue sites. In addition, blood flow is variable, influenced by adrenergic receptors, and subject to variations in tissue pressure affecting cancer implantation. Whether traumatic injury to soft tissue is a risk factor for soft tissue metastases remains undetermined.

Solitary bone metastases

Sacral metastases – A 68-year-old male with papillary Ca thyroid s/p completion thyroidectomy operated in 1999.

Patient was on T4 and had not received any ¹³¹I therapy. Patient had persistent severe pain at left gluteal region and urinary incontinence. MRI LS spine with contrast was done. A well-defined expansile lesion was present, measuring 3.6 × 3.2 × 2.6 cm involving S3, S4 vertebrae at left paramedian region with anterior exophytic component likely to be a chordoma. Patient was referred for WBI scan. Scan showed focal ¹³¹I uptake in sacral vertebrae in planar and SPECT-CT imaging confirming functioning thyroid metastases in sacrum. WBI scan helped in the diagnosis as chordomas are iodine-negative lesions. Patient underwent S2–S5 sacrectomy followed by high-dose ¹³¹I therapy [Figure 10]. Histopathology reported features suggestive of moderate to poorly DTC favoring metastasis. IHC reported CK7: positive, CK20: negative, TTF-1: positive, Tg: positive, CEA: negative. Patient received two doses of high-dose ¹³¹I therapy at an interval of 6 months. Patient was kept on regular follow up and was found to be doing well and pain free. Radioiodine is highly specific and concentrates in presence of active NIS.

Humeral metastases [Figure 11] – A 38-year-old lady presented with long-standing goiter. FNAC reported papillary carcinoma thyroid. Total thyroidectomy along with left radical neck dissection was performed. Histopathology revealed metastasis to left level II cervical and left recurrent laryngeal nodes. Residual thyroid and WBI scan showed moderate to significant residual thyroid tissue. She was orally ablated with 113 mCi of ¹³¹I. A post-therapy WBI scan showed significant ¹³¹I uptake in thyroid bed as expected and a new focal ¹³¹I uptake in left humerus raising a suspicion of unsuspected solitary skeletal metastases. Patient was further investigated with a plain CT scan for the left humeral lesion. Stimulated Tg was 179 ng/ml. Based on the location of the lesion and need for metastectomy and additional shoulder

stabilisation, patient opted for second dose of high-dose ¹³¹I therapy.

Scapular deposit [Figure 12] – A 56-year-old lady presented with goiter. She was investigated and underwent total thyroidectomy with central compartmental neck dissection. Histopathology suggested papillary thyroid carcinoma with lymph nodal metastases. WBI scan revealed minimal residual thyroid tissue with left lower cervical nodal metastases and unsuspected ¹³¹I concentrating right scapular deposit. As stimulated Tg was 659 ng/ml, whole body FDG PET/CT was suggested. PET/CT confirmed FDG avid left thyroid bed lesion, highest mediastinal nodal and right scapular metastatic deposit.

Bone metastases represent a frequent complication especially of follicular thyroid cancer. Palliative treatment is frequently the only option at diagnosis. These osteolytic lesions reduce severely the quality of life causing pain, fractures, and spinal cord compression. More than 80% of bone metastases from all tumors including DTC are located in axial skeleton red marrow where blood flow is high (vertebrae, ribs, and hips). Surgical option is preferred wherever feasible. Higher dose of ¹³¹I (150–200 mCi) is recommended in presence of skeletal metastatic deposits. Patients usually need multiple doses of high-dose ¹³¹I therapy. External radiotherapy is also indicated in these cases.

Benign sites of I 131 uptake

Benign causes of ¹³¹I have been encountered in day-to-day practice. False-positive radioiodine uptake can be classified according to the underlying mechanism as follows; (1)

