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Importance of fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) in detection of post-thyroidectomy recurrence in differentiated thyroid cancer with negative radio-isotope iodine scan, yet, elevated serum thyroglobulin level

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Abstract

Background: Thyroid cancer considered the 6th common cancer in female and represents approximately 1% of all cancers. Thyroid cancer is generally characterized by good prognosis, long term survival and low aggressiveness. Its prognosis is related to tumor dimensions, extra capsular extensions, the age at diagnosis and distant metastases sites. Combination between positron emission tomography and computed tomography allow anatomic, functional & molecular information.

Aim: To demonstrate Fluorine 18 fluorodeoxyglucose positron emission tomography)/computed tomography role for evaluation of post-thyroidectomy recurrence either local or distant metastatic lesions in differentiated cancer thyroid patients with negative radio-isotope iodine scan, yet showing elevated serum thyroglobulin level.

Procedure: A prospective study included twenty patients with previous history of differentiated thyroid cancer. All patients after history taking and revising the medical sheet underwent Serum Thyroglobulin level & I-131 whole body scan examinations and then Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography study. The findings of Positron Emission Tomography/Computed Tomography imaging compared with results of histopathology or follow-up clinical results as a gold standard.

Results: Fluorine 18 fluorodeoxyglucose positron emission tomography/computed tomography based analysis showed that nineteen true positives and one was true negative as confirmed by the gold standard (Histopathology and clinical follow-up). Thirteen patients had either local recurrence or lymph node metastases without distant metastatic disease, six patients had different distant metastasis. Fluorine 18 fluorodeoxyglucose positron emission tomography/computed tomography based analysis showed that nineteen true positives and one was true negative as confirmed by the gold standard (histopathology and clinical follow-up). The accuracy and sensitivity of Fluorine

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18 fluorodeoxyglucose positron emission tomography/computed tomography (95%) were significantly better than those of the Computed Tomography alone (84.2% and 80%, respectively).

Conclusions: Fluorine 18 Fluorodeoxyglucose positron emission tomography/computed tomography provided a critical role in assessment and management of patients with suspected differentiated thyroid recurrence, presenting with high serum thyroglobulin level and negative radio-isotope iodine scan. It enhances diagnostic accuracy through giving exact anatomical localization of recurrent and/or metastatic tumor foci.

Keywords: Cancer thyroid, Post-thyroidectomy, Thyroglobulin, Fluorodeoxyglucose, Positron emission tomography/computed tomography

Background

Cancer thyroid records for around 1% of all tumor cases & it is the 6th common cancer among females [1].

Differentiated thyroid cancer (DTC) characterized by good prognosis, long survival and low aggressiveness. Its prognosis is identified with tumor measurement, the age at analysis, additional capsular expansion and site of metastases. Distant is uncommon, with occurrence going from 4 to 27% [2].

Patients of differentiated cancer thyroid (DTC) have good prognosis, yet recurrence documented in up to 30% of them [3].

Most patients with cancer thyroid underwent total thyroidectomy concurrent with ablation by radio-active iodine. After treatment has completed patients will undergo regular checkups. Some visits, patients may do laboratory investigations, ultrasound, CT, MRI and radio-isotope iodine study [4].

Generally, serum thyroglobulin (Tg) estimation and I-131 whole body scan (WBS) considered the backbones of DTC standard assessment after treatment and in continued follow-up. In spite of the fact that the I-131 scan show high specificity, but large number of papillary and follicular thyroid carcinoma recurrences are not positive for I-131 uptake. though, an indication is presented by patients with high levels of Tg, yet, lack of recurrent cancer identification with conventional imaging devices, for example, the iodine-131 entire body scan [3].

It has been shown that F-18 FDG uptake illustrate less differentiated thyroid cancer cells or differentiated cells yet impregnable to 131-Iodine treatment. The uptake of F-18 FDG is a poor prognosis [5].

Positron emission tomography (PET) and computed tomography (CT) combination allow functional, anatomic and molecular data. The upsides of this combined system over PET alone have turned out to be self-evident. There is expanding confirmation to recommend that PET/CT includes corresponding data in in staging, re-staging and follow-up in post-thyroidectomy patients, prompting changes in management plans [6].

