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Sub-segmenting Metastatic Thyroid Carcinoma into specific groups by Molecular functional imaging features: evolving Individualized Treatment Strategies, with emphasis on TENIS

Authors:

Sandip Basu

Rahul Vithalrao Parghane

Institutions where the work was performed:

Radiation Medicine Centre (BARC), Tata Memorial Hospital Annexe, Parel, Bombay 400012, India.

Reprint requests/Correspondence Address: Dr Sandip Basu, RADIATION MEDICINE CENTRE, Bhabha Atomic Research Centre, Tata Memorial Hospital Annexe, Jerbai Wadia Road, Parel, Bombay 400 012. Email: drsanb@yahoo.com

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Abstract

The process of radioiodine refractoriness, de-differentiation and development of TENIS (radioiodine [RAI] negative and elevated thyrogloblin differentiated thyroid cancer [DTC]) in metastatic differentiated thyroid carcinoma (DTC) could be viewed as a "disease continuum" rather than a single event or an "all or none" phenomenon. In this invited perspective, the important role of molecular functional imaging (MFI) in systematically exploring the disease biology and course of metastatic DTC is presented. Making this as the base, this report proposes a novel clinical classification for TENIS syndrome with a view of individualized treatment strategies using molecular functional imaging (MFI). Such endeavour, in authors' view, would aid in classification into subgroups and development of an individualized treatment strategy for each, thereby resulting in a personalized management model for patients of metastatic DTC. Case illustrations are presented that substantiate the viewpoint including the value of combined assessment in selected cases and the requirement of multi-pronged treatment approach for certain specific case scenarios. In addition to multiple other considerations, the authors believe that MFI based characterization of metastatic lesions could evolve as an important determinant for defining the optimal treatment strategy in patients of metastatic DTC and making the clinical management more rational and scientific.

Introduction

The optimal treatment strategy for patients of metastatic differentiated thyroid cancer encompasses multi-factorial considerations such as site and size of the metastatic lesions, radioiodine uptake in the lesion, tumour histology, patient characteristics, clinical status and symptoms. The overall response and final outcome has been a function of these factors, although, the clinical behaviour, disease course and the final outcome varies considerably between two individuals even with matched anatomical features of the metastatic lesions.

The management of patients with elevated serum thyroglobulin and negative radioiodine scintigraphy (TENIS) has been a topic of considerable interest and debate amongst the attending physicians and is emphasized in recent years particularly in view of the poor outcome, challenges associated and the absence of a definitive consensus on management (1-4). The management continues to evolve at present, with a number of routine and investigational therapeutic approaches being continuously explored with respect to their place and efficacy in this challenging clinical situation including the role of empirical 131I therapy and whether such therapy is justified (1-4). It is imperative that with more critical look into this entity, an individualized treatment approach would be adopted, with the broad group being divided into various smaller segments based upon the lesional characteristics both from clinico-pathological and molecular imaging features.

In this present communication, we explored the spectrum of metastatic DTC and TENIS with the multitracer molecular imaging to demonstrate the potential of this modality in sub-segmenting them into various subgroups and targeting individualized management approach for each. This in our view would aid in more rational and scientific approach for these groups of patients. Special emphasis on dedifferentiation and TENIS has been made and decision-tree type classification and risk stratification is proposed along with predictive personalized management strategies.

[A] Metastatic Differentiated Thyroid Carcinoma with fewer lesions demonstrating radioiodine uptake: Need for adopting a combined comparative diagnostic and a multipronged treatment approach

Patients with differentiated thyroid cancer (DTC) and elevated thyroglobulin/negative radioiodine scintigraphy (TENIS) have been often construed as an "all or none phenomenon" in clinical parlance of thyroid cancer practice. However, from theoretical standpoint and also from the management viewpoint, they should be ideally viewed as a "disease continuum" considering the fact that the process of de-differentiation of the metastatic DTC lesions is a progressive phenomenon that may evolve over months. Hence, in practice, a subset of metastatic DTC patients could be encountered (though not commonly), whose lesions are in this interim phase of evolution of dedifferentiation. In the first case illustration, the disease biology and progression of such a patient of DTC is illustrated, in whom part of the metastatic lesions showed radioiodine uptake, while others did not.

Case 1. The patient was a 62 year old male, diagnosed case of papillary carcinoma of thyroid with bilateral lung metastasis who was treated with multiple doses of radioiodine therapy (with cumulative dose of 485 millicurie or 17945 MBq till date). The last two years' radioiodine large dose scan continued to shows iodine positive lesions in both lungs. 18F-FDG PET/CT in 2013 also showed 18F-FDG positive lesions in bilateral lungs; right lung involvement was more than left (the entire right hemothorax had multiple pleural based nodules), the lesions were more numerous compared to that observed on the previous diagnostic and post-treatment radioiodine planar scans (Fig 1A and 1B respectively) and SPECT (Fig 1C). In 2014, the follow-up 18F-FDG-PET/CT (Fig 1E-F) demonstrated substantial disease progression in both lung but more prominent on the right side. Serum thyroglobulin was more than 300 ng/ml on both the occasions. Hence, the alternative additional treatment modalities were sought for: from the nature of involvement it was inferred by the radiation oncologist that the patient is unlikely to benefit from palliative radiotherapy to right chest wall and was considered

for treatment with tyrosine kinase inhibitor sorafenib 400 mg twice daily after clinical evaluation of the fitness. At 2 months following therapy the dose was reduced to 75% in view of hand foot syndrome. At 5 months, he is now under observation with daily sorafenib.