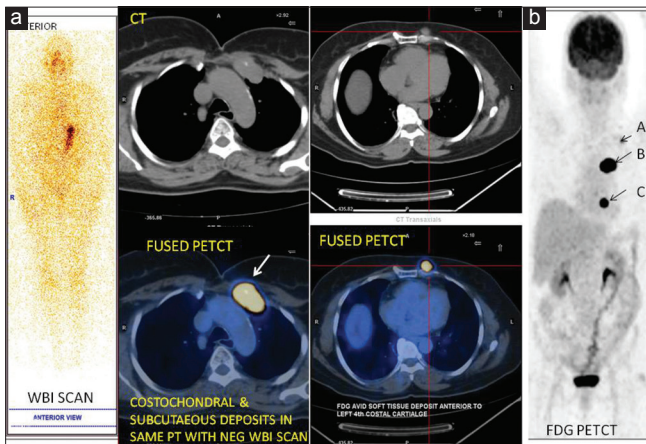


Figure 9: A 62-year-old patient with follicular ca thyroid s/p total thyroidectomy and high dose ¹³¹I therapy presented with swelling in chest region of 2 months. (a) WBI scan was negative with stimulated Tg of 346 ng/ml. Whole body FDG PET/CT (b) off T4 showed a large FDG avid lesion in (A) left 1st costal cartilage (SUV Max 40.9) (B) anterior to left 4th costal cartilage (SUV Max 29.0) and a small subcutaneous deposit in anterior chest wall at parasternal region toward left side (C) (Arrows and crosshair depict the lesions as described)

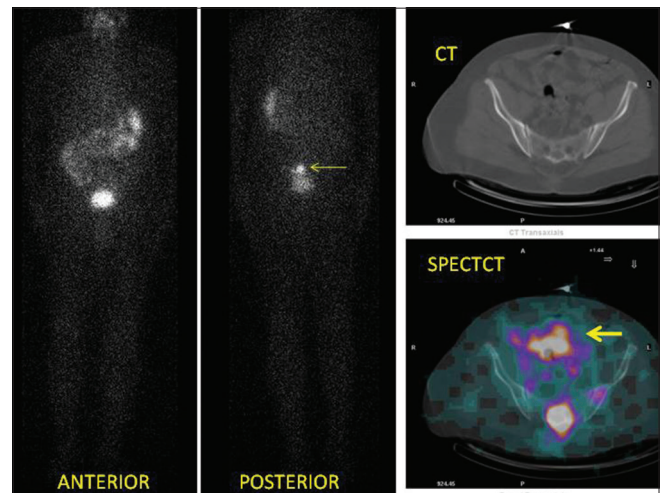


Figure 10: Solitary functioning sacral metastasis in a 68-year-old male with papillary Ca thyroid s/p completion thyroidectomy. WBI scan showed focal ¹³¹I uptake in sacral vertebrae, confirmed with SPECT-CT, confirming functioning thyroid metastases in sacrum. MRI LS spine (arrow shows the sacral lesion) with contrast reported: Well-defined expansile lesion measuring 3.6 × 3.2 × 2.6 cm involving S3, S4 vertebrae at left paramedian region with anterior exophytic component likely to be a chordoma. Patient had S2–S5 sacrectomy and high-dose ¹³¹I therapy. HPR reported moderate to poorly differentiated carcinoma favoring metastasis

Physiological uptake (breast, blood-pool activity, gastric and colonie mucosa). (2) Pathological activity (lung, pleura, pericardium, thymus, meninges). (3) Internal retention of body secretions (esophagus, trachea). (4) External contamination (skin, hair, garment). The uptake in soft tissues has been reported at the following sites and disease conditions; in fat necrosis of the breast,^[16] lactating breasts, patient on hormonal therapy, or oral contraceptive pills (Figure 13 thick arrow). Patients display false positive I131 uptake in tracheostomy, inflamed cysts like ovarian/lymphoepithelial cyst, skin burns, skin wound, and even in a psoriatic plaque. Iodine uptake in rib may be due to benign causes also. Iodine uptake in the pleura and mediastinum

has also been described in pleuropericardial cyst, saliva and esophageal-retained saliva (thin arrow Figure 13), Barrets esophagus, Zenker’s diverticulum, and sites of ectopic thyroid tissue, can also produce false-positive scans with radioiodine. Benign ¹³¹I uptake has been reported in pericardial effusion and myocardial infarction. It is also seen in infective and inflammatory lung diseases. Inflamed tissues undergo certain biological events like increased blood flow and capillary permeability. Increased permeability can result in an abundance of cells in tissue or vessels, and stasis of radio-iodinated blood can also occur due to an increase in the concentration of cells within blood. All these lead to false-positive WBI scan. Tg estimation serves as a robust tumor marker to identify any such benign cause of ¹³¹I uptake from a malignant thyroid deposit.

Retroverted uterus/ovarian neoplasm or cysts

Retroverted uterus: A premenopausal patient with papillary Ca thyroid underwent total thyroidectomy for goiter. WBI scan showed moderate to significant residual thyroid tissue with focal ¹³¹I uptake in pelvis. SPECT-CT localized this focus to retroverted uterus [Figure 14]. No obvious lesion was seen on CT pelvis. The ¹³¹I uptake in this case is most likely physiological in uterus being a vascular organ.

