UDONTHANI
CANCER HOSPITAL

Pitfalls and Concerning issue of Radioiodine treatment

20th November 2024

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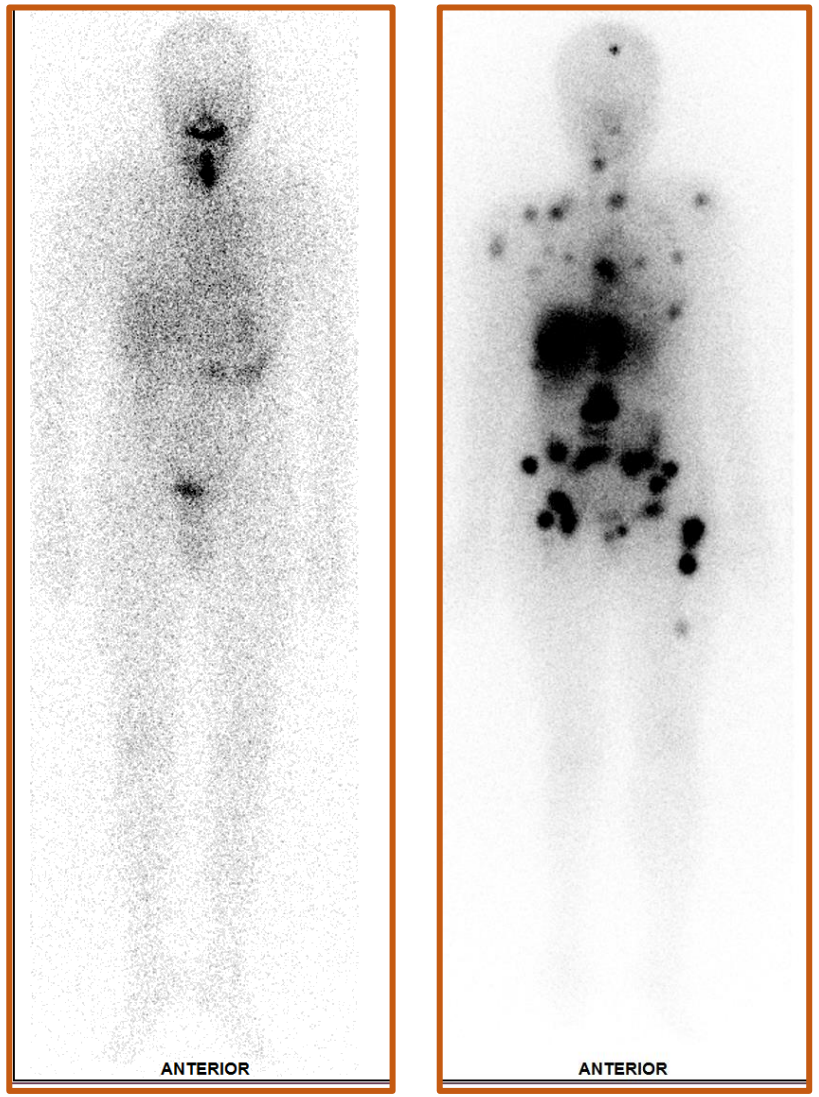
Nuclear Medicine Department

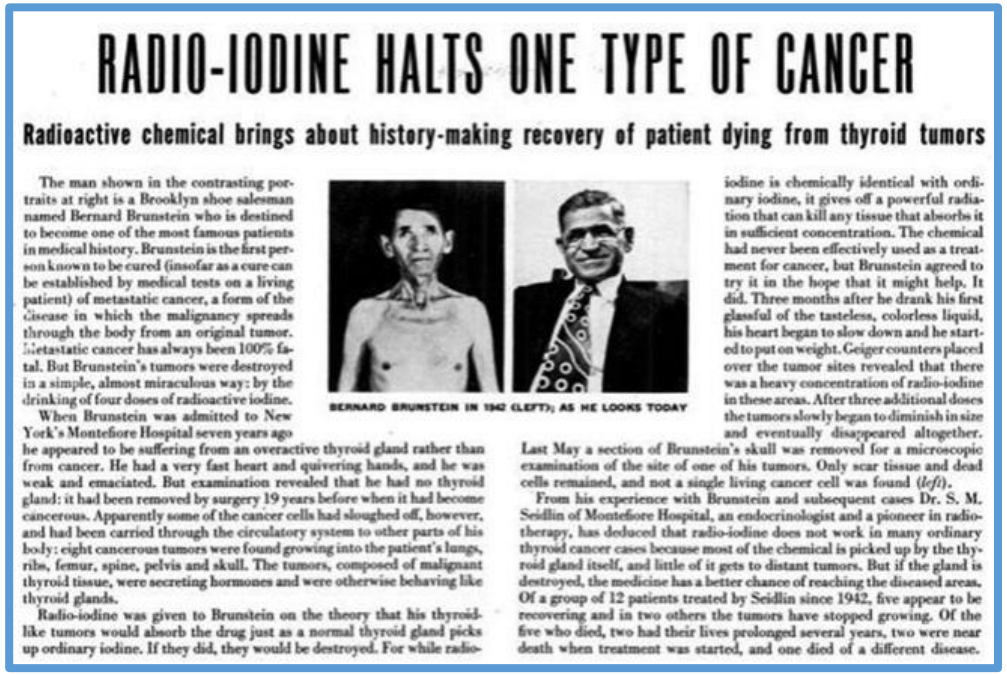
Outline

- Background
- Causes of false-positive RAI uptake in differentiated thyroid cancer (DTC)
- Interesting cases
- Q & A



Background

- Thyroid cancer: DTC > 90%, includes papillary and follicular histologic types
- Since the 1940s, RAI has been an integral component of care for DTC after thyroidectomy
- RAI whole-body scan (WBS) informs disease staging and RAI avidity of any structural disease
- Critical tool in treatment and surveillance



RADIO-IODINE HALTS ONE TYPE OF CANCER

Radioactive chemical brings about history-making recovery of patient dying from thyroid tumors

The man shown in the contrasting portraits at right is a Brooklyn shoe salesman named Bernard Brunstein who is destined to become one of the most famous patients in medical history. Brunstein is the first person known to be cured (insofar as a cure can be established by medical tests on a living patient) of metastatic cancer, a form of the disease in which the malignancy spreads through the body from an original tumor. Metastatic cancer has always been 100% fatal. But Brunstein's tumors were destroyed in a simple, almost miraculous way: by the drinking of four doses of radioactive iodine.

When Brunstein was admitted to New York's Montefiore Hospital seven years ago he appeared to be suffering from an overactive thyroid gland rather than from cancer. He had a very fast heart and quivering hands, and he was weak and emaciated. But examination revealed that he had no thyroid gland: it had been removed by surgery 19 years before when it had become cancerous. Apparently some of the cancer cells had sloughed off, however, and had been carried through the circulatory system to other parts of his body: eight cancerous tumors were found growing into the patient's lungs, ribs, femur, spine, pelvis and skull. The tumors, composed of malignant thyroid tissue, were secreting hormones and were otherwise behaving like thyroid glands.

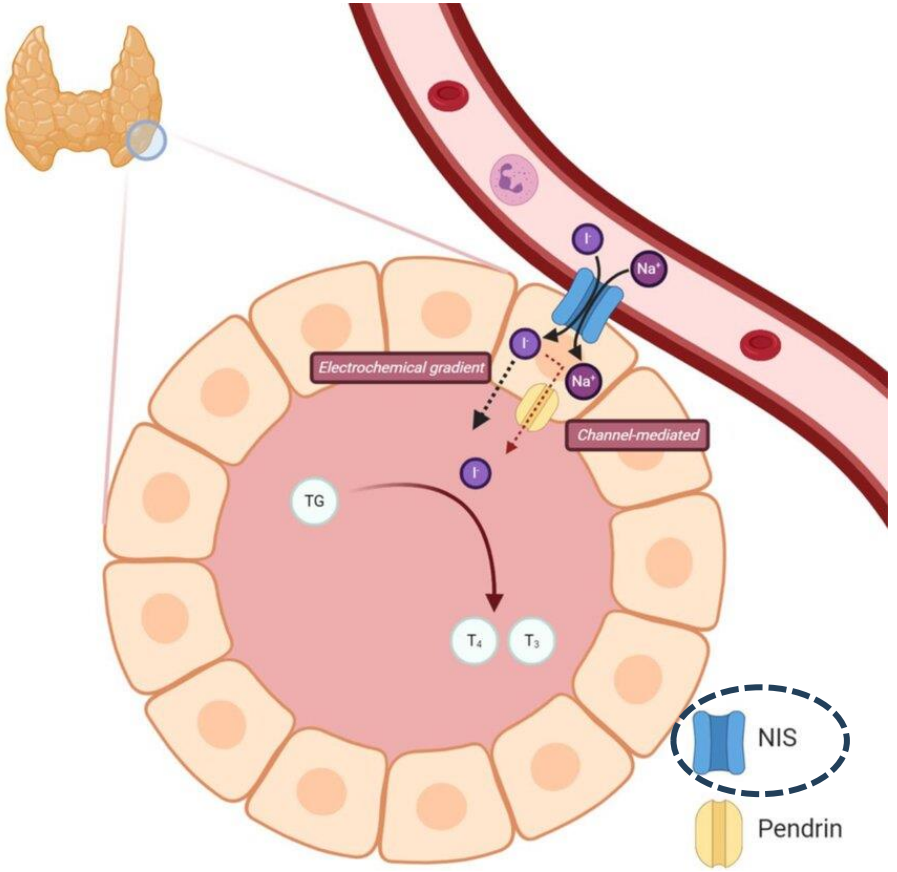
Radio-iodine was given to Brunstein on the theory that his thyroid-like tumors would absorb the drug just as a normal thyroid gland picks up ordinary iodine. If they did, they would be destroyed. For while radio-iodine is chemically identical with ordinary iodine, it gives off a powerful radiation that can kill any tissue that absorbs it in sufficient concentration. The chemical had never been effectively used as a treatment for cancer, but Brunstein agreed to try it in the hope that it might help. It did. Three months after he drank his first glassful of the tasteless, colorless liquid, his heart began to slow down and he started to put on weight. Geiger counters placed over the tumor sites revealed that there was a heavy concentration of radio-iodine in these areas. After three additional doses the tumors slowly began to diminish in size and eventually disappeared altogether. Last May a section of Brunstein's skull was removed for a microscopic examination of the site of one of his tumors. Only scar tissue and dead cells remained, and not a single living cancer cell was found (*left*).