Management Rationale: In the aforementioned case discussion, therefore, we come across a group of patients with partial de-differentiation of metastatic lesions, where the requirement of multimodality treatment is underscored. While I-131 therapy could be one possible approach, intended primarily for the radioiodine positive lesions; the 18F-FDG avid (and radioiodine negative) metastatic lesions, on the other hand, could behave in an aggressive fashion and unlikely to benefit or stabilize from I-131 therapy alone. Hence, radioiodine therapy cannot be the sole management approach in these patients unlike those where all metastatic lesions demonstrate radioiodine uptake. Taking this into consideration, the optimal therapeutic strategy need exploration of a multi-pronged approach with existing routine (e.g. external radiotherapy where indicated) and investigational approaches (such as tyrosine kinase inhibitors e.g. sorafenib and lenvatinib or peptide receptor radionuclide therapy with ^{177}Lu based somatostatin receptor analogues, if they demonstrate adequate uptake in diagnostic studies with ^{68}Ga-DOTA-NOC/TATE PET/CT), decided based upon the lesional characteristics.

The choice and sequence of the therapies in the combined approach is an issue that needs decision in multidisciplinary meetings and would need prospective studies for further clarification. Administration of I-131 therapy before the other approaches is the usual rational choice in order to maximize the benefit of this targeted therapy with minimal adverse effects.

[B] TENIS with progressively increasing 18F-FDG-PET/CT depicted lesions demonstrating 68Ga-DOTATATE avidity

Case 2. A 48 year old female patient, diagnosed to be follicular variant of papillary carcinoma thyroid with poorly differentiated component, had undergone total thyroidectomy followed by radioiodine ablative therapy with post-treatment scan (PTS) only demonstrating neck focus and rest of the whole body unremarkable. The patient presented 3 years later with neck recurrence (USG neck showing metastatic left level IV cervical lymphadenopathy), for which she underwent nodal resection. She presented 2 years later with rising thyroglobulin levels and negative radioiodine scintigraphy. 18F-FDG-PET/CT demonstrated abnormal foci in right lung (infrahilar region) and bilateral axillary lymph nodes (biopsied and as diagnosed to be metastatic poorly differentiated thyroid carcinoma), the patient received empirical radioiodine therapy of 200mCi and the PTS was negative. She was observed on levothyroxine suppression, the subsequent follow-up 18F-FDG-PET/CT showed increase in size and uptake in the lung lesion and further increased serum Thyroglobulin level (135.7 ng/ml). A ^{68}Ga-DOTATATE PET/CT showed tracer uptake in the axillary lymph nodes and lung lesions **(Fig 2)** and the patient planned for PRRT in view of increasing metastatic lesions on PET-CT, though she was clinically asymptomatic.

Management Rationale: In this diagnosed case of TENIS, the disease burden was relatively less and the patient was asymptomatic, though the lesions showed an increase in the 6 month follow-up 18F-FDG-PET/CT. Empirical radioiodine was of no benefit and no abnormal disease focus noted in the PTS. She was counselled on available options and she opted for PRRT.

Czepczyński et al (5) undertook a retrospective analysis of 11 patients of TENIS who received PRRT with four doses of 90Y-DOTA-TOC. RECIST criteria and Thyroglobulin value were used in this study for response evaluation. Median survival was 21 months from the first course of PRRT. Only minor and transient hematological

toxicity was observed in some patients. They conclude that PRRT is generally well-tolerated and may be a valuable option for some patients with radioiodine-refractory DTC. In our own study by Jois et al (6), we observed that avid uptake on Ga-DOTATATE PET-CT/Tc-HYNIC-TOC scintigraphy in non-I-concentrating metastatic differentiated thyroid cancer is observed in a relatively low fraction of patients, in this series 3 out 19 had high enough uptake score (i.e. grade III and IV), that could favor the feasibility of Lu-DOTATATE therapy. Also, interestingly, it was observed that the chromogranin A level was increased in 3 patients with intense tracer uptake which could suggest a possible neuroendocrine differentiation in the affected tissues leading to the expression of chromogranin A with SSTR-avid expression in DTC with non 131I avid cases.

PRRT is expected as a next treatment option of RAI in TENIS, but the data regarding the efficacy of PRRT for DTC supposed insufficient in the present circumstances. With regard to the states of PRRT for DTC, further investigation is warranted.