Aim of the study

To demonstrate Fluorine 18 Fluorodeoxyglucose Positron Emission Tomography)/Computed Tomography role for evaluation of post-thyroidectomy recurrence either local or distant metastatic lesions in differentiated cancer thyroid patients with negative radio-isotope iodine scan, yet showing elevated serum thyroglobulin level.

Methods

A prospective study contained twenty patients distributed from patients under follow up at PET/CT unit and nuclear medicine at Nasser institute oncology centre amid the time from June 2018 till June 2021.

Each patient included within the study has the following:

- Full history.
- Medicinal sheet Reviewing at whatever point accessible.
- **Inclusion criteria**:
  - Histopathologically known differentiated thyroid carcinoma.
  - Thyroid total radio-surgical ablation.
  - I-131 WBS:Negative.
  - Serum Thyroglobulin levels: Elevated (> 10 ng/ml in patients with stimulated TSH level and > 1 ng/ml in patients with suppressed TSH).
- **Exclusion criteria**:
  - Radio-surgical Incomplete thyroid ablation.
  - Positive I-131 whole body scanning.
  - Low thyroglobulin level (< 10 ng/ml in patients with stimulated TSH level and < 1 ng/ml in patients with suppressed TSH).
  - Pathology not DTC (e.g. medullary thyroid or undifferentiated carcinoma).

- FDG PET-CT study was done using a dedicated diagnostic PET-CT scanner (Biograph, True-Point; Siemens).
- All patients fasted for at least four hours before the infusion of 370-555 MBq 18F-FDG. Scanning began after 60-90 min of tracer administration. Glucose in blood levels should not exceed 150 ng/dL. Intravenous contrast agent usually used in patients unless contra indicated. Approximately one hour after the IV injection of the radiopharmaceutical, whole body CT was acquired from skull base to mid-thigh with the arms extended above the head. PET over the same region was performed immediately after acquisition of the CT images.
- CT was acquired for the purpose of anatomic localization, attenuation correction and diagnostic purpose.
- The findings of PET/CT scanning were compared with results of histopathology or clinical follow-up results as a gold standard.

The implementation of ALARA

- Concerns revolving around radiation safety have existed for quite some time, as there's an assumption that every radiation dose, regardless of its magnitude, can produce some level of harmful effects. For example, radiation exposure may result in an increased risk of genetic mutations or cancer. Because of ALARA, practical and cost-effective measures can help provide patients with peace of mind that everything possible is being done to keep them safe and healthy.
- PET/CT imaging users committed to provide an effective ALARA program for all of our patients. We implement the following safety principles to help make ALARA as effective as possible.

We aim to minimize the time spent exposed to radiation

We double the distance between the patient's body and the source of radiation to ultimately reduce exposure by a factor of 4.

We utilize absorber materials to reduce the exposure of beta particles and gamma rays.

Image interpretation

Images were studied at an equipped workstation with fusion software (Syngo; Siemens) that provides multiplanar reformatted images and enables viewing of the PET images, CT images, and fused PET/CT images in any percentage relation. Side-by-side image interpretation was accomplished by two experienced nuclear medicine physicians.

Using the following method of calculation FDG activity at site of concern:

$$\text{SUV} = \frac{\text{Mean ROI activity (MBq/g)}}{\text{Injected dose(MBq)/body weight in gram}}$$

where Mb_q = Mega Becquerel and g = gram.

Considering normal liver FDG uptake as a reference guideline (~ 2.5) & the following FDG SUV parameters in different tissues with.

Tissue	Typical FDG SUV
Lung	0.7
Bone marrow	1.0
Breast	0.5
Liver	2.5
Tumor	>3-4

Statistical analysis was applied on per patient basis and per lesion basis.

The following locations used for anatomic assignment of tumor lesions:

Locally recurrent masses at the operative bed.
Cervical lymphadenopathy.
Distant metastases.
Mediastinal lymphadenopathy.
Pulmonary deposits.
Bone deposits.

Results

Thirteen patients had either local recurrence or lymph node metastases without distant metastatic disease six patients had different distant metastasis.