BERNARD BRUNSTEIN IN 1942 (LEFT); AS HE LOOKS TODAY

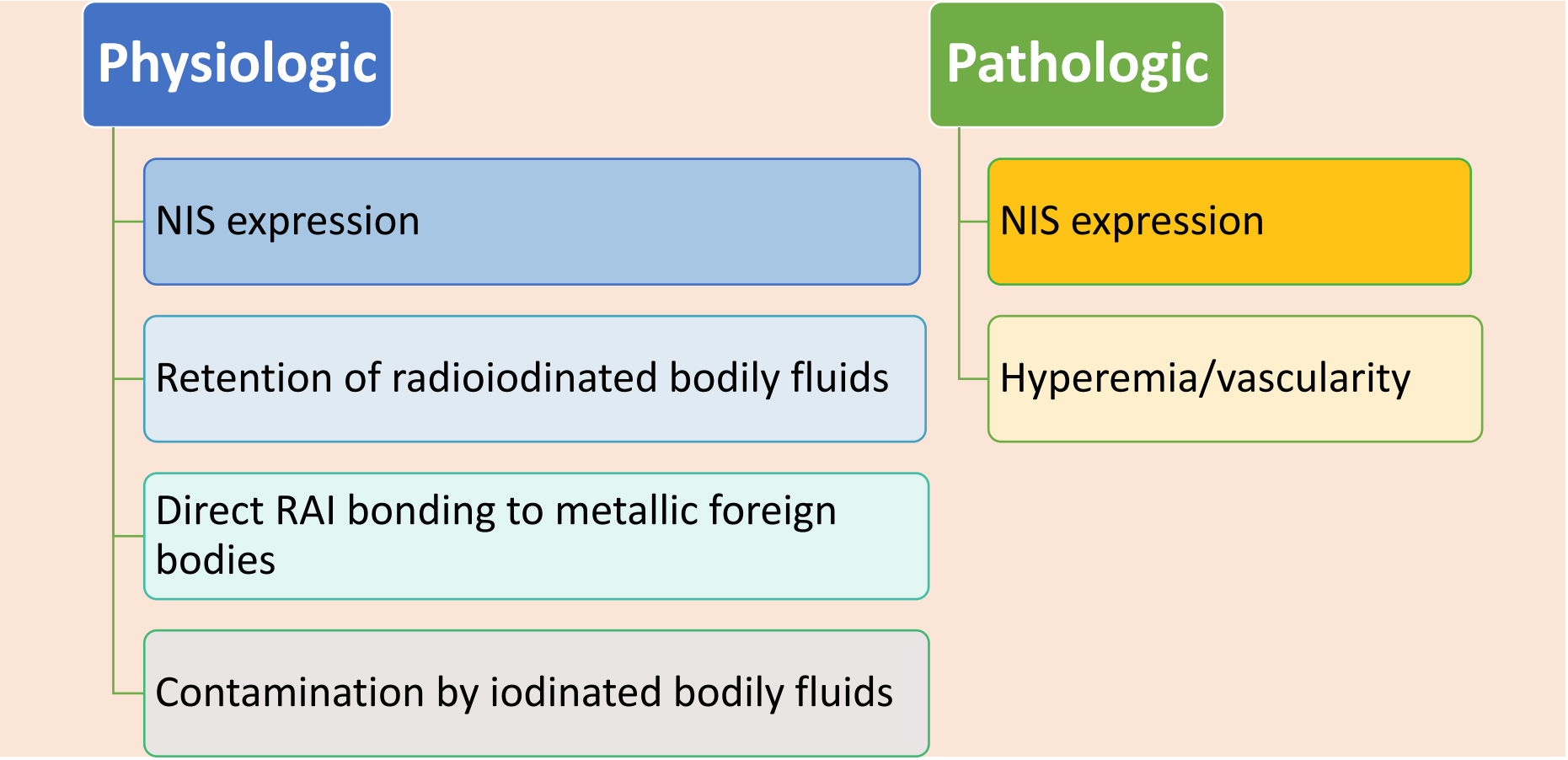
From his experience with Brunstein and subsequent cases Dr. S. M. Seidlin of Montefiore Hospital, an endocrinologist and a pioneer in radio-therapy, has deduced that radio-iodine does not work in many ordinary thyroid cancer cases because most of the chemical is picked up by the thyroid gland itself, and little of it gets to distant tumors. But if the gland is destroyed, the medicine has a better chance of reaching the diseased areas. Of a group of 12 patients treated by Seidlin since 1942, five appear to be recovering and in two others the tumors have stopped growing. Of the five who died, two had their lives prolonged several years, two were near death when treatment was started, and one died of a different disease.

Principle of RAI WBS

- Thyroid cancer cells retain expression of sodium-iodide symporter (NIS)
  - plasma membrane glycoprotein
  - facilitates active iodide transport
- NIS expression is not specific to thyroid cells
- There can be false-positive RAI uptake
  >> misdiagnosis and misclassification of staging
- Recognizing causes of false positivity
  >> avoid unnecessary testing and treatment as well as emotional stress



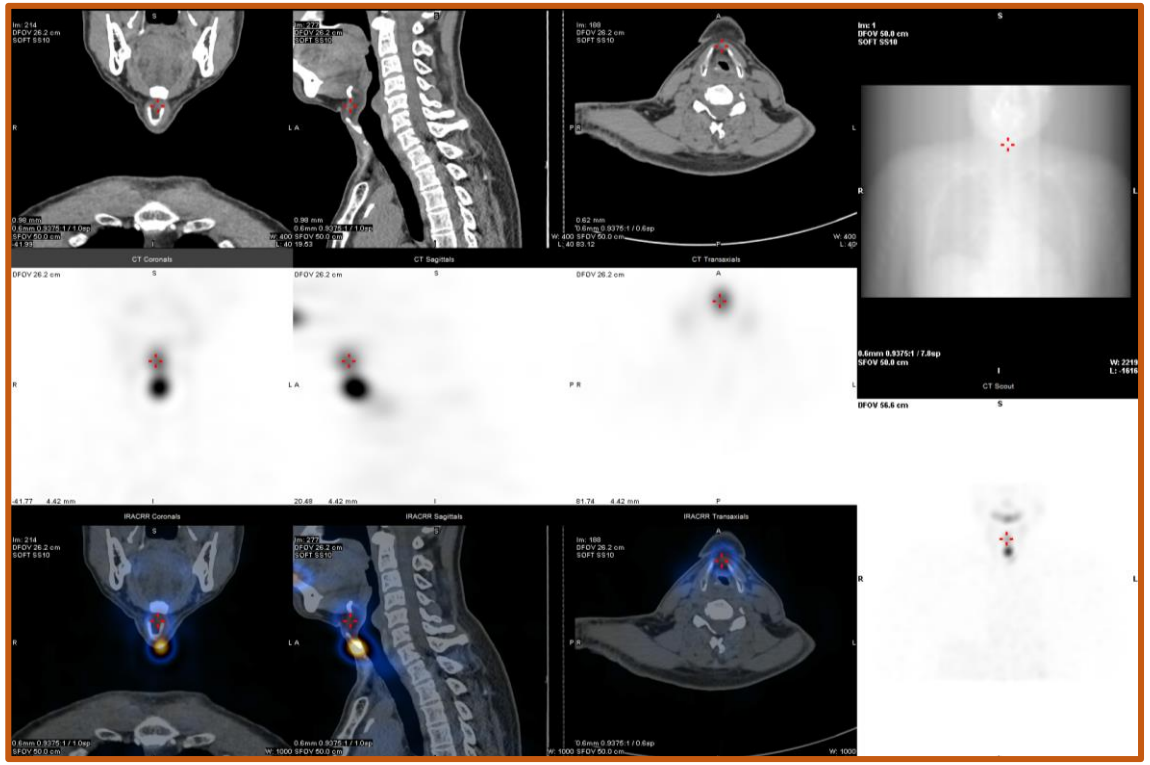
Causes of false-positive RAI uptake in WBS



Physiologic Causes

1) ***Extraglandular Thyroid Tissue***

- Embryologically, thyroid tissues originate at base of tongue and migrate caudally along the midline via thyroglossal duct
- Failure of decent leads to ectopic thyroid tissues
  - Most common locations: ***base of tongue and along thyroglossal duct***
  - Other rarer sites: mediastinal and subdiaphragmatic regions
- Ectopic thyroid tissues are functional >> can take up RAI similarly to normal thyroid gland

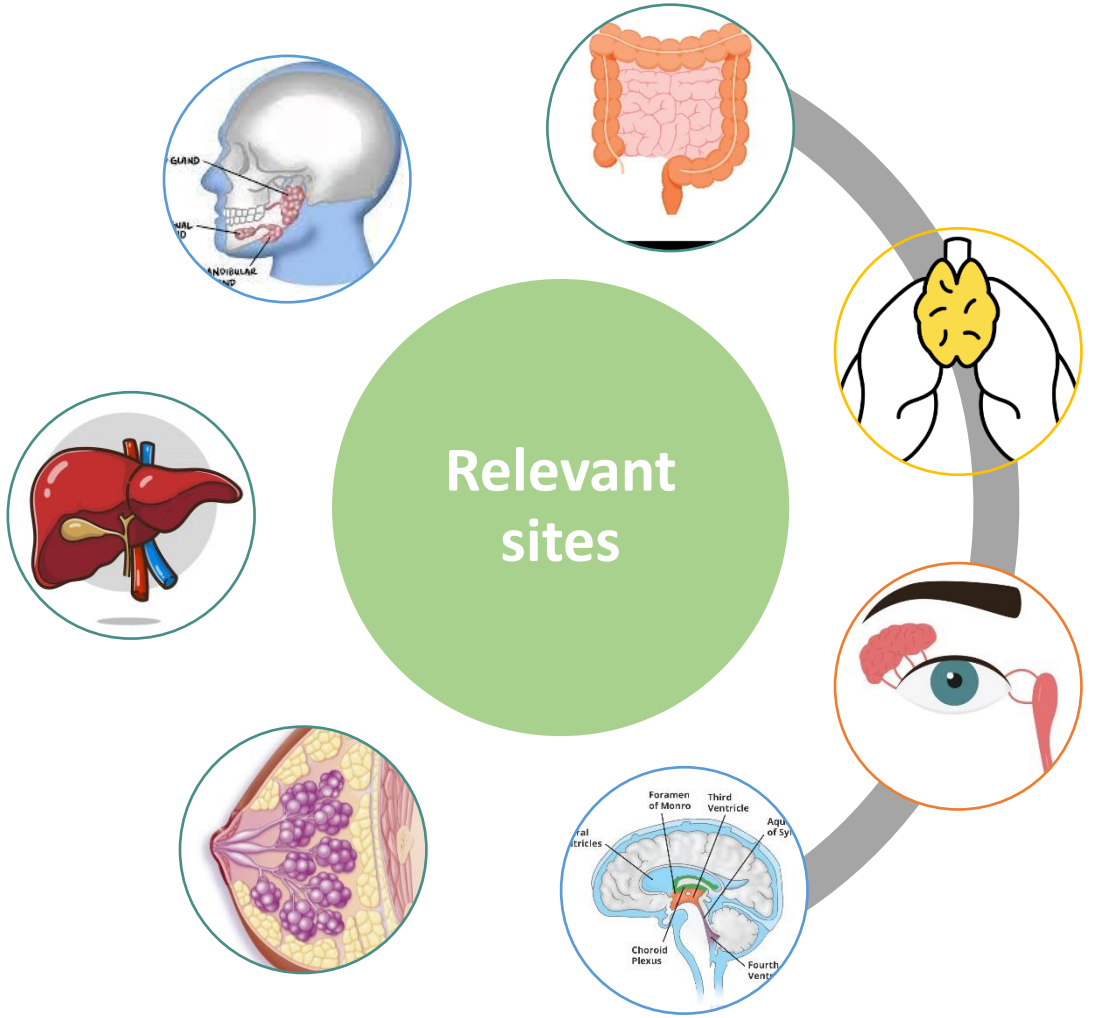


Wu, K., Ozomaro, U., Flavell, R. *et al.* Causes of False-Positive Radioactive Iodine Uptake in Patients with Differentiated Thyroid Cancer. *Curr Radiol Rep* **9**, 6 (2021).