Ovarian etiology: Two cases of papillary Ca thyroid, post-total thyroidectomy are being described. A case of papillary Ca thyroid [Figure 15a], post-thyroidectomy shows focal ¹³¹I uptake in left upper cervical nodal metastases on WBI scan. An additional site of focal ¹³¹I uptake is revealed intrapelvically. SPECT-CT of pelvis localized the uptake to ovary raising a suspicion of left ovarian pathology. Further investigation with ultrasound and CT confirmed inflamed corpus luteal cyst. Another case [Figure 15b] of DTC depicting ¹³¹I uptake in bilateral ovaries, confirmed on further investigation to be bilateral ovarian teratomas.

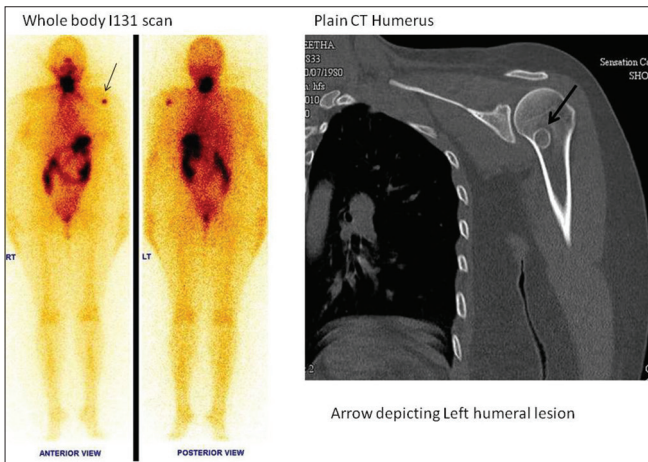


Figure 11: Solitary functioning humeral metastasis in a 38-year-old lady with papillary carcinoma thyroid s/p total thyroidectomy and left radical neck dissection. Residual thyroid and WBI scan showed moderate to significant residual thyroid tissue. She was orally ablated with 113 mCi of ¹³¹I. A post-therapy WBI scan showed significant ¹³¹I uptake in thyroid bed and a new focal ¹³¹I uptake in left humerus raising a suspicion of unsuspected solitary skeletal metastasis. Stimulated Tg was 179 ng/ml

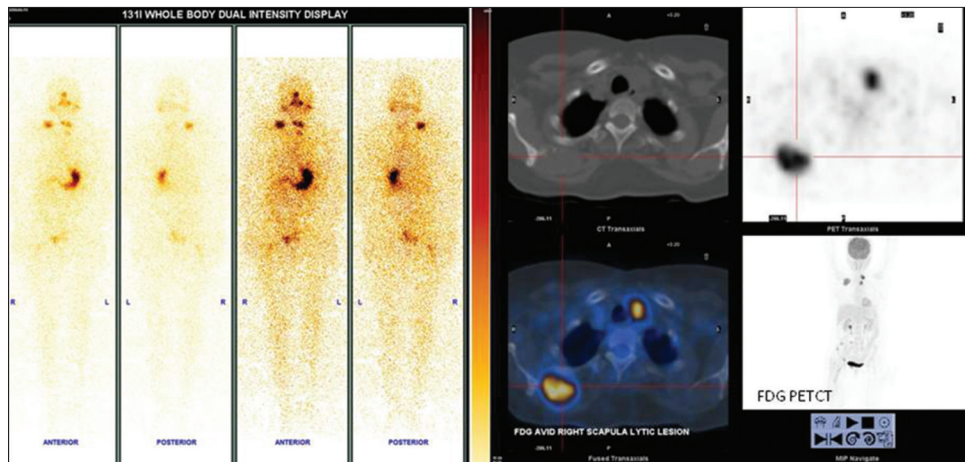


Figure 12: Scapular deposit in a 56-year-old patient s/p total thyroidectomy and central compartmental neck dissection. Patient is a proven case of papillary thyroid carcinoma with lymph nodal metastases. WBI scan revealed minimal residual thyroid tissue with left lower cervical nodal metastases and ¹³¹I concentrating right scapular deposit. Stimulated Tg was 659 ng/ml. PET/CT showed FDG avid left thyroid bed lesion, highest mediastinal nodal and right scapular metastatic deposit. Note: Patient shows same number of positive lesions in both Whole body I 131 and FDG PETCT scan suggesting varying grades of cellular differentiation in the same patient