[C] TENIS with 18F-FDG-PET/CT concentrating metastases that are ^{68}Ga-DOTATATE non-avid/minimally concentrating

Case 3. A 55 yr male, diagnosed case of papillary carcinoma of thyroid had undergone total thyroidectomy, central compartment clearance and right modified neck dissection in 2011 with histopathology suggestive of papillary carcinoma thyroid with lymph node metastasis; the patient received radioiodine total thyroidectomy and PTS showed only neck focus. Four years after this, he presented with left supraclavicular lymphadenpathy: the FNAC from the lymph node demonstrated metastatic PCT. 18F-FDG-PET/CT demonstrated intense 18F-FDG uptake in multiple cervical, supraclavicular, mediastinal lymphadenopathy and lung nodules, while radioiodine scan was negative. A trial of redifferentiation therapy with retinoic acid was unsuccessful with radioiodine scan negative and the serum stimulated Thyroglobulin at

this instant was 273 ng/ml. ^{68}Ga-DOTATATE PET-CT demonstrated faint tracer uptake in the 18F-FDG avid lesions, hence PRRT was not an option. The patient is being followed up with 18F-FDG-PET/CT to observe the lesional progress/symptoms and will be considered for tyrosine kinase inhibitors should the metastatic lesions demonstrate a fast increase.

Management Rationale: In a patient of TENIS, large volume and rapidly progressing symptomatic disease, the definition criterion of which yet to be finalized, are indications for considering oral tyrosine kinase inhibitors. Our experience with redifferentiation therapy with Retinoic acid has not been gratifying to recommend its routine use in patients of TENIS.

We must mention here that for painful non-iodine concentrating skeletal metastases external beam radiotherapy (EBRT) is a frequently considered option in practice, though it is not suited for patients with pulmonary metastases. Romesser et al (7) studied 66 patients with gross residual/unresectable non-anaplastic non-medullary thyroid cancer were treated with EBRT. They concluded that, EBRT is a safe and effective treatment modality with greater than 85% locoregional control in patients with non- metastatic disease and 90% locoregional control in patients treated with concurrent chemotherapy. Similarly, Sun et al (8) suggested adoption of this approach to elderly patients, massive primary disease, extensive extracapsular spread and macroscopic iodine-negative components inconsistently indicate) patients. They concluded that, intensity modulated radiation therapy (IMRT) offers clear dosimetric advantages on tumor coverage and organ sparing such as the larynx, thus reducing late toxicities to less than 5%.

[D] TENIS with normal 18F-FDG-PET/CT: implications for Disease Prognosis

Case 4. A 22 yr female patient, known case of papillary carcinoma of thyroid with lymph node metastasis, who was earlier treated with total thyroidectomy with nodal

dissection and radioiodine ablation, presented with elevated serum Thyroglobulin (stimulated thyroglobulin 55 ng/ml) and negative radioiodine scintigraphy. The USG (Neck) was normal and the whole body 18F-FDG-PET/CT was negative for any anatomical disease. The patient was decided to be observed and follow up with annual USG (Neck) and 18F-FDG-PET/CT.

Management Rationale: In our experience, negative 18F-FDG PET in the setting of elevated serum Thyroglobulin level forecasts favourable disease prognosis and long progression free survival.

One, in the setting of TENIS, would need to look critically the post-treatment scan (PTS) before designating a case as TENIS. Not infrequently, where I-131 is used for diagnostic scan small focus may be missed which becomes obvious on PTS (4).

Case 5. A 56 year male patient of Papillary Carcinoma of Thyroid diagnosed in 2012, had undergone total thyroidectomy and nodal dissection in 2012 followed by radioiodine ablation. He presented recently with serum thyroglobulin of 205 ng/ml, which increased to 300 ng/ml following TSH stimulation during follow-up, while the diagnostic I-131 whole body scan was negative for any obvious disease focus. A 18F-FDG-PET/CT (non-contrast) showed a tiny left lung nodule (Fig 5): she was considered for empirical I-131 therapy and the PTS showed tracer activity in left thoracic region corresponding to the 18F-FDG-PET/CT depicted lesion (Fig 5).

[E] Aggressive tumor biology of a particular metastatic lesion predicted by dual tracer MFI features:

Typically, a "flip-flop" has been described between radioiodine scan and 18F-FDG-PET with regard to the DTC metastases, though the feasibility of concurrent 18F-FDG and radioiodine uptake has been reported subsequently, with avid 18F-FDG uptake in the metastatic lesions being postulated to be an important adverse prognostic factor over the recent years (9, 10, and 11). The use of 18F-FDG-PET/CT in radioiodine

concentrating metastatic DTC is not advocated on a routine basis at present. However, a dual tracer evaluation (with radioiodine and 18F-FDG-PET) can provide valuable information with respect to the future course of a particular lesion **(Case 6).**

Management Rationale: The prognostic value of 18F-FDG-PET for DTC is often controversial, but intense 18F-FDG uptake generally regarded as an indicator of progression. Also, the advantage of 18F-FDG-PET, compared to other risk factors, is capability of assessing lesion heterogeneousness.

Case 6. A 66-year-old female, diagnosed patient of differentiated thyroid carcinoma (DTC) with extensive skeletal metastases throughout the body, presents with progressively increasing scalp lesion (Fig 6a-c) and had been treated with I-131 therapy two times previously. The whole body 18F-FDG-PET (Fig 6a), in contrast to the radioiodine scan, demonstrated solitary focus of abnormal uptake corresponding to the scalp lesion with none of the other skeletal metastatic disease showed any 18F-FDG uptake. Interestingly, a review of the previous PTS showed relatively low uptake in the scalp lesion, compared to other lesions, suggesting a heterogeneous behaviour of this particular metastasis compared to the rest.