Physiologic Causes

2) Uptake in Non-thyroidal Tissue

- Expression of NIS in other tissues
  >> RAI uptake outside of the thyroid
- Clinically relevant sites:
  - Salivary glands
  - Lacrimal glands
  - GI tract
  - Liver
  - Thymus
  - Choroid plexus
  - Mammary glands



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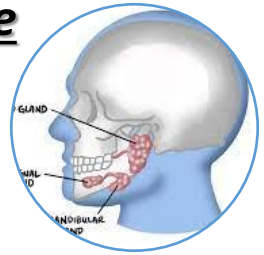
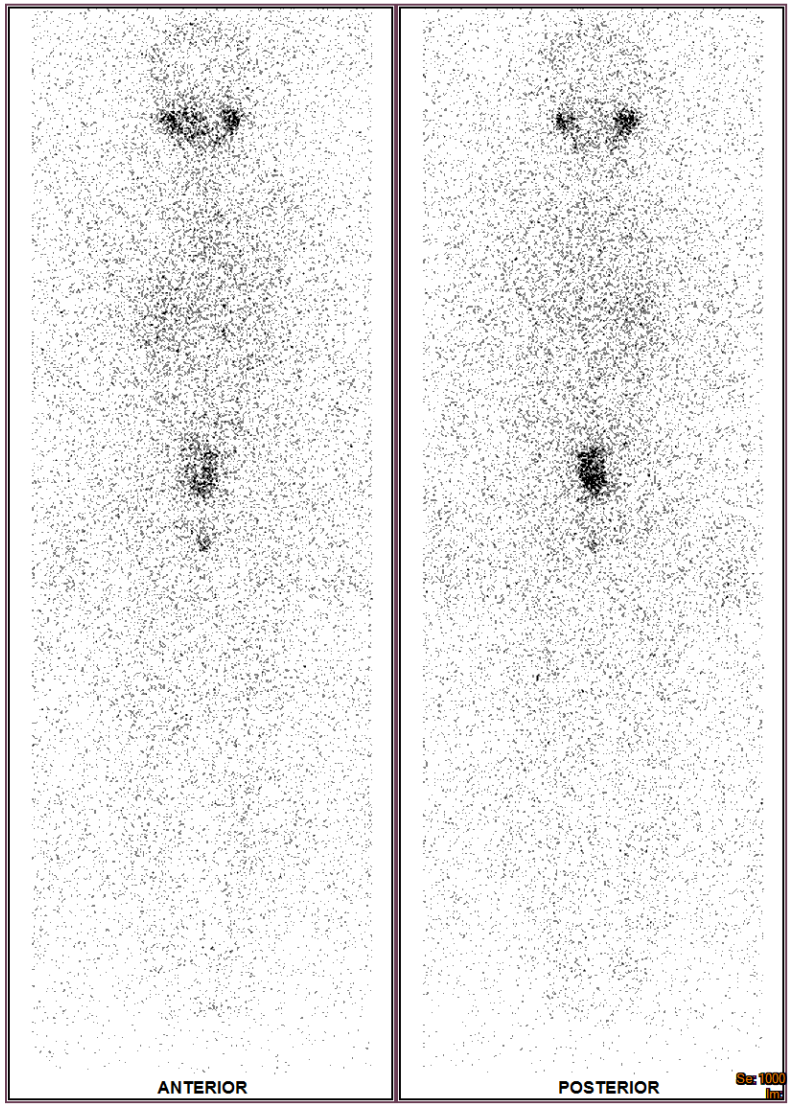
Physiologic Causes

2) Uptake in Non-thyroidal Tissue

Salivary glands



- Physiologic uptake of RAI in salivary glands: commonly observed salivary gland-related side effects
  - Dry mouth, sialadenitis, altered taste
  - Up to 40% of patients receiving RAI doses ≥ 75 mCi
  - Recent systemic review found salivary gland dysfunction in 16–54% of patients receiving RAI



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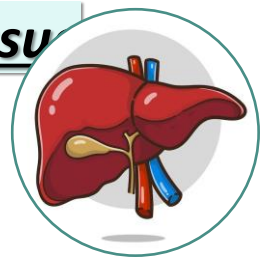
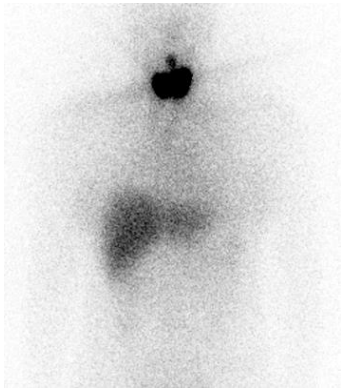
Physiologic Causes

2) Uptake in Non-thyroidal Tissu

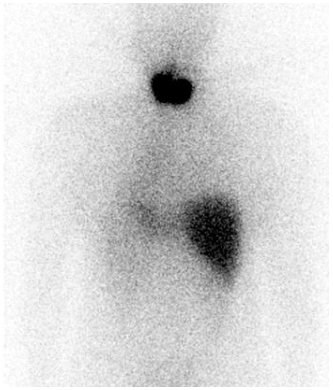


Liver

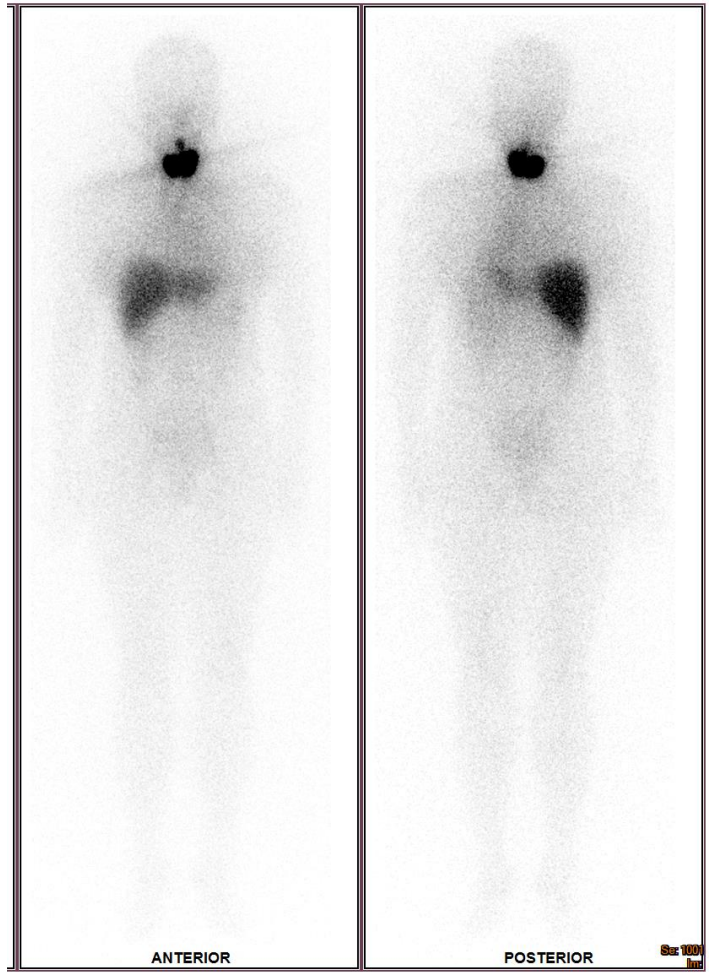
- Diffuse RAI uptake in the liver:40–94%
- The exact mechanism is unknown
- Proposed mechanisms
  - Hepatic metabolism of organified RAI released from the thyroid tissue
  - Intrahepatic bile duct NIS expression
- Mechanisms are debated
  - Association with residual thyroid tissue
  - No correlation with Tg or presence of thyroid tissue or disease
- Fatty liver and elevated hepatic enzymes also show RAI uptake
  - Delayed de-iodination and iodine excretion leading to higher liver retention



Anterior



Posterior



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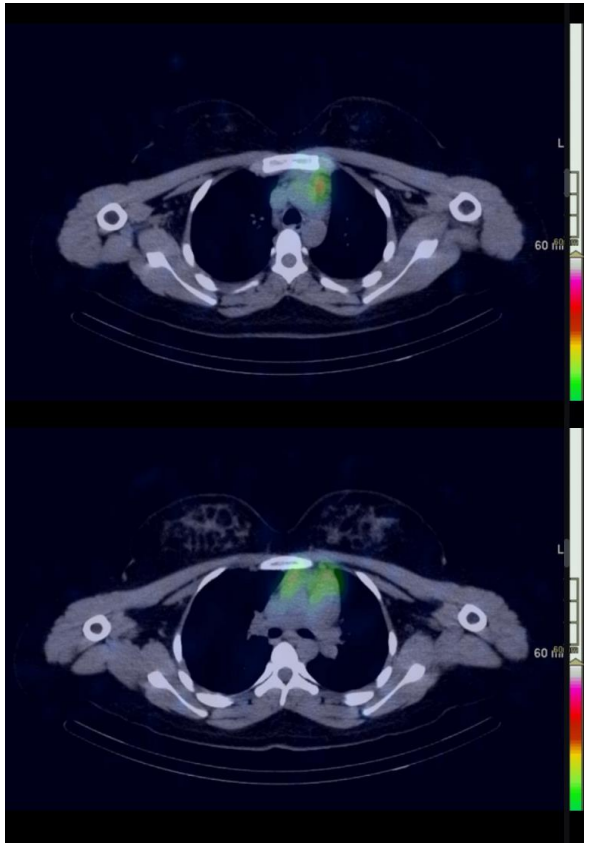
Physiologic Causes

2) Uptake in Non-thyroidal Tissue

Thymus gland

- RAI uptake most often in young patients (< 50 yr)
- Mechanism: Expression of NIS and thyroid-related proteins in human thymic tissues
- Older patients have lower thymic tissue volume since the thymus involutes with age >> thymic RAI uptake is less frequently seen

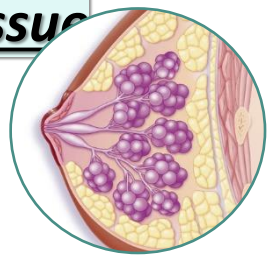


Banks K, Thymus uptake on whole-body iodine scintigraphy (I-131). Case study, Radiopaedia.org (Accessed on 17 Nov 2024)

