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Review

FDG PET and alternative imaging in the management of thyroid carcinoma

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Abstract

Differentiated carcinoma of the thyroid are one of rare malignancies that is associated with excellent prognosis. Follow-up with regular thyroglobulin assay and ^{131}I whole-body scan is capable of detecting residual or recurrent disease with great sensitivity and specificity. However, there is overwhelming evidence to suggest that this approach is not fail-safe due to increasing reports of false negative and false positive results, which may result in missed or unwarranted therapy with ^{131}I.
This article will review the current management of differentiated carcinoma of the thyroid and the possible causes of the reported inadequacy of thyroglobulin and ^{131}I whole-body scan to detect residual or recurrent disease, and the increasing role of alternative imaging, particularly ^{18}F-FDG PET in the management of this curable malignancy.
Key words: differentiated carcinoma of the thyroid, thyroglobulin, ^{131}I, ^{99m}Tc-MIBI, ^{99m} Tc-tetrofosmine,^{201}Tl, ^{18}F-FDG-PET

Introduction

Differentiated carcinoma of the thyroid (DCT) is regarded as one of the most curable neoplasms. Nevertheless, it has a tendency to develop loco-regional recurrences and distant metastases in 5–20% and 5–10% respectively, generally in the first years of follow-up, but sometimes after many years. The American 10-year survival rates of a large cohort of patients with papillary and follicular carcinoma have recently been shown by Schlumberger et al to be 93% and 85% respectively [1].

The European 5-year survival rates for DCT are somewhat lower at 72% for men and 80% for women [2] with even lower figures for the UK (64% for men and 75% for women). Concerns have been raised that DCT is not well managed in Britain and Europe and that efforts should be made to improve adequacy of initial treatment (surgery and radioiodine therapy) and follow-up procedures [3]. The provision of agreed protocols and centralisation of expertise is strongly emphasised.

The post surgical management of DCT is well established and consists of:

— total or near-total thyroidectomy;
— ablation of remnant thyroid tissue with iodine-131 (^{131}I);
— suppression of endogenous TSH with life-long thyroxine replacement;
— regular thyroglobulin (Tg) assays;
— periodic ^{131}I whole-body scan (^{131}I WBS) to detect possible recurrence or metastasis.

The value of the first three elements of this strategy is undisputed. Total thyroidectomy followed by remnant ablation are known to minimise recurrence rate and improve survival and effectiveness of Tg assay by eliminating normal Tg production. In addition, they will enhance the sensitivity of ^{131}I WBS by keeping competitive uptake of residual thyroid tissue to the minimum.

However, there is increasing evidence to suggest that reliance on the last two elements of this strategy (periodic Tg assays and ^{131}I WBS) does not bestow full confidence in ruling out recurrent or metastatic disease. False positive and false negative Tg results [4–7] and ^{131}I WBS [5, 8] are well documented with the potential of missed or needless ^{131}I therapy.

Imaging with ^{131}I

^{131}I WBS remains by far the most cost-effective and widely used imaging method for follow-up of patients with DCT. It has favourable features that include low cost and availability, physiological uptake by thyroid and differentiated tumour cells and a gamma emission that is far from ideal but adequate for imaging. Its dis-

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advantages include relatively low specificity and sensitivity, its tendency to induce stunning and the need for intensive patient preparation including withdrawal of thyroxine for 4–6 weeks and adopting a strict iodine-free diet that may not appeal to all patients.

Limitations of ^{131}I WBS

Low sensitivity

Comparative studies have shown higher sensitivity of Tg measurements over ^{131}I WBS in DCT. In a study by Ronga et al [9] the sensitivity of ^{131}I WBS was 48% compared to 96% for Tg. Others have shown variable sensitivities but not exceeding 70–80%.

The low sensitivity of ^{131}I WBS can result from one or more of the followings:

— saturation of sodium-iodide symporters (NIS) by iodine rich diet, medications or use of contrast media;
— inadequate TSH elevation mostly due to non-compliance;
— metastases too small to be detected by camera resolution;
— loss of ability to take up ^{131}I due to de-differentiation of tumour cells as a result of an acquired mutation of NIS. Immunohistochemical staining of malignant thyroid cells has shown a reduction in Na/I symporters in primary DTC and lymph node metastasis that did not accumulate ^{131}I [10].

Measures to overcome these difficulties include strict patient preparation and the use of recombinant human TSH (rhTSH) to establish a satisfactory TSH levels, improving image quality and resolution by administering higher ^{131}I doses [11] and the use of retinoic acid in unresponsive tumours. However, in clinical practice, an alternative imaging is usually employed.

Low specificity

Acquisition errors, artefacts, physiologic distribution and non-thyroidal pathologic uptake of ^{131}I constitute the majority of false positive results. A list of possible causes of a false positive scan is shown in Table 1. It is prudent to keep a comprehensive and updated list of these conditions to aid in the interpretation of scans [12]. Correlation with ultrasound, computed tomography and other imaging modalities can be helpful (Fig. 1).

De-differentiation of DCT

Throughout the long-term survival of patients with DCT, loss of differentiation is noted in one third of patients resulting in loss of thyroid specific function and increased tumour grading and severity. As a consequence of that, lesser Tg production and higher rate of false negative ^{131}I WBS will be noted.