Management Rationale: A heterogeneous behaviour of one or few metastatic lesions compared to the rest is possible and the high 18F-FDG uptake would suggest an aggressive biology of those lesions. Special emphasis needs to be given to these lesions for management with other modalities as they would likely give rise to radioiodine refractory clones in the due course of the disease. A neurosurgical opinion was taken for this particular progressively increasing lesion but was denied in view of widespread metastases.

[E] 18F-FDG uptake as a determinant for forecasting outcome in Radioiodine Avid Metastatic lesion

Case 7. A 56 year old male diagnosed with follicular variant of papillary thyroid carcinoma (FVPTC) with lung and mediastinal nodal metastasis had undergone total thyroidectomy and lymph node dissection. He received multiple therapeutic doses of I-131 upto a cumulative dose of 1 Ci, though the disease persisted and stimulated Thyroglobulin was 300 ng/ml. An 18F-FDG-PET/CT demonstrated 18F-FDG avid disease foci in all the mentioned metastases **(Fig 7)** which could be indicative of their radioiodine refractoriness.

Case 8.

A 51 year old male diagnosed with FVPCT with nodal, skeletal and pulmonary metastases in 2014, had undergone total thyroidectomy with bilateral neck dissection; the whole body 18F-FDG-PET was negative. He was treated with radioiodine therapy of 250 mCi (9250 MBq), the PT scan demonstrating uptake in the neck, lung lesions and rib lesion. The 6-month follow-up scan showed response in the whole body radioiodine scan was negative for any disease and stimulated serum thyroglobulin reduction from 200 ng/ml to 0.26 ng/ml (Fig 8a-c). The negative ^{18}F 18F-FDG PET/CT in this patient (Fig 8c) was commensurate with excellent response and favourable outcome in this patient.

Conclusion

Overall, the present illustrative communication provides a thoughtful analysis of the need for individualized treatment regimens for patients with metastatic thyroid carcinoma and TENIS. The current therapy provided in the field is far from ideal with various approaches suggested including by our group [4]. This article used a gamut of representative cases, where molecular functional imaging was used as a method of metastatic lesion characterization for sub-classification of patients and treat each sub group differently forming the basis for a variety of individualized treatment regimens.

The authors believe such argument for individualized treatment and better stratification of these patients would be valuable information to better and systematize the management of thyroid carcinoma and also to develop a clinical algorithm in the future.

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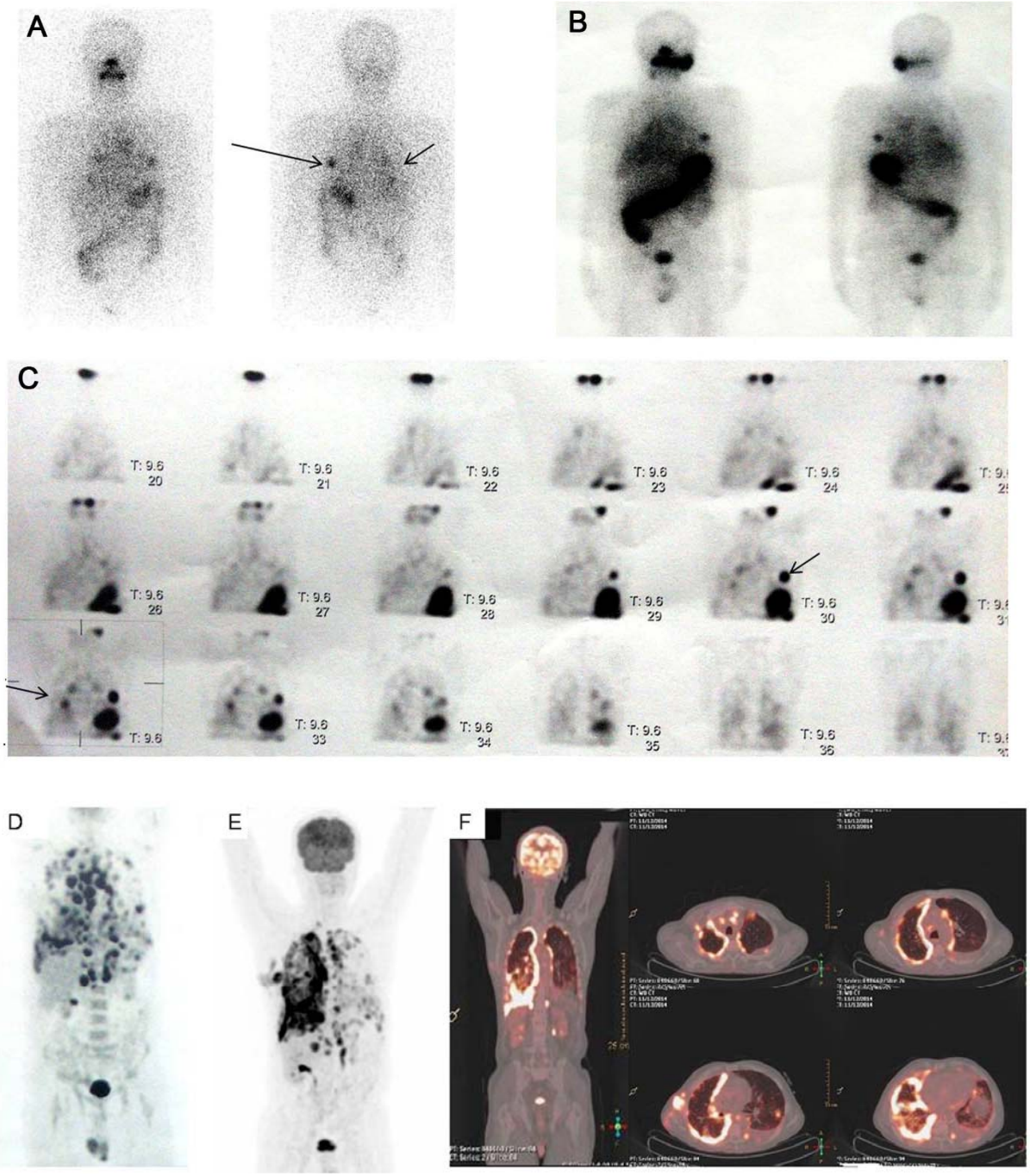