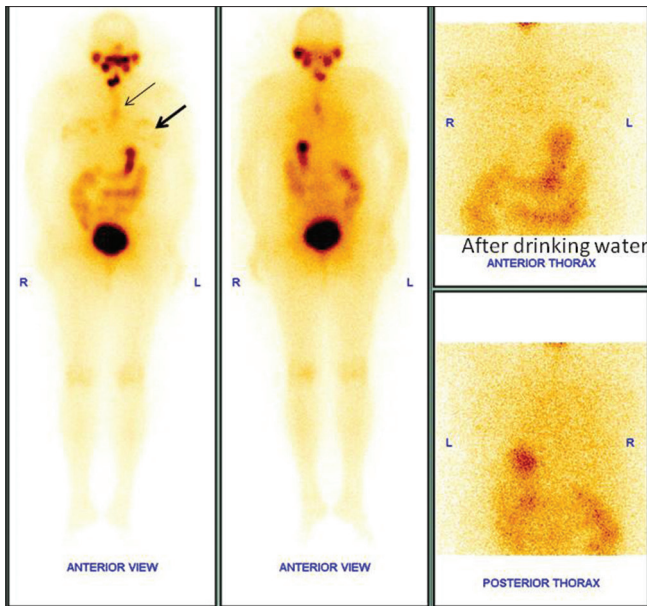


Figure 13: Young patient with DTC underwent total thyroidectomy. WBI scan shows residual thyroid tissue along with diffuse ^{131}I uptake in bilateral breast parenchyma (thick arrow). On close interrogation patient was found to be on prolonged oral contraceptive pills. She also shows ^{131}I uptake in retained saliva in esophagus (thin arrow) which clears after gulping water.

Teratomas are slow-growing tumors that contain elements from multiple germ cell layers and are best assessed with ultrasound. They usually occur in young women 20–30 years of age. Uncomplicated ovarian teratomas tend to be asymptomatic and are often discovered incidentally. Mature cystic teratomas are encapsulated tumors with mature tissue or organ components. They are composed of well-differentiated derivatives from at least two of the three germ cell layers (i.e., ectoderm, mesoderm, and endoderm). They, therefore, contain developmentally mature skin complete with hair follicles and sweat glands, sometimes with luxuriant clumps of long hair, and often pockets of sebum, blood, fat, bone, nails, teeth, eyes, cartilage, and thyroid tissue. They can be bilateral in 10–15% cases. Being slow-growing tumors, a non-surgical conservative management is generally implemented.

Ovarian cysts are fluid-filled sacs which are usually asymptomatic. Most ovarian cysts are related to ovulatory cycles, being either follicular or corpus luteal cysts. Other types include cysts due to endometriosis and cystadenomas apart from teratomas. Pelvic inflammatory disease and polycystic ovarian disease can also result in ovarian cysts.

Other cystic structures known to show false-positive findings on radioiodine, include nasolacrimal sac, pleuropericardial, bronchogenic, thymic, breast, hepatic, renal, ovarian, epithelial, and sebaceous cysts. Entry of radioiodine into cysts occurs via passive diffusion or partially active transport. Due to the slow exchange of water and chemical elements between the cysts and their

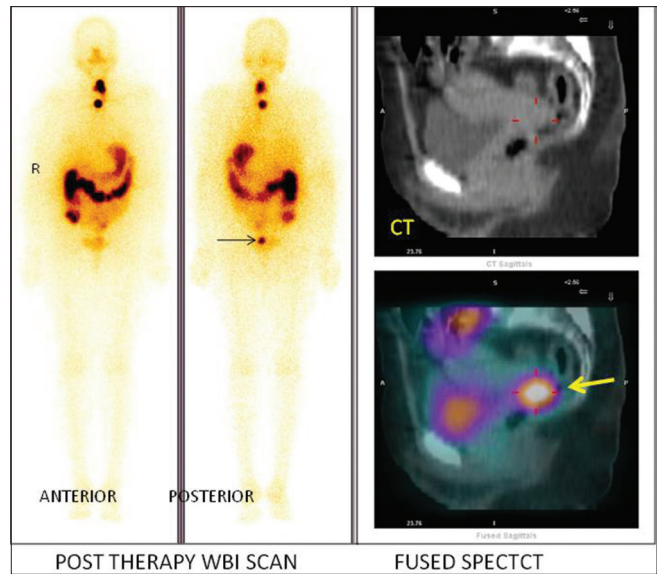


Figure 14: A 45-year-old papillary Ca thyroid s/p total thyroidectomy. WBI scan showed moderate to significant residual thyroid tissue. Incidentally focal ^{131}I uptake is also seen in retroverted uterus which is confirmed with SPECT-CT (arrow). No obvious lesion seen on CT at the corresponding to that site. The ^{131}I uptake is most likely physiological being a vascular organ

surrounding extracellular/extravascular environment, radioiodine gets trapped within the cysts^[17] producing false-positive scans.