Physiologic Causes

2) Uptake in Non-thyroidal Tissue

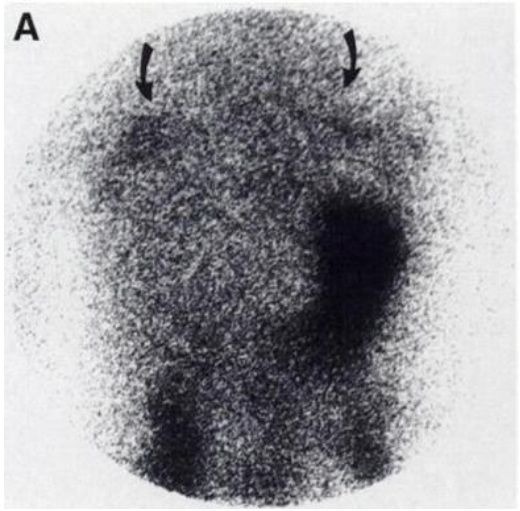
Mammary glands



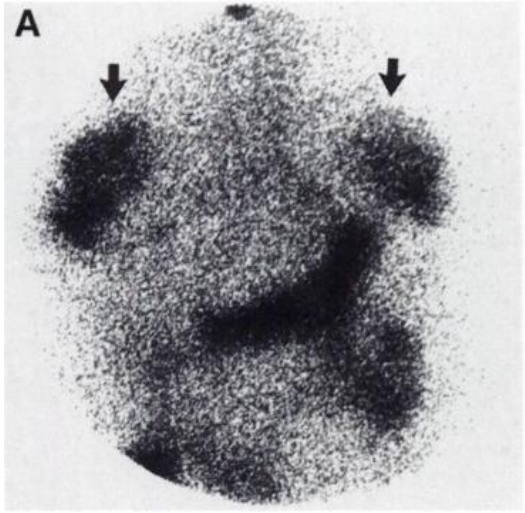
- Major organ expressing NIS
- Marked upregulation during lactation by oxytocin and prolactin
- Uptake in non-lactating breasts as well
  - Hyperprolactinemia >> upregulation of NIS expression >> bilateral breast RAI concentration in pituitary macroprolactinoma
  - Individual variation
- Essential to correlate with clinical and SPECT/CT: Uptake can be misinterpreted as pulmonary metastases
- Bakheet et al.: analysis of patterns of radioiodine uptake in lactating breasts on 20 radioiodine scintigraphy
  - Four patterns of uptake: full (most common), focal, crescent, irregular
  - Asymmetry in 60% (left > right in 45%, right > left in 15%), symmetry in 25%, and unilateral in 15% of cases

Radioiodine Breast Uptake in Nonbreastfeeding Women: Clinical and Scintigraphic Characteristics Muhammad M. Hammami and Siema Bakheet.
J NucÃ-Med 1996; 37:26-3

Physiologic Causes



(A) Iodine-123 diagnostic scan. Anterior chest view obtained 3 mo. after discontinuation of breastfeeding. Curved arrows delineate +, irregular breast uptake, bilaterally, mimicking lung metastasis



(A) Iodine-123 diagnostic scan. Anterior chest view obtained 6 mo. after discontinuation of breast feeding. Arrows delineate + ++, full, in (A) breast uptake bilaterally

RAI uptake in bilateral breast tissue

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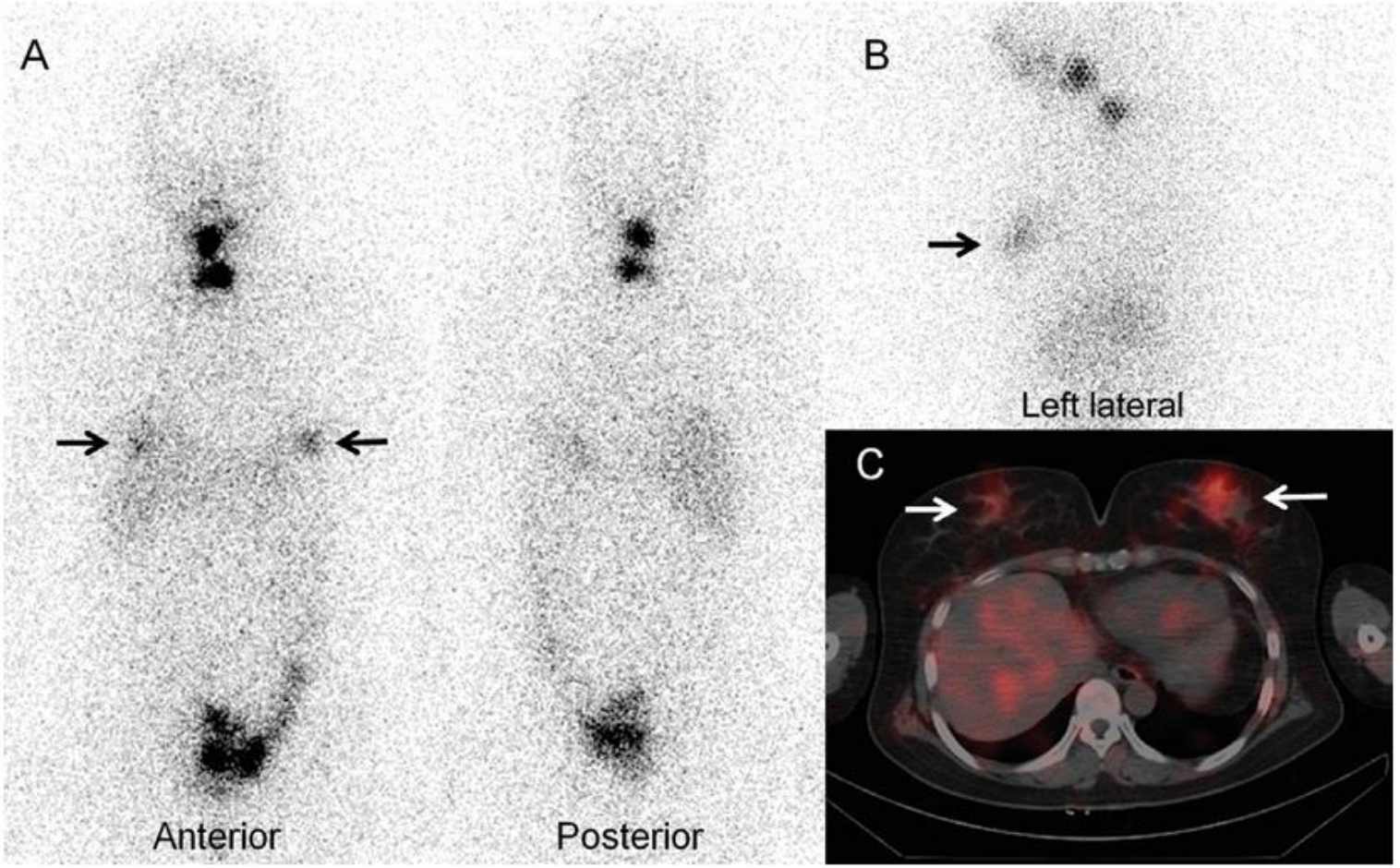


Physiologic radioiodine uptake in the breast; A and B - planar scintigraphy, C - SPECT/CT. Unusual uptakes in lower thorax are observed in **non lactating**, 48 year-old female

Following MMG and breast US showed negative results.

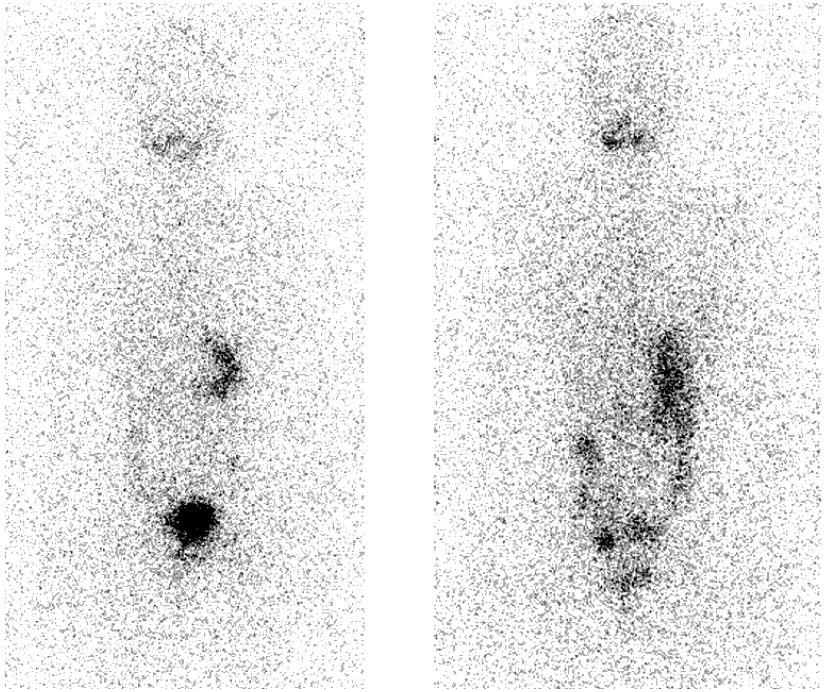
>> more confidently recognized as physiologic change rather than lung metastasis by recognition of its specific patterns, bilateral and symmetric, anteriorly located position in lateral image (B), even though in the absence of SPECT/ CT

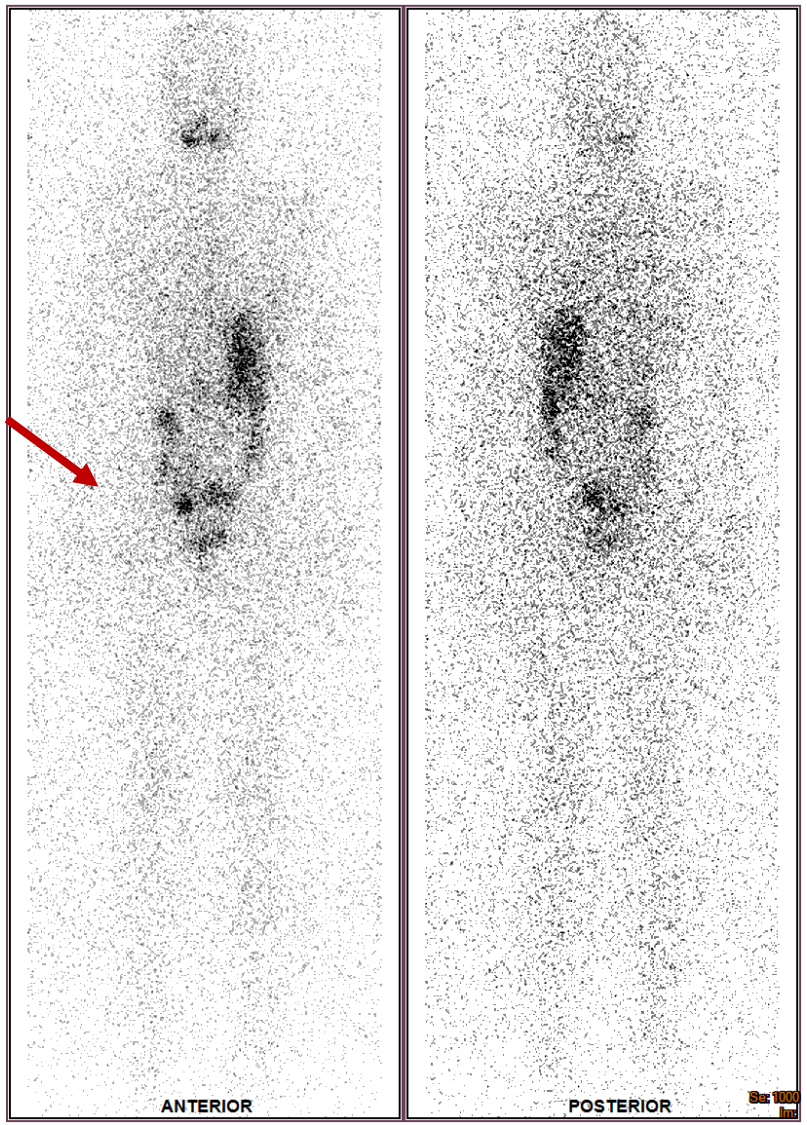
Oh JR, Ahn BC. False-positive uptake on radioiodine whole-body scintigraphy: physiologic and pathologic variants unrelated to thyroid cancer. Am J Nucl Med Mol Imaging. 2012;2(3):362-85. Epub 2012 Jul 10.