Fig 1. The diagnostic radioiodine scan (Fig 1A-C) in both 2013 and 2014 showed some iodine avid foci in bilateral lungs, though the lesions demonstrated on FDG-PET/CT (Fig 1D) were much more than that on iodine scan, demonstrating multiple metabolically active foci in bilateral lungs, pleurae as well as the mediastinal foci. The

lesions demosntrated in the post-treatment I-131 scan (Fig 1B and 1C: planar and SPECT) also was similar to what was observed in the diagnostic radioiodine study (Fig 1A). Comparative FDG-PET/CT 1 year previously (Fig 1D: left panel) and the present one (Fig 1E-F: right panel) demonstrating progressive disease. Serum thyroglobulin was more than 300ng/ml on both the occasions. The patient has been started on tyrosine kinase inhibitor (sorafenib) based upon progressive symptomatic disease on FDG-PET/CT.

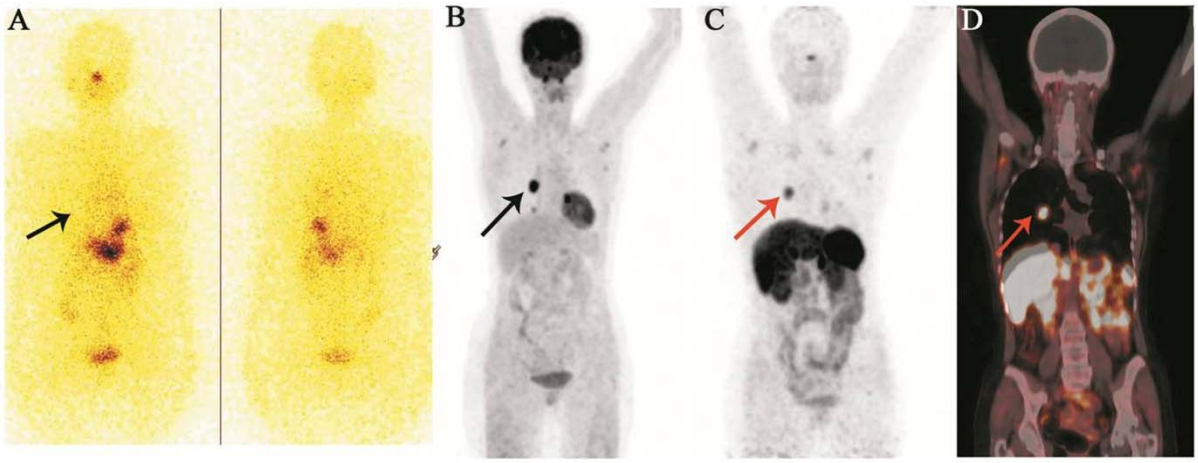

Fig 2. Whole body ^{131}I diagnostic scintigraphy (A), ^{18}F FDG PET/CT scan MIP(B), ^{68} Ga DOTATATE scan MIP (C) and coronal fused image (D) in this known case of FVPCT showing no abnormal tracer activity in thoracic region in radioiodine scan (A, black arrow), FDG avid lesion (B, black arrow) and somatostatin receptor avid lesion (C and D, red arrow) in thoracic region and the axillary nodes.