		Frequency	Percent
Loco-regional recurrence	Local recurrence. only	1	5.2%
	CX LNs only	10	52.6%
	Both	2	10.5%
Distant metastases	Lung metastasis	4	10.5%
	Mediastinal LNs	2	10.5%
	osseous	1	5.2%
	Both	4	14.2%

The accuracy & sensitivity of PET&PET/CT (95%) were significantly better than those of the CT alone (84.2% and 80%, respectively).

Parameter	CT	PET	PET/CT
Sensitivity	84.21	100	100
Specificity	0.00	100	100
PPV	94.12	100	100
NPP	0.00	100	100
Accuracy	80	100	100

FDG PET/CT based analysis reviewed that nineteen true positives and one was true negative as confirmed by the gold standard (Histopathology and clinical follow-up).

Parameter	CT	PET	PET/CT
True positive	16	19	19
True negative	0	1	1
False positive	1	0	0
False negative	3	0	0

Discussion

Thyroid carcinoma is the sixth common malignancy in female and records for around 1% of all cancers [1].

Differentiated cancer of the thyroid (DTC) is characterized by good outcome, long time survival and low aggressiveness. Its prognosis is related to tumor measurement, the patient's age at time of diagnosis, additional capsular extension & distant metastatic deposits. Distant metastases moderately uncommon with rate running from 4 to 27% [2].

The vast majority determined to have thyroid malignancy underwent total thyroidectomy followed ablation by radio-active iodine. Following treatment has been completed patients will have regular check-ups. Some visits, patients may do laboratory investigations, ultrasound, CT, MRI and radio-isotope iodine study [4].

The thyroglobulin is fundamentally utilized as a tumor marker to assess the outcome of treatment for cancer thyroid & to screen for recurrence. Not all thyroid malignancies will produce thyroglobulin, but most widely recognized types are papillary and follicular thyroid cancer, frequently do, bringing about expanded levels of serum (TG) level. The level of thyroglobulin might be identified with tumor lesion, classification of differentiation and regions of metastasis. Low level of Tg (1 ng/ml or less); results in a sensitive test, whereas higher cut-off levels give a greater specificity at the onus of decreasing sensitivity in detection of recurrent carcinoma. Thyroid suppression & withdrawal of suppression enhances the serum thyroglobulin levels. Thyroglobulin detection is the only screening test for cancer thyroid recurrence in patients with low risk & no recurrence evidence before I-131 scan [7].

I-131 whole body scan had been at the focal point of detection of recurrent cancer thyroid; it distinguishes iodine-avid cancers & is insufficient in undifferentiated lesions. Another advantage of I-131 WBS over the other follow up imaging modalities is its capacity to clarify distant metastasis. Similar to Thyroglobulin, I-131 turns out to be much more sensitive after thyroid suppression withdrawal & stimulation of thyrotropin [7].

The differentiated cells of cancer thyroid after total thyroidectomy &radioiodine ablation may develop a transformation process in which losing all their capacity to absorb and hold 131-iodine, yet regardless they hold the capacity to retain FDG [7].

As of late announced, the loss of I-131 take-up in recurrences depends not just on an abatement in vitality subordinate transport interceded by the Na + /I-symporter (NIS) gene but potentially on a decrease in the particles managing its metabolism intracellularly. In addition, high glucose transporter type1 (GLUT-1) gene expression underpins the utilization of PET with particular tracers within the clinical administration of such carcinomas [2].

The role of F-18 FDG PET/CT in differentiated cancer thyroid is entrenched, especially in patients presented with high thyroglobulin measures and negative (WBS). It has been shown that F-18 FDG uptake reveals less differentiated cancer thyroid cells or dedifferentiated cells and PET positive lesions are more liable to be resistant to 131-Iodine treatment. The take-up of F-18 FDG is identified with tumor estimate, invasion of the capsule and histological variations with a poor prognosis [5].

Combination between (PET) (CT) permit anatomic, functional & molecular date. The upsides of this combination over PET alone have turned out-obvious. There is expanding proof to recommend that PET/CT includes corresponding data in staging, re-staging and follow-up in post-thyroidectomy patients, prompting changes in treatment plans [6].

The sensitivity of utilizing FDG PET/CT in the recognition of thyroid cancer is very high and show more accuracy than other imaging modalities as it is fit for of differentiating between tumors, fibrosis, scars and necrosis [9].