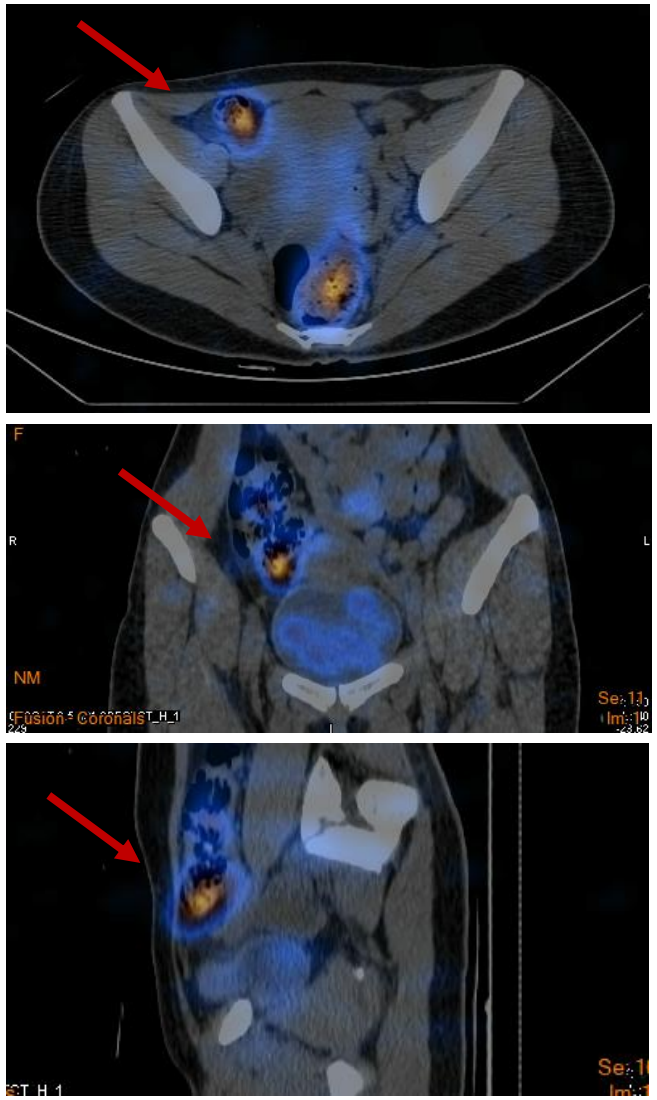
Physiologic Causes

3) Radioiodinated Bodily Fluid Retention

- Oral RAI is quickly and almost entirely absorbed via GI tract
- > 90% excreted through kidney over 5 days
  majority disposed in first 24 hr
- Remaining RAI is excreted via sweat, gut, and other bodily secretions
- Any retention of body fluids with or without anatomical abnormalities can be seen on WBS
- Commonly: radioiodinated urinary retention in the bladder, salivary retention in the esophagus, and large intestinal retention of feces







Large intestinal retention of feces

Physiologic Causes

3) Radioiodinated Bodily Fluid Retention

- Many anatomical variations lead to false-positive RAI retention
- Examples: cystic and pouch-like structures: cyst, diverticulum, appendix
- Arterial dilation >> stasis of blood flow
  >> false-positive RAI retention
- Mechanism: passive diffusion of iodine into cysts and diverticula
  >> becomes trapped due to the slow drainage
- Ovarian cysts: commonly found in reproductive age woman,
  vast majority being physiologically functional >> retain RAI uptake

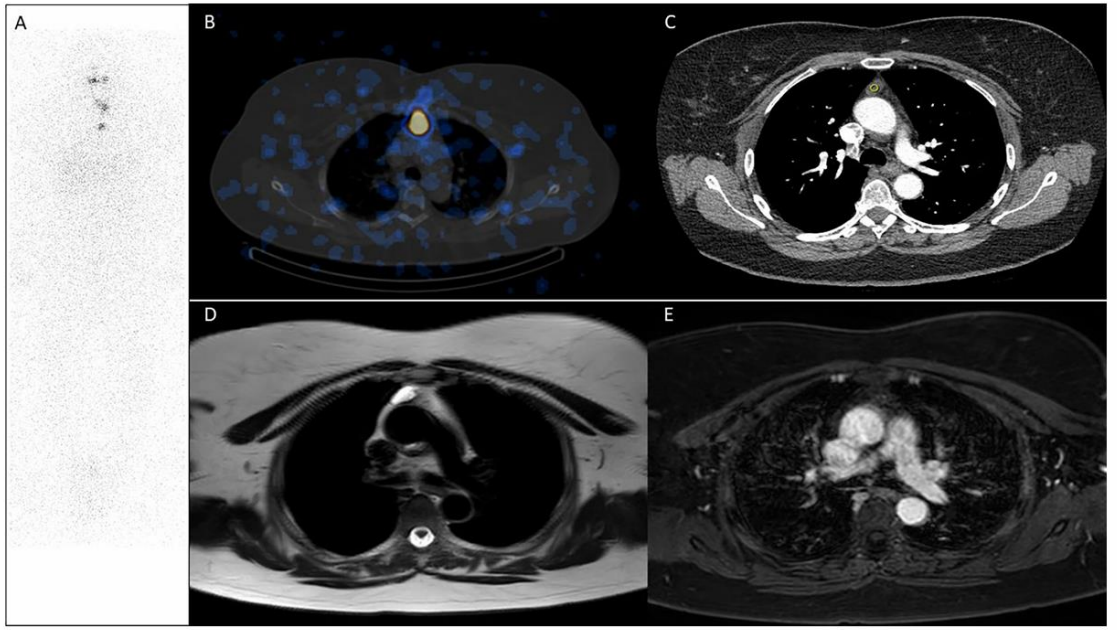


Fig. 4 I-131 retention in thymic cyst. **a** RAI-WBS, **b** SPECT/CT, **c** CT with contract, **d** MRI T2-weighted, **e** MRI post-gadolinium identified I-131 retention in thymic cyst

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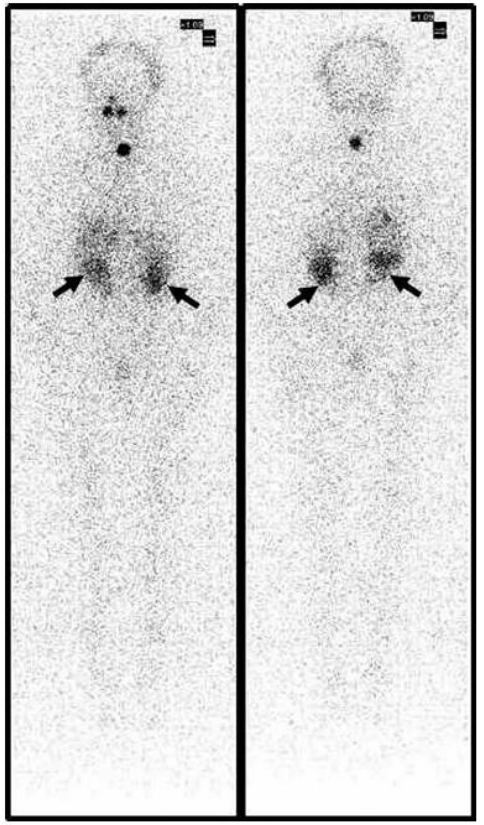


Figure 1. The post-therapy radioiodine scintigraphy images demonstrated intense radioiodine uptake in the region of neck, which was suggestive of the remnant thyroid tissue. There was diffuse increased activity in the region of liver, which was likely associated with the thyroid remnant. Unexpectedly, increased activity in the regions of bilateral upper abdomen was noted with unknown etiology (arrows).

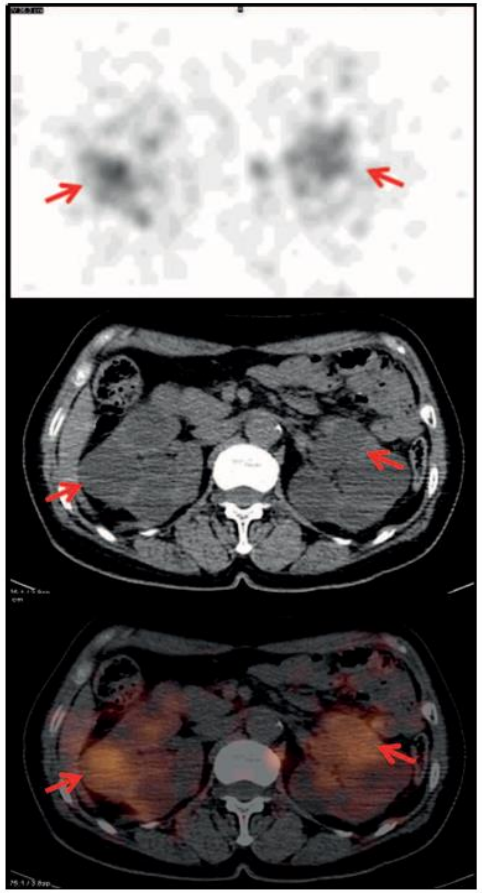
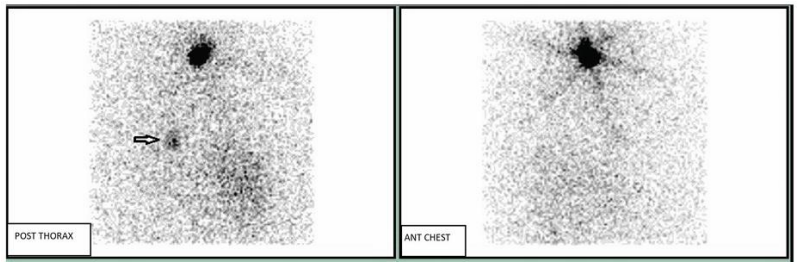
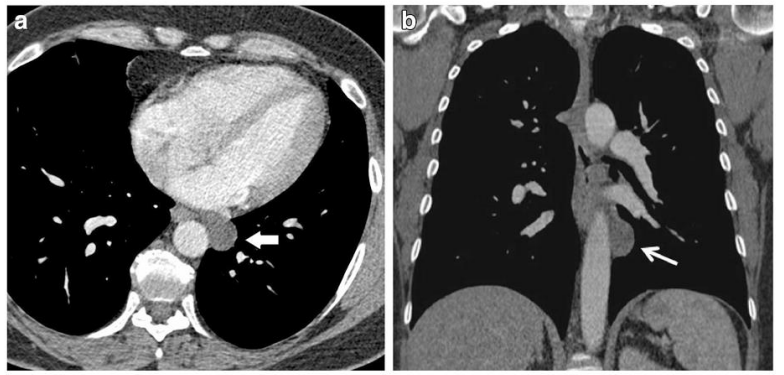


Figure 2. SPECT/CT images revealed that the 2 foci of elevated activity in the regions of bilateral upper abdomen were corresponded to multiple irregular cystic low densities in the bilateral kidney on the low-dose CT images and the diagnosis of polycystic kidney disease was confirmed (arrows). CT = computed tomography, SPECT/CT = single photon emission computed tomography/computed tomography.