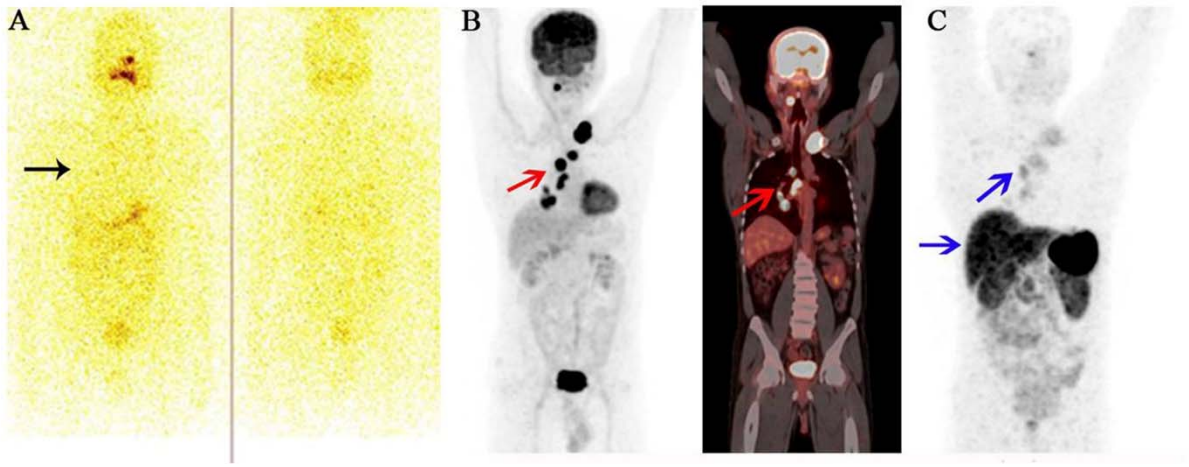

Fig 3. Whole body ^{131}I diagnostic scintigraphy(A), ^{18}F FDG PET/CT scan MIP and coronal fused images (B) ^{68} Ga DOTATATE scan MIP (c) of known case of papillary ca thyroid patient with raised serum thyroglogulin level shows no abnormal tracer activity in thoracic (A, black arrow)and neck regions, intense FDG activity seen in thoracic (B, red arrow), left supraclavicular and right upper parapharygeal region on ^{18} F FDG PET/CT(B), whereas ^{68} Ga DOTATATE scan MIP (C) show faint tracer activity in these region as compared to liver (C, blue arrow)

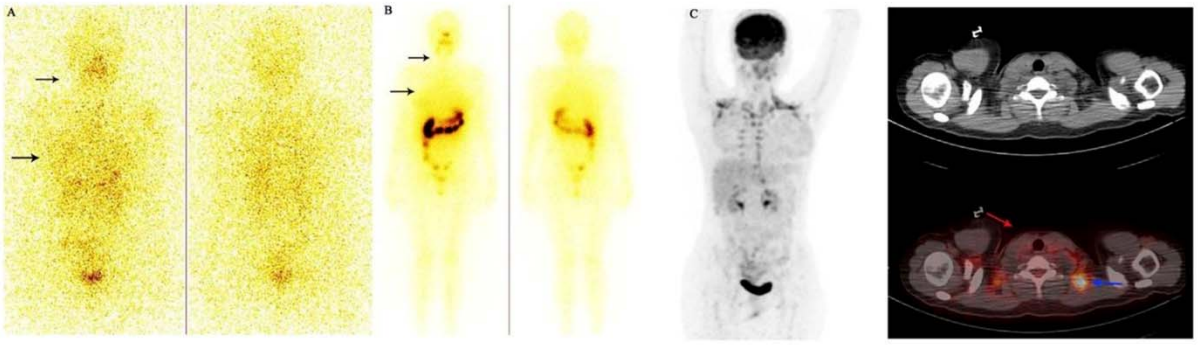

Fig 4. Whole body ^{131}I diagnostic scintigraphy(A), post therapy (radioiodine ablation) scintigraphy(B), ^{18}F FDG PET/CT scan(C) in known case of PCT with raised serum thyroglobulin level show no abnormal tracer activity neck and thoracic regions in whole body ^{131}I diagnostic scintigraphy (A, black arrow), post therapy scan (B, black arrow) and also in ^{18}F FDG PET/CT scan(C, red arrow). FDG PET/CT show brown fat uptake in neck (C, blue arrow).