Additionally PET/CT pictures of the whole body could show uptake at abnormal areas indicating the spread of the thyroid malignancy to lymph nodes, bones, lungs, or CNS [9].

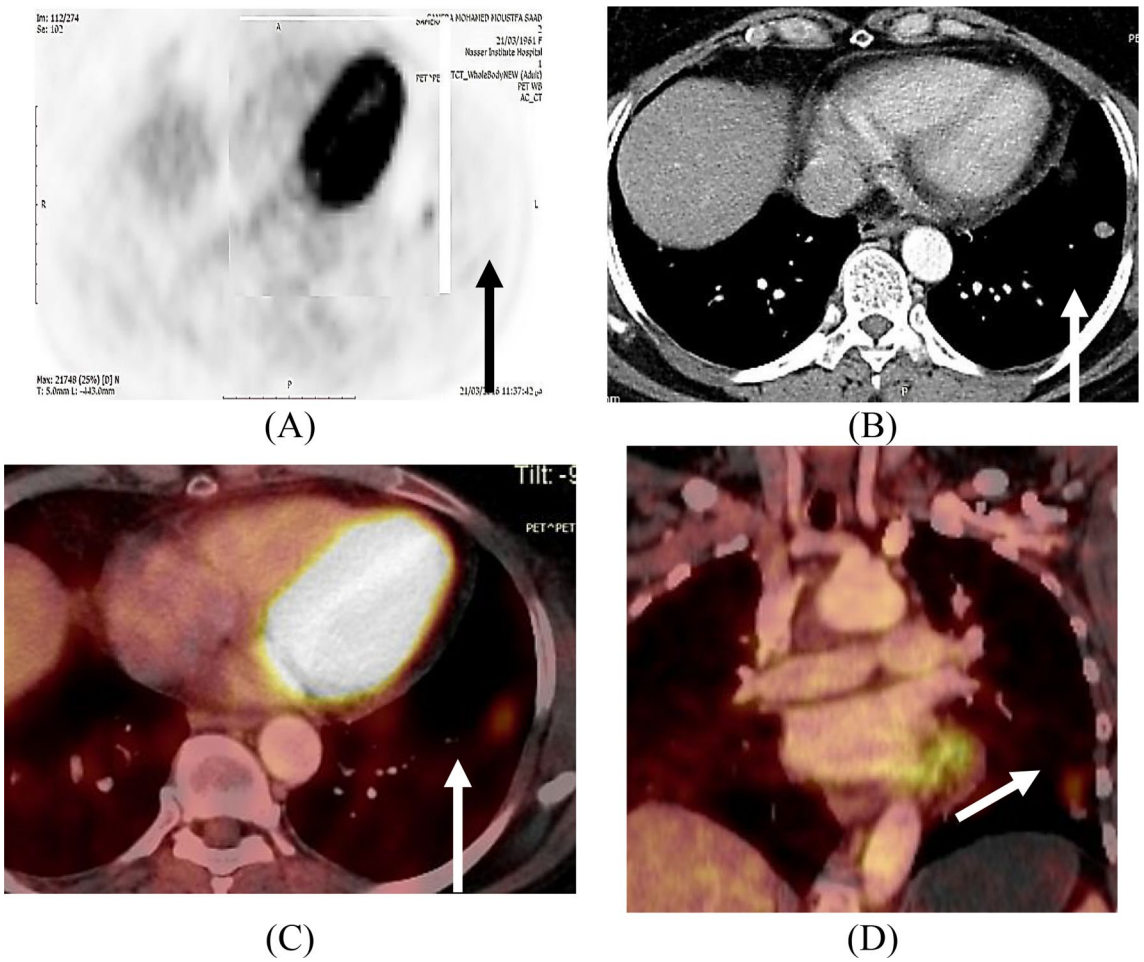

Fig. 1 A fifty years old female patient, diagnosed with multi-centric papillary differentiated cancer thyroid,underwent total thyroidectomy, followed by 120 mCi RAI-131 ablation for. At follow up thyroglobulin level elevation 15 mg/dl detected, Iodine whole body diagnostic scan and ultrasound of the neck were negative, PET/CT was done and showed solitary small sized left lower lung lobe pulmonary nodule SUVmax ~ 11.8. Which ensure the metastatic nature of this lesion. Axial PET only (**a**), CT (**b**) Axial & Coronal fused PETCT images (**c**, **d**) showed pulmonary nodule (Arrows)

Aim of the work

The combination of the metabolic and morphologic data in PET/CT could expand the indicative diagnostic accuracy, lessens pitfalls and changes therapeutic strategies in an impressive of patients [10].