Polycystic kidney disease





a Contrast-enhanced axial CT: well-demarcated ellipsoid lesion between the left atrium and the descending aorta (arrow).
b Coronal contrast-enhanced CT: the mass shows no enhancement and the attenuation characteristics of this mass are indicative of a cystic lesion (arrow)

a MRI: sagittal T2 weighted image shows a well-de fined, thin-walled, lobulated le sion (arrow) in contact with the left atrium and the descending aorta. b MRI: axial fat-saturated T2-weighted image: fatty content can be excluded (arrow). c MRI: axial DWI: no restriction of the diffusion (arrow)

Pleuropericardial Cyst

Mi YX, et al. Incidentally polycystic kidney disease identified by SPECT/CT with post-therapy radioiodine scintigraphy in a patient with differentiated thyroid carcinoma: A case report. Medicine (Baltimore). 2017 Oct;96(43):e8348.

Calabria F, et al. ^{131}I Uptake in Bronchiectasis Detected by Single Photon Emission Computed Tomography/Computed Tomography during Follow-up of Thyroid Cancer. Indian J Nucl Med. 2019 Jul-Sep;34(3):235-236.

Physiologic Causes

4) Direct RAI Bonding to Metallic Foreign Bodies

- Various metallic foreign bodies appear increased RAI uptake
- Most common: dental amalgam
- Mechanism: interaction and chemical binding of negatively charged iodide ions to the positively charged metal ions
  - Copper intrauterine devices, metallic surgical clips, and metallic sutures also retain RAI tracer
- Foreign bodies induce local inflammatory response >> RAI uptake in surrounding tissues

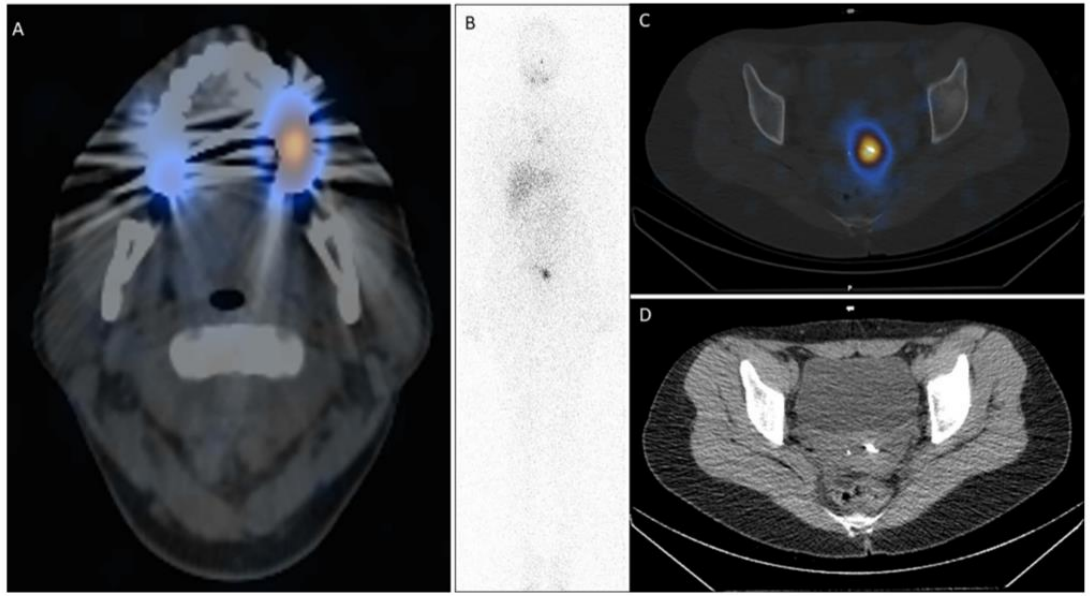


Fig. 5 I-131 retention by direct chemical binding to metallic foreign bodies. **a** SPECT/CT with RAI retention in dental amalgam. **b** RAI-WBC, **c** SPECT/CT, and **d** CT showing uptake by copper intrauterine device

RAI retention in dental amalgam

RAI uptake by copper intrauterine device

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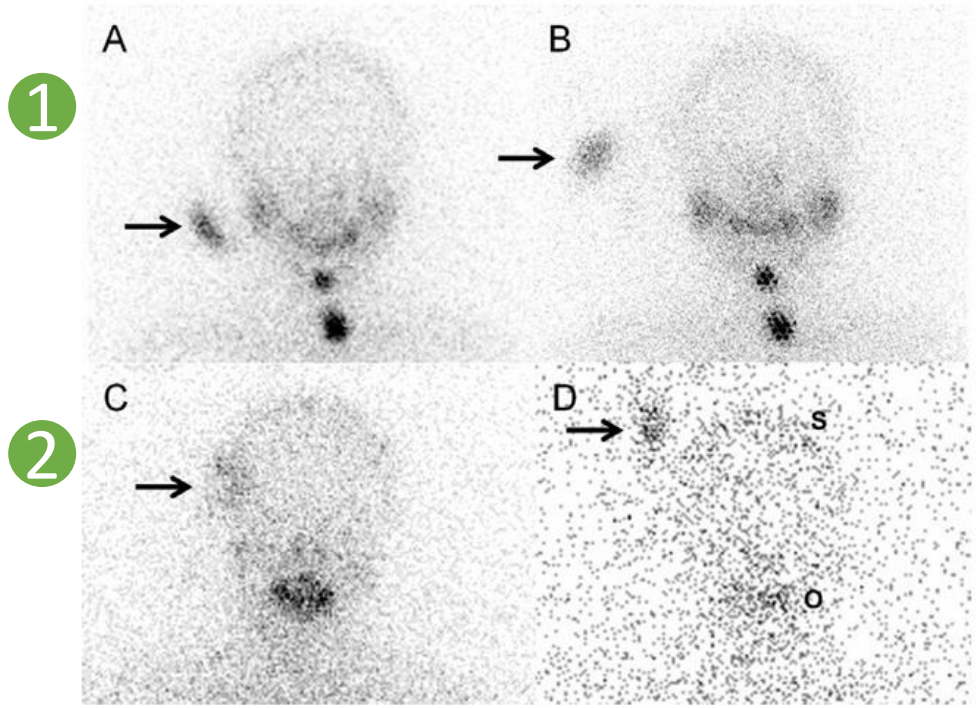
Physiologic Causes

5) Contamination by Radioiodinated Bodily Fluid

- Sweat, breast milk, urine, vomitus and nasal, tracheobronchial, lacrimal, salivary secretions and feces contain radioiodine contamination on skin, hair, and clothes, within tracheostomy sites
- Perspiration result in skin and hair contamination in axilla and scalp
- Contamination in artificial eyeballs by tear contamination
- Tends to be superficial can be easily corrected by washing



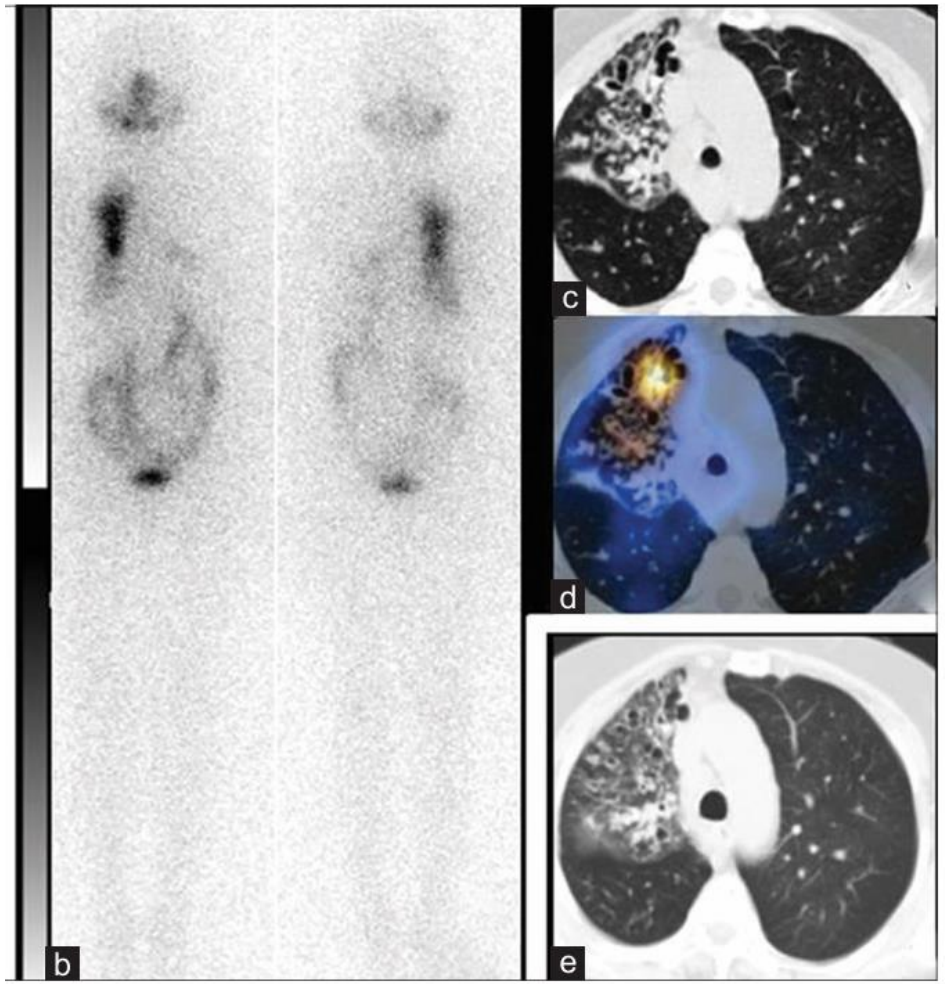
Contamination of radioiodine by hair in two patients (A-B and C-D). Unexpected radioiodine up takes in the outside (A) and on (C) the skull are observed (arrows). On the additional image after rolling up the hair (B and D), the uptakes were moved up ward (arrows). The change or disappearance of up take on additional image after rolling up the hair, showering, or removal of stained clothing can help to differentiate unusual uptake by the radioiodine contamination from pathologic condition.

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(3):362-85. Epub 2012 Jul 10.

Pathologic Causes

1) Inflammation and Infection

- Mechanisms:
  - inflammation-mediated hyperemia
  - ↑ vessel permeability
  - ↑ retention of organified I-131 by leukocytes during bactericidal activity
- Lung disease: important clinical entities because of mimicry of pulmonary metastases
- Typical distribution of pulmonary metastasis: a miliary or randomly pattern of nodules throughout all lobes, often basilar predominance
- Conditions of RAI uptake in lungs: bronchiectasis, acute respiratory infection, asthma exacerbation, and fungal infections like aspergilloma and tuberculosis.