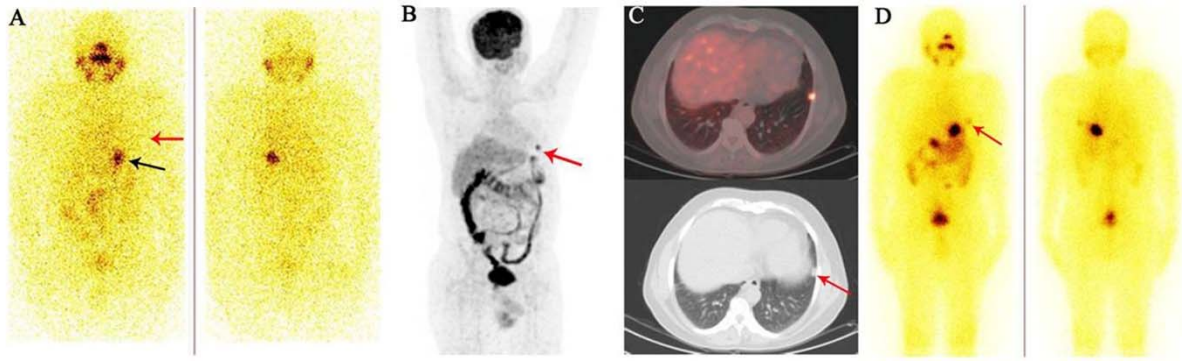

Fig 5. Whole body ^{131}I diagnostic scintigraphy(A), ^{18}F FDG PET/CT scan MIP(B), axial images (C), post therapy (radioiodine ablation) whole body scintigraphy (D) in known case of PCT with raised serum thyroglobulin level. Whole body ^{131}I diagnostic scintigraphy show physiological tracer activity in stomach(A, black arrow) and no abnormal tracer activity in thoracic region, whereas FDG activity seen in left lung nodule (B and C, red arrow) and also post therapy scan show tracer activity in left thoracic region(D, red arrow).

Fig 6A. The whole body fluorodeoxyglucose positron emission tomography FDG-PET demonstrates no FDG uptake in any of the metastatic lesions in the skeleton except for the scalp lesion. (for which the patient presented to the clinic) [Reproduced with permission[11]]

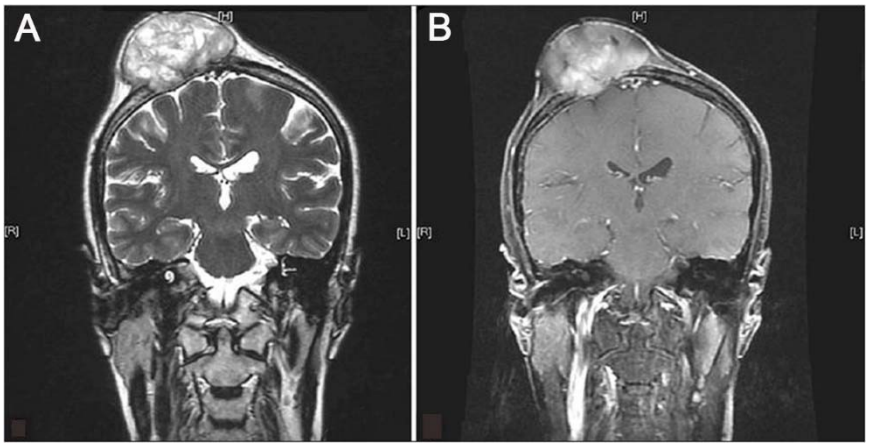

Fig 6B. Coronal magnetic resonance MR (a) T2-weighted and (b) post.contrast images demonstrating hyper intense. (on T2-image) well defined invasive and heterogeneously enhancing soft tissue lesion involving both the tables of skull and reaching up to dural lining but, remains extra axial [Reproduced with permission[11]]

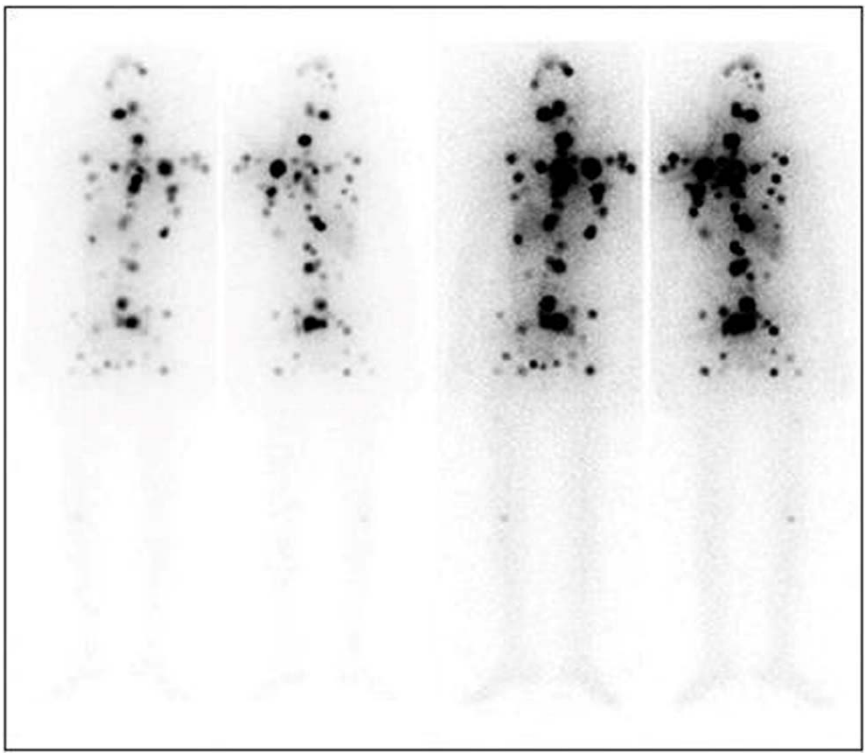

Figure 6c: Post-treatment radioiodine scan undertaken just before discharging the patient from the ward following the second dose of I-131, demonstrating extensive skeletal metastases concentrating radioiodine avidly. Incidentally, noted is relatively low uptake in the scalp lesion [Reproduced with permission[11]]