Studies on the importance of 18F-FDG PET for DTC have focused on patients with negative radioiodine scan & expansion of TG level. It has been demonstrated that 18F-FDG PET is the most accurate strategy in such circumstance, and sensitivities and specificities go somewhere in the range of 85% and 94%. for treating iodine-negative tumor tissue, surgery is the only curative therapy healing treatment alternative; subsequently correct limitation of 18F-FDG tumor foci is obligatory for effective removal of disease in these cases [9, 10]. In our study, FDG PET/CT demonstrated to have a critical part in patients with suspected differentiated thyroid recurrence, presenting with high serum thyroglobulin level and negative radi-isotope iodine scan. The co-enlisted 18F-FDG PET/CT enhances diagnostic accuracy through giving exact anatomical localization of recurrent and/or metastatic tumor foci [8].

The overall specificity and sensitivity in our study for the detection of tumor itself by 18F-FDG PET/CT per individual patient were 100%, and so with a diagnostic accuracy of 100% also. Comparison between CT alone & PET/CT in our study clearly demonstrated that both accuracy & sensitivity of PET/CT (100%) were obviously

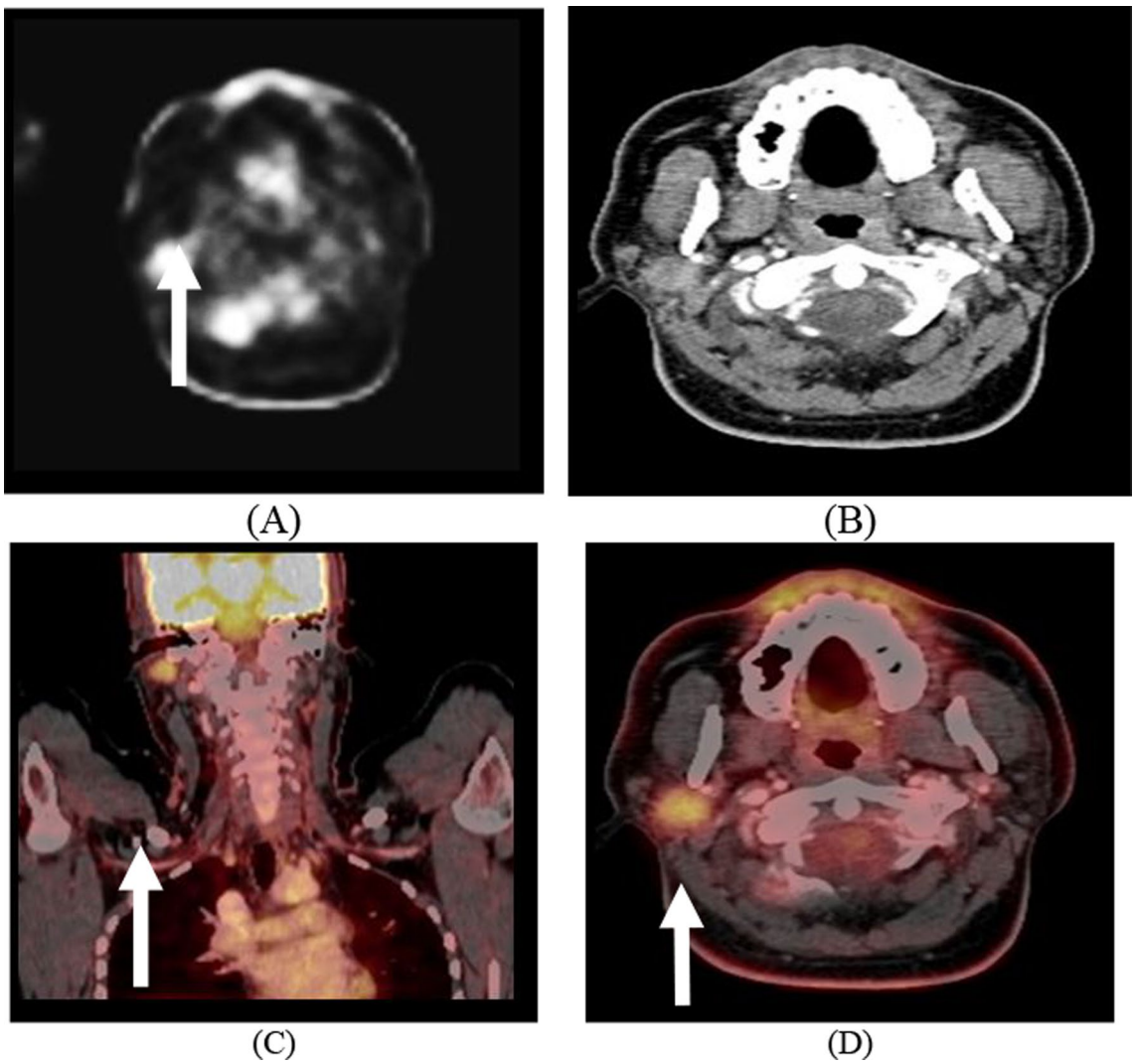

Fig. 2 A twenty seven years old male patient, diagnosed with papillary differentiated cancer thyroid. underwent total thyroidectomy, followed by 120 mCi RAI-131 ablation. Follow up negative iodine whole body scan done 1 year later, inspite of elevated thyroglobulin level (= 12 mg/dl). PET/CT was done and showed right retro-mandibular/pre-auricular soft tissue nodule (nodal) with SUVmax ~ 7.2. Axial PET only (**a**), CT (**b**) Axial & Coronal fused PETCT images (**c**, **d**) showed right retromandibular/retro-auricular soft tissue lesion/Lymph node (Arrows)

higher than those of CT alone (85.7% and 44.5%, respectively) with a significant difference of (P = 0.03) [9].

Conclusion

18F-FDG PET/CT play a role in patient with differentiated cancer of thyroid, specifically those show elevated serum thyroglobulin level and negative iodine 131 scan. Applying 18F-FDG PET/CT together provide definite anatomical localization of recurrent and/or metastatic carcinoma of the thyroid, improving the diagnostic accuracy. Combined 18F-FDG PET/CT has a higher accuracy and sensitivity than those of CT or PET alone, as regard as the loco-regional nodal cervical metastases as well as the distant metastasis deposits (Figs. 1, 2, 3).