131I whole-body scan confirms diffuse 131I uptake in the right hemithorax (b);
CT (c) and SPECT/CT (d) showed 131I uptake in association with bronchiectasis in the RML.
A CT of the thorax (e) performed at follow-up, showed partial resolution of bronchiectasis.

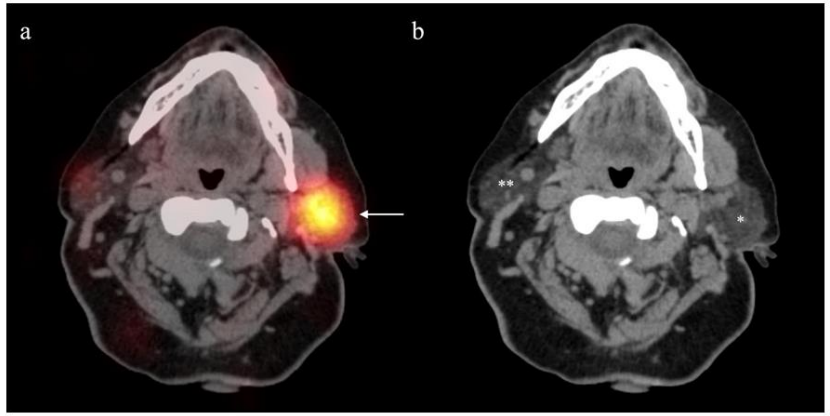
Bronchiectasis

Calabria F, et al. ^{131}I Uptake in Bronchiectasis Detected by Single Photon Emission Computed Tomography/Computed Tomography during Follow-up of Thyroid Cancer. Indian J Nucl Med. 2019 Jul-Sep;34(3):235-236.

Pathologic Causes

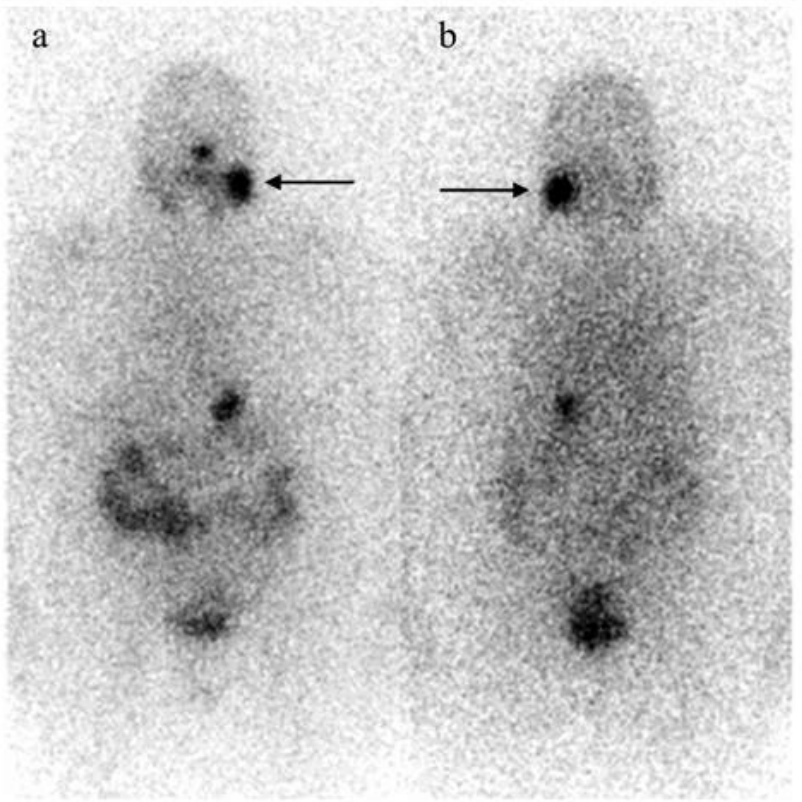
1) Inflammation and Infection

- RAI uptake in other body sites include rheumatoid arthritis, folliculitis, sialadenitis, sinusitis, cholecystitis, and liver abscess.
- Sialadenitis: Typically enlarged gland, increased uptake during acute & sub-acute phase



a) Axial view of the fused SPECT-CT shows increased I131 uptake in the left parotid gland (arrow).
b) Axial CT portion of SPECT-CT showing relative increased size of left parotid

Acute sialadenitis



a) Anterior view shows abnormal increased uptake in the left parotid gland (arrow). b) Posterior view shows abnormal increased uptake in the left parotid gland (arrow)

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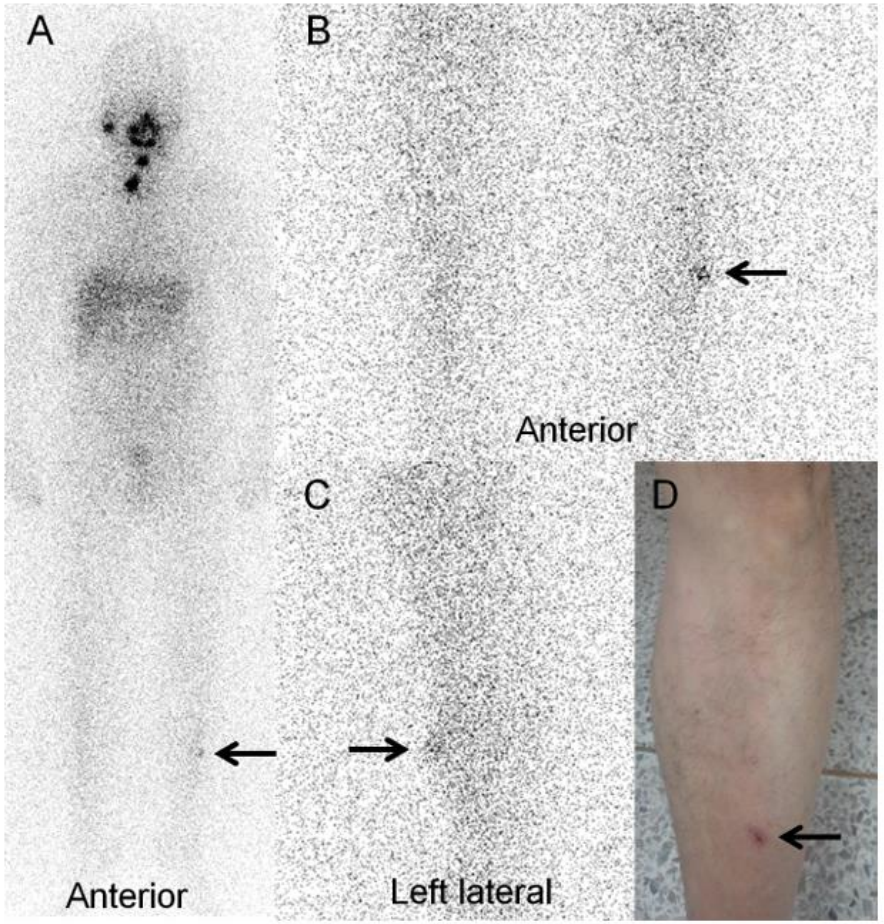
Pathologic Causes

2) Trauma

- Mechanism:
  - ↑ blood flow and capillary permeability >> abundance of cells in tissue or vessels, and stasis of radioiodinated blood
  - Mediator molecules also alter blood vessels >> permit migration of leukocytes outside of the vessels into tissue
    - Leukocytes induce iodide organification >> retention of RAI in posttraumatic clots or tissues



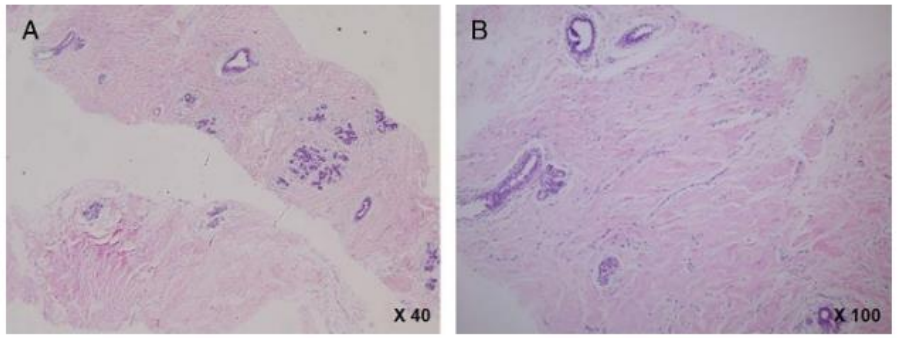
Pathologic uptake of radioiodine in a superficial scab; A, B, and C – planar scintigraphy, D – photograph. Localized uptake of radioiodine is observed in left lower leg (A and B, arrows). On the lateral view, the uptake is considered to be located in anterior superficial portion of left lower leg (C, arrow). This finding suggests that the unusual uptake might not be related to skeletal metastasis. On physical examination, a superficial scab in the healing process of skin wound was detected in the shin of left leg (D, arrow).

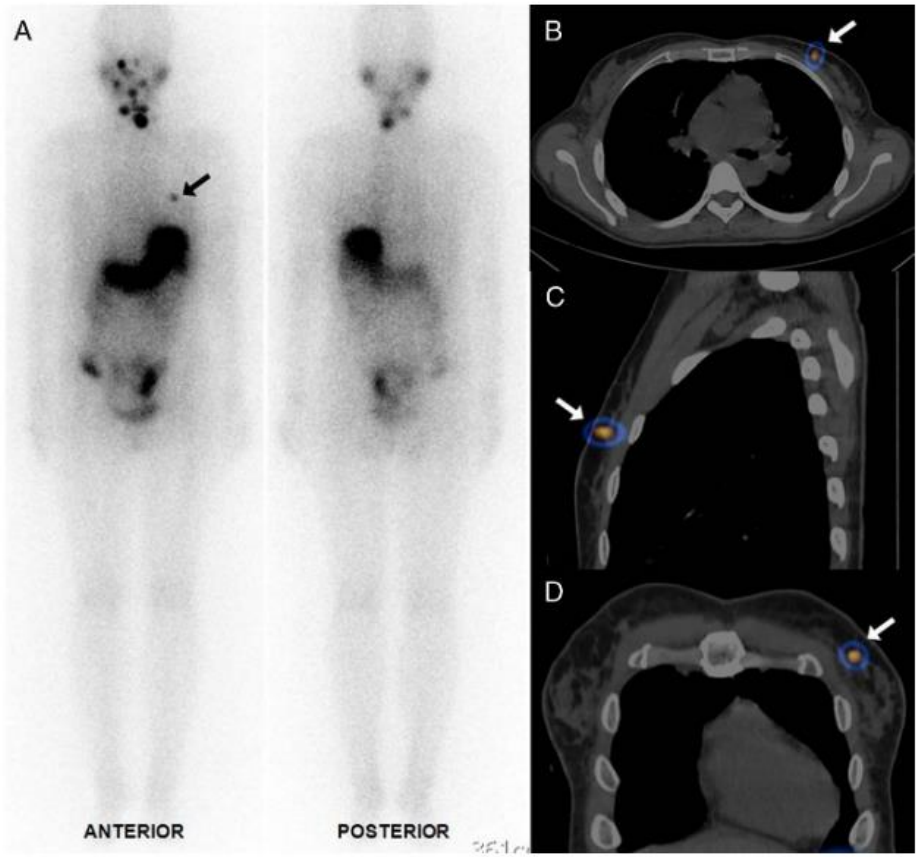
Oh JR, Ahn BC. False-positive uptake on radioiodine whole-body scintigraphy: physiologic and pathologic variants unrelated to thyroid cancer. Am J Nucl Med Mol Imaging. 2012;2(3):362-85. Epub 2012 Jul 10.