^{131}I uptake in recent fracture

67 year old lady with follicular carcinoma thyroid following post total thyroidectomy underwent diagnostic WBI scan. In view of her age, histology and presence of minimal residual thyroid tissue, patient was treated with high dose ^{131}I therapy. Image [Figure 16a] shows minimal residual thyroid tissue in anterior neck 5 days after high-dose ^{131}I therapy, on the day of her scheduled post-therapy WBI scan, patient sustained a fall 1 h prior to her arrival at the center. Scan shows ^{131}I uptake in residual thyroid tissue as expected in an immediate post-therapy setting. There was an abnormal diffuse ^{131}I uptake in the right clavicular region corresponding to her site of injury. Subsequent X-ray confirmed fracture of lateral third clavicle on right side.

Inflammation and infection attribute a major chunk of false-positive ^{131}I uptake sites. It is thought that leukocytes stimulate the formation of inflammatory exudates in chronic inflammatory processes. It alters blood vessels to permit migration of leukocytes outside of the vessels into the tissue. As part of their bactericidal effect, leukocytes are known to induce iodide organification by means of a myeloperoxidase. Therefore, retention of radioiodine in leukocytes in clotted blood and tissues may also explain various reports of false-positive uptake in sites of inflammation.^[17]

CONCLUSION

DTC, which ordinarily behaves in an indolent manner, can have unusual metastatic presentations and patterns.

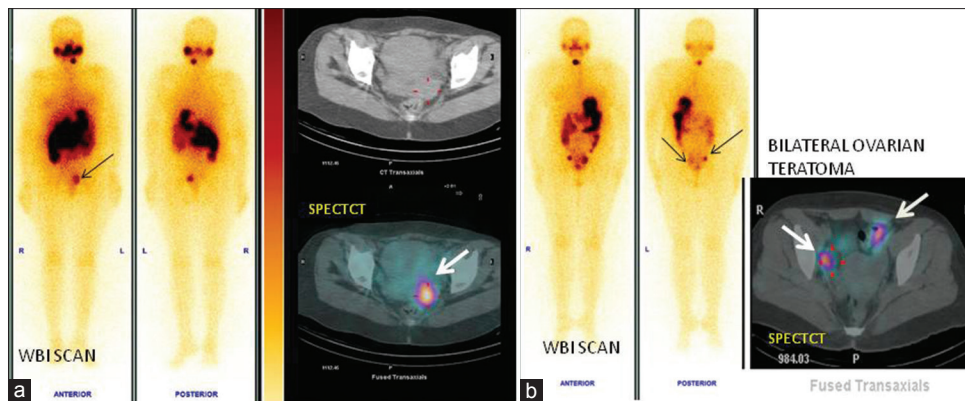


Figure 15: Two cases of papillary Ca thyroid, post-total thyroidectomy. The first case (a) shows focal ^{131}I uptake in left upper cervical nodal metastases. There is additional site of focal ^{131}I uptake intrapelvically. SPECT-CT of pelvis localized the uptake to ovary indicating left ovarian pathology (Arrow indicating ^{131}I uptake in left ovary). Further investigation confirmed inflamed corpus luteal cyst. (b) Another case depicting ^{131}I uptake in bilateral ovaries (arrows), confirmed on further investigation to be bilateral ovarian teratomas