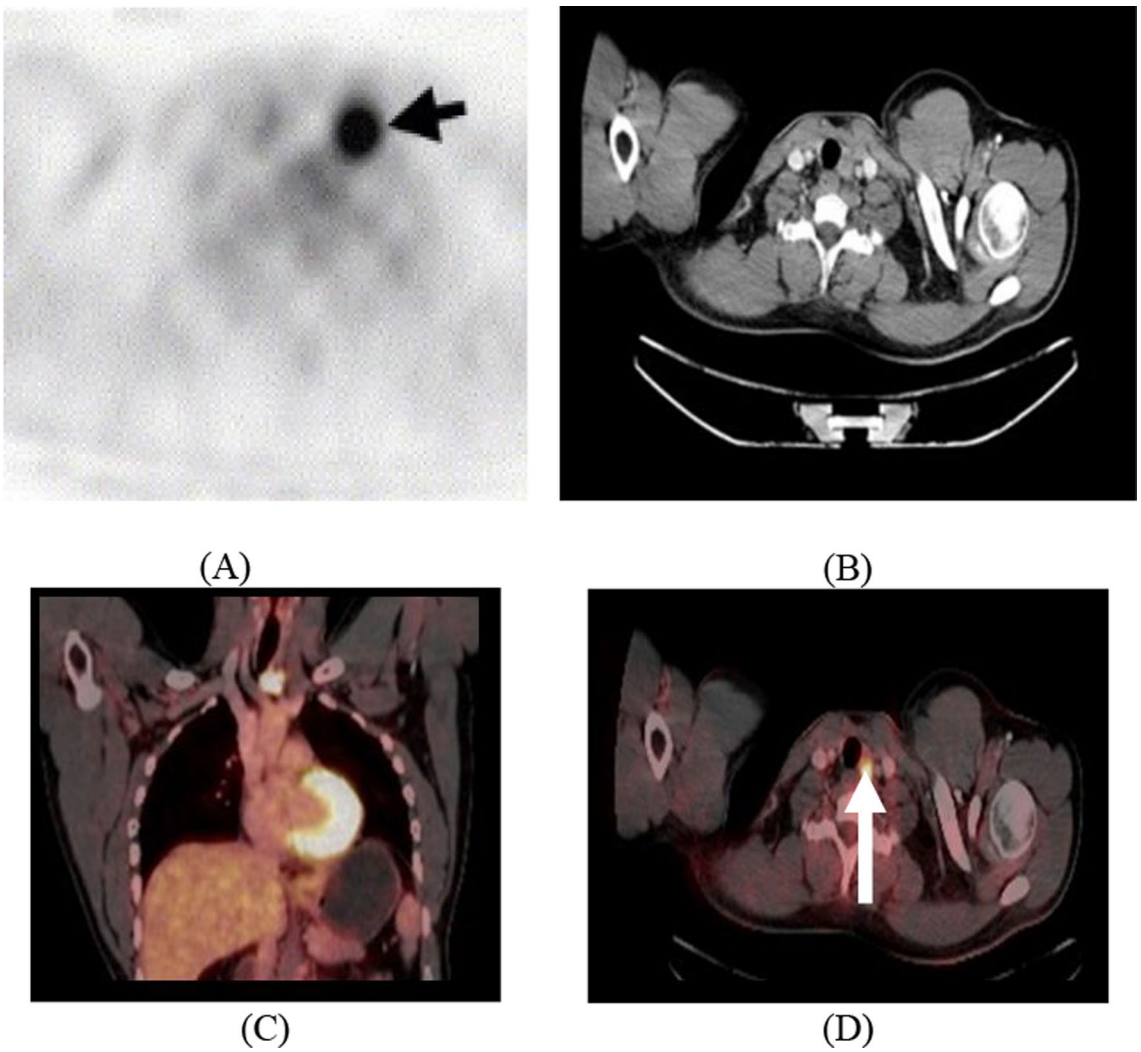

Fig. 3 A seventy years old female patient, diagnosed with follicular differentiated cancer thyroid. Underwent total thyroidectomy, followed by 100 mCi RAI-131 ablation. Follow up iodine whole body scan was negative,yet, elevated thyroglobulin level (= 15.5 mg/dl). Ultrasound of the neck showed operative bed ill-defined soft structure of indeterminate sonographic nature, PET/CT demonstrates operative bed soft tissue lesion with increased activity (SUV ~ 4) denoting operative bed local recurrence. Axial PET only (**a**), CT (**b**) Axial & Coronal fused PETCT images (**c**, **d**) show operative bed soft tissue lesion

Abbreviations

AJCC: American joint committee on cancer; ATA: American thyroid association; CNS: Central nervous system; CT: Computed tomography; CXLN: Cervical lymph nodes; CXR: Chest X-ray; DTC: Differentiated thyroid cancer; Dx-WBS: Diagnostic whole body scan; F-18 FDG: Fluorine 18-fluoro-deoxy glucose; FDG: Fluoro-deoxy glucose; FNAC: Fine needle aspiration cytology; LN: Lymph node; MBq: Mega Becquerel; mCi: Milli-curies; MRI: Magnetic resonance imaging; mU: Milli unit; PET: Positron emission tomography; PTC: Papillary thyroid carcinoma; PTMC: Papillary thyroid micro-metastases; Px-WBS: Post-therapy whole body scan; RAI-131: Radio-active Iodine 131; SUV: Standardized uptake value; TG: Thyroglobulin; Tg-Ab: Thyroglobulin antibodies; TSH: Thyroid Stimulating Hormone; US: Ultrasound; WDTC: Well differentiated thyroid cancer; μCi: Micro-curies.

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Author contributions

AF wrote the manuscript and collected patient data and is responsible for correspondence to the journal. AF is the author of the research idea. HK participated in the design and review of the study. AF participated in the design and review of the study. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Department of Radiology, Benha Faculty of Medicine Research Ethics Committee, University of Benha, Egypt (ethics committee reference number is not available). A written consent was obtained from each patient involved in this research before performing the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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