Pathologic Causes

3) Benign Tumors

- Benign tumors may have unexpected uptake of RAI
- Mechanism: functional physiologic NIS expression in the parenchymal tissues, such as in salivary gland tumors, breast fibroadenomas, and ovarian tumors
- Tumors with high vascularity, such as meningiomas and angiomas/hemangiomas >> RAI pooling





She complained of a mild pain in her left breast for several days thereafter. A physical examination showed no palpable mass in the bilateral breast. A whole-body planar radioiodine scan performed 2 days after 131I administration showed multifocal 131I accumulation in the thyroid bed and left chest region (A). Chest SPECT/CT revealed increased focal uptake in a tumor located in the upper inner quadrant of the left breast (B-D)

Fibroadenoma of left breast

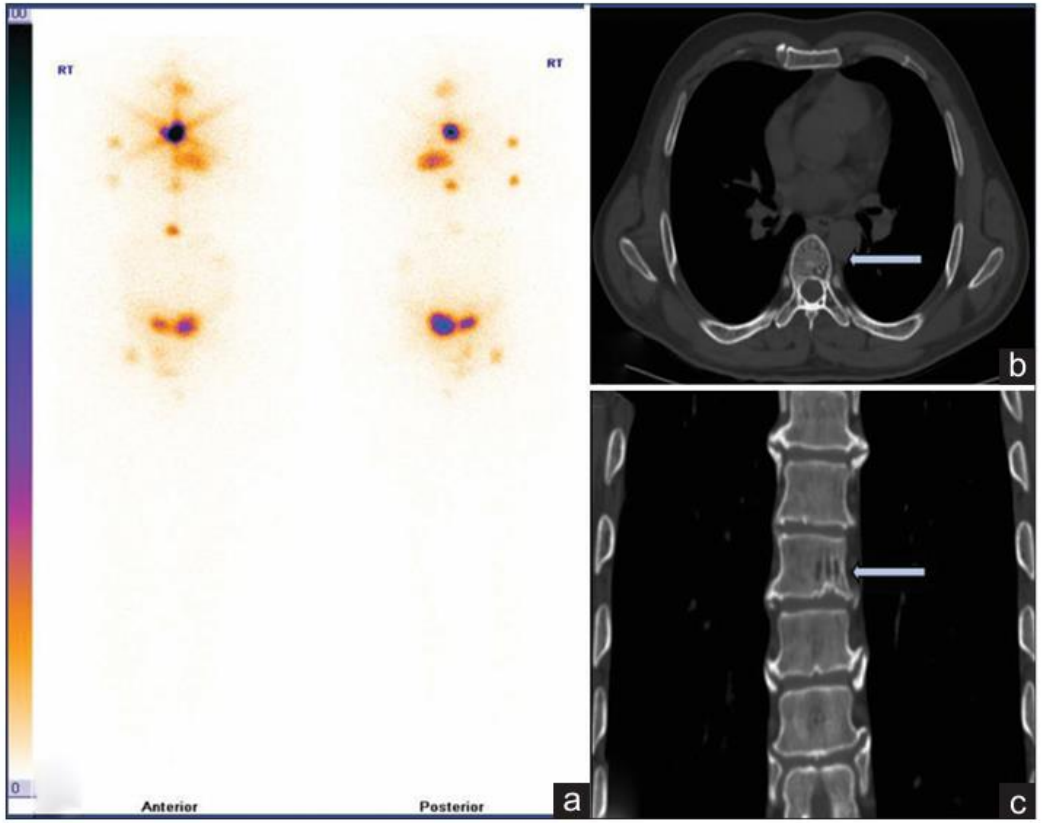


Figure 5: (a) Iodine 131 whole body scan anterior and posterior views showing evidence of RAI avid thyroid bed residue with lung, liver and bone metastases. (b) Axial section CT image showing polka dot appearance (arrow) and (c) Coronal section CT image showing corduroy sign (arrow) in T7 vertebra suggestive of hemangioma

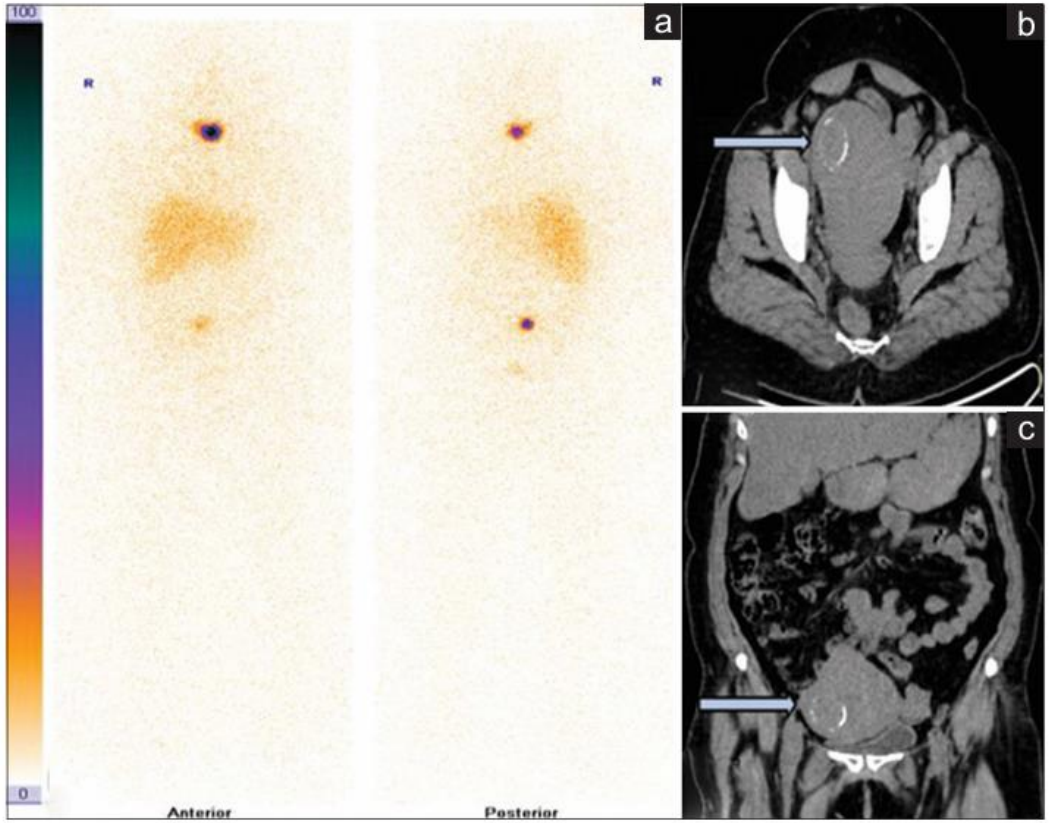


Figure 2: (a) Post high dose therapy scan with anterior and posterior views showing RAI avid focus in thyroid bed region and another focus in the pelvic region. (b and c) Axial and coronal sections CT images showing peripherally calcified heterogeneous lesion in uterus favoring uterine leiomyoma as depicted by arrows

Pathologic Causes

3) Malignant Tumors

- Pathologic RAI accumulation in non-thyroid malignancies and their metastases occurs in various body sites
- Mechanism: NIS expression, high vascularity, local tumoral inflammatory response in malignancies
- NIS expression is shown in carcinomas of the prostate, ovary, lung, colon, endometrium, and breast

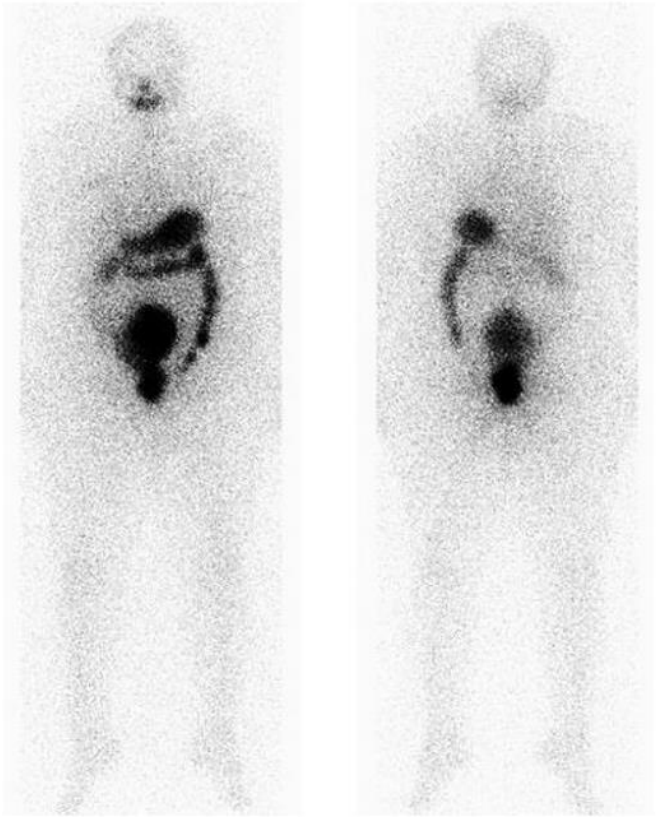


Figure 1: post-therapeutic whole body scanning showing a mild uptake in the neck (thyroid remnants), and a large radioiodine accumulation in the median lower abdomen and pelvis

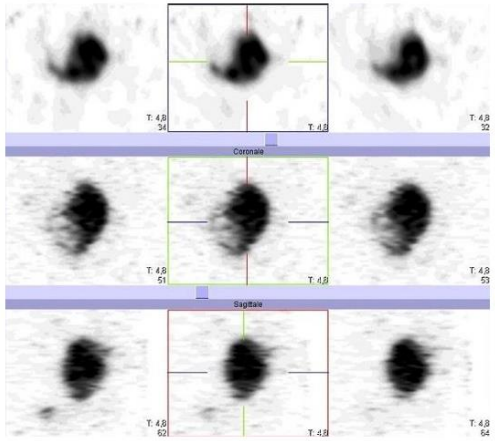


Figure 2: SPECT of the pelvis showing a large and heterogeneous radioiodine accumulation

Figure 3: ultrasonography showing a right adnexal mass measuring 126 mm with a double tissue and cystic components

Mucinous adenocarcinoma of ovary

Shaik R, Hemalatha DS, Rallapeta RP, Sireesha P, Gavini ST, Kalawat T. Pitfalls of Iodine-131 Whole-Body Scan Mimicking Metastases in Differentiated Thyroid Carcinoma: A Case Series. Indian J Nucl Med. 2024 Jan-Feb;39(1):47-51.

THANK YOU