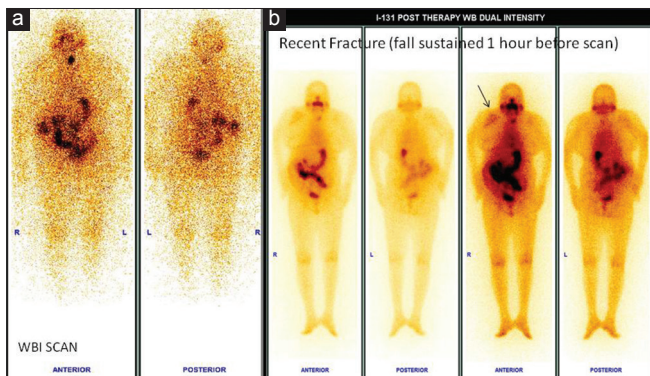


Figure 16: ^{131}I uptake in recent fracture: A 67-year-old case of follicular Ca thyroid, post-total thyroidectomy. WBI scan (a) shows minimal residual thyroid tissue. Five days after high-dose ^{131}I therapy on the day of scan, patient sustained a fall 1 h before her arrival. (b) Scan shows ^{131}I uptake in residual thyroid tissue as expected in an immediate post-therapy setting. There was an abnormal diffuse ^{131}I uptake in right clavicular region (arrow). Subsequent chest X-ray confirmed fracture of lateral third clavicle on right side

Increasing importance should be given to rare metastases in DTC patients. This pictorial review highlights the need to create an awareness to detect 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 patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Mazzaferri EL. Management of a solitary thyroid nodule. *New Engl J Med* 1993;328:553-9.
- Reddy RM, Grigsby PW, Moley JF, Hall BL. Lymph node metastases in differentiated thyroid cancer under 2 cm. *Surgery* 2006;140:1050-4; discussion 1054-55.
- Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, *et al*. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009;19:1167-214.
- Shaha AR, Shah JP, Loree TR. Differentiated thyroid cancer presenting initially with distant metastasis. *Am J Sur* 1997;174:474-6.
- Aggarwal V, Bhargav PR, Mishra A, Agarwal G. Clinico-pathological characteristics and long-term outcome in patients with distant metastases from differentiated thyroid carcinoma. *World J Sur* 2007;31:246-7.
- Feine U, Lietznmayer R, Hanke JP, Wöhrle H, Müller-Schauenburg W. ^{18}F FDG whole-body PET in differentiated thyroid carcinoma. Flip flop in uptake patterns of ^{18}F FDG and ^{131}I . *Nuklearmedizin* 1995;34:127-34.
- Parker LN, Wu SY, Kim DD, Kollin J, Prasasvinichai S. Recurrence of papillary thyroid carcinoma presenting as a focal neurologic deficit. *Arch Intern Med* 1986;146:1985-7.
- Ritland JS, Eide N, Walaas L, Hoie J. Fine-needle aspiration biopsy diagnosis of a uveal metastasis from a follicular thyroid carcinoma. *Acta Ophthalmol Scand* 1999;77:594-6.
- Arat YO, Boniuk M. Red lesions of the iris, choroid, and skin secondary to metastatic carcinoma of the thyroid: A review. *Surv Ophthalmol* 2007;52:523-8.
- Hammami MM, Bakheet S. Radioiodine breast uptake in nonbreastfeeding women: Clinical and scintigraphic characteristics. *J Nucl Med* 1996;37:26-31.
- Shim HK, Kim MR. Incidental findings of intense radioiodine uptake in struma ovarii and bilateral nonlactating breasts simultaneously on postablation ^{131}I SPECT/CT for papillary thyroid cancer. *Nucl Med Mol Imaging* 2016;50:353.
- Dahl PR, Brodland DG, Goellner JR, Hay ID. Thyroid carcinoma metastatic to the skin: A cutaneous manifestation of a widely disseminated malignancy. *J Am Acad Dermatol* 1997;36:531-7.
- Salvatori M, Perotti G, Rufini V, Maussier ML, Summaria V, Fadda G, *et al*. Solitary liver metastasis from Hurthle cell thyroid cancer: A case report and review of the literature. *J Endocrinol Invest* 2004;27:52-6.
- Liou MJ, Lin JD, Chung MH, Liau CT, Hsueh C. Renal metastasis from papillary thyroid microcarcinoma. *Acta Oto-Laryngologica*

- 2005;125:438-42.
15. Pucci A, Suppo M, Lucchesi G, Celeste A, Viberti L, Pellerito R, *et al.* Papillary thyroid carcinoma presenting as a solitary soft tissue arm metastasis in an elderly hyperthyroid patient. Case report and review of the literature. *Virchows Archiv* 2006;448:857-61.
 16. Itani M, Lewis HD. I 131 uptake in fat necrosis. *Radiol Case Rep* 2016;12:161-7.
 17. Oh JR, Ahn BC. False-positive uptake on radioiodine whole-body scintigraphy: Physiologic and pathologic variants unrelated to thyroid cancer. *Am J Nucl Med Mol Imaging* 2012;2:362-85.