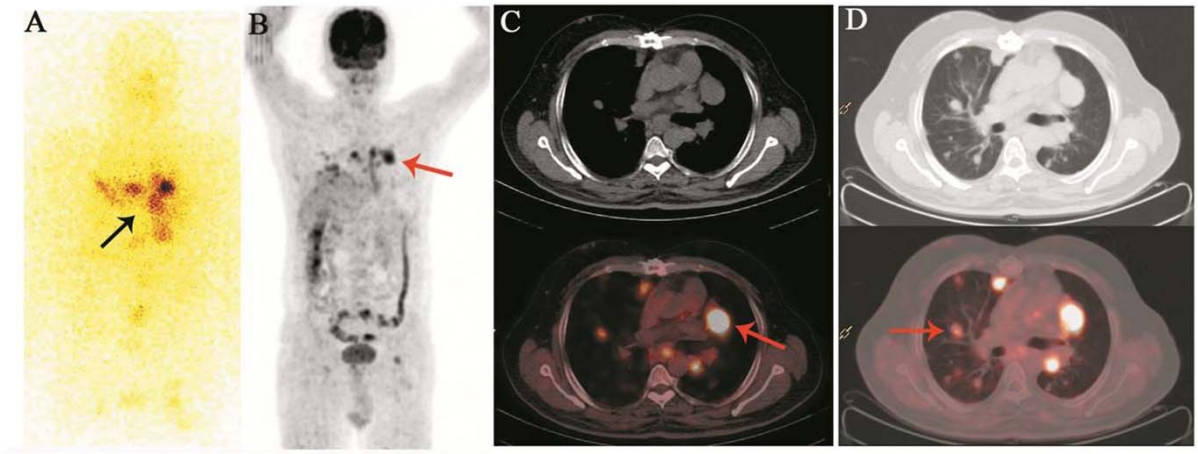

Fig 7. Post therapy (RAI with 131-I)whole body scintigraphy (A), ^{18}F FDG PET/CT scan MIP (B) axial thoracic (C and D) images of a known case of FVPCT with the patient receiving total cumulative dose of 1 Ci of radioiodine till date and raised serum thyrogloblulin level shows persistent tracer activity in thoracic region (A, black arrow) and also FDG uptake in mediastinal lymph nodes (C, red arrow) and lung nodules (D, red arrow).

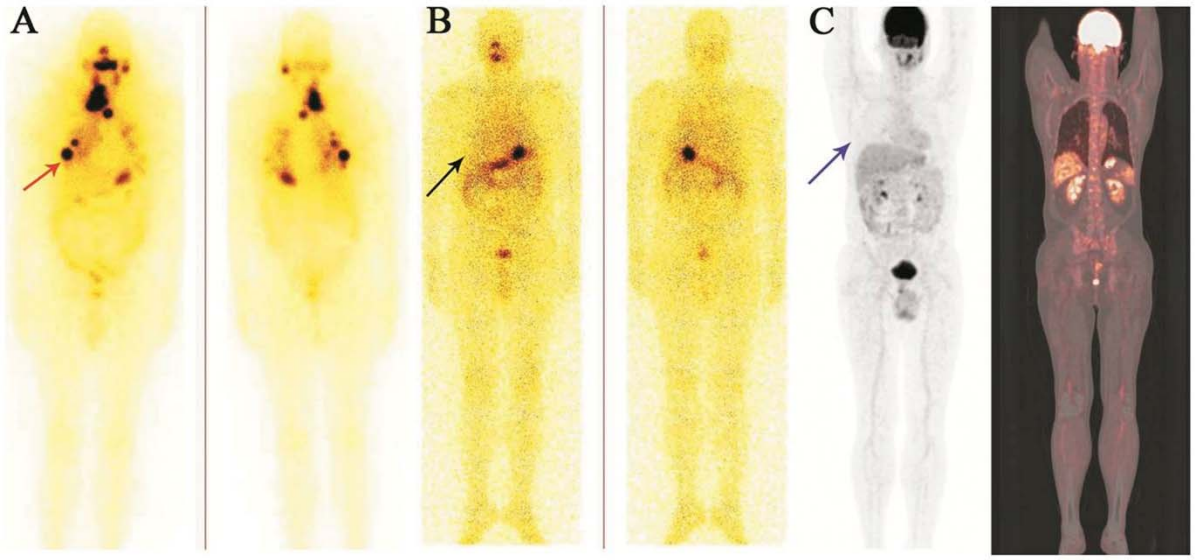

Fig 8. Whole body post therapy (radioiodine ablation) scintigraphy (A), follow-up ^{131}I diagnostic scintigraphy (B) in a ptient of DTC with lung and rib metastasis. Post therapy (radioiodine ablation) scintigraphy (A) showed abnormal tracer uptake in thoracic region in lung (red arrow) and solitary rib metastasis (posterior view) and neck region. ^{18}F FDG PET/CT scan (C, blue arrow) showed no abnormal tracer activity in thoracic and neck regions in this case. Subsequent follow-up ^{131}I diagnostic scintigraphy (B, black arrow) showed excellent response to single fraction of radioiodine normal and serum Tg was 0.26 ng/ml