The use of retinoic acids can reverse de-differentiation of DCT and improve diagnostic and therapeutic potential of ^{131}I. Simon et al [13] used 13-cis-retinoic acid in 50 patients with DCT and noted an increase in ^{131}I uptake in 21 patients with an overall response (changes in Tg production, ^{131}I uptake and tumour regression) in 38%.

Limitations of Tg measurements

Since the introduction of Tg assay as a tumour marker for DCT in the early 80s, comparative studies have shown its sensitivity in detecting residual or recurrent disease [9]. While it is still regarded as the gold standard against which other investigations, specially imaging, are compared, careful interpretation of results must be undertaken in the presence of thyroglobulin antibodies (TgAbs) that may invalidate them and contribute to false negative values. Another source of false negative Tg value is measurement under thyroxine suppressive effect, and it is strongly recommended that Tg measurement be done under TSH stimulation that is similarly achieved by withdrawal of thyroxine or administration of recombinant human TSH (rhTSH) [14]. Different assay methods can produce different values and establishing a normal reference value for each laboratory is essential [15]. De-differentiation is another major factor in producing false negative results, and Tg assay has been shown to have a reduced sensitivity of 55% in patients with negative ^{131}I WBS who had proven metastasis [5].

The above discussion raises a critical question: How confident are we in ruling out disease when both ^{131}I and Tg are negative?

Alternative imaging to ^{131}I

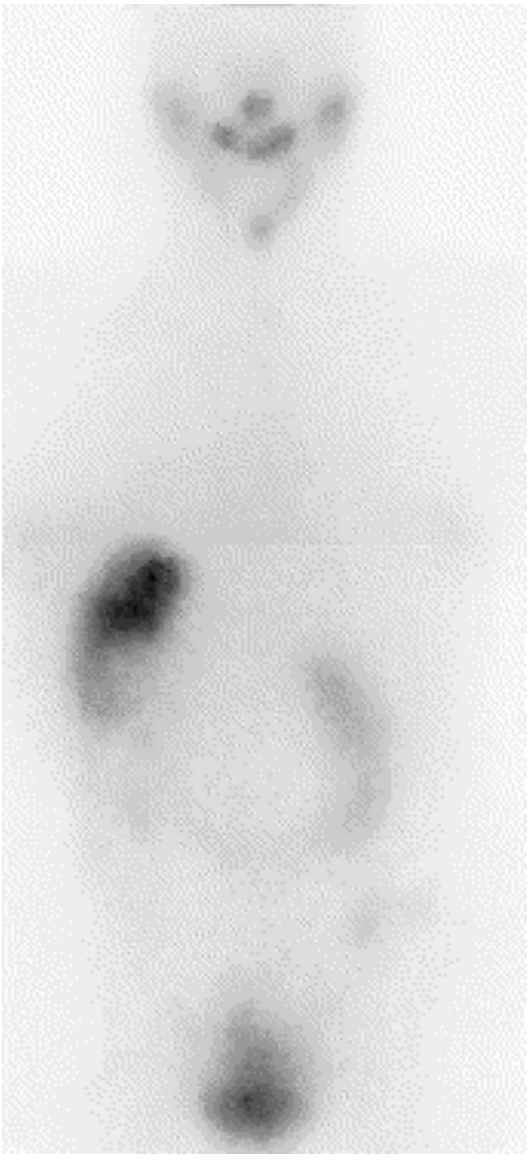
Despite loss of differentiation, tumour cells may continue to show elevated Tg as selective destruction of iodine-avid cells following therapy may leave behind clones that show no ^{131}I uptake while retaining their ability to produce Tg [16, 17]. Thus, the entity of 'Tg positive-^{131}I WBS negative' recurrence or metastasis has emerged. There are clear indications that these lesions are associated with worse prognosis and shortened survival compared to lesions that show avidity to ^{131}I [10, 18, 19] due to higher de-differentiation and growth rate. Some authors have suggested blind ^{131}I therapy in all such cases and express doubt on the value of non-iodine imaging [20–22]. However, pre-treatment imaging remains valuable to assist in the choice of therapeutic approach and post-therapy follow-up. This is done using one or more alternative radiopharmaceuticals supplemented with cross sectional imaging (CT, MRI, high resolution US) if and when necessary (Fig. 2). Contrast CT is to be avoided if a therapy dose is planned.

Various reports described the use of ^{201}Tl, ^{99m}Tc-MIBI, ^{99m}Tc-tetrofosmin ^{99m}Tc-MDP ^{111}I-octreotid and positron emission tomography with ^{18}F-fluorodeoxyglucose (^{18}F-FDG-PET) for the detection of Tg positive-^{131}I negative DCT. There is a wealth of literature, spanning the last 2 decades, that examines the individual roles of these radiopharmaceuticals and compares each against one or more of the others. For practical purposes, they can be reviewed as two separate groups.

Table 1. Some causes of false positive ^{131}I WBS

Head and neck	Thymus, dacryocystitis, chronic sinusitis, artificial eye, wig
Pulmonary	Tracheostomy, inflammatory disease, carcinoma
GIT	Meckel's, gastric adenocarcinoma, constipation
GUT	Poor renal function, cysts, ectopic kidney, cystadenoma, hydrocele
CVS	Pectus excavatum
CNS	Meningioma
Miscellaneous	Body secretion, skin burns, psoriasis, lactating breast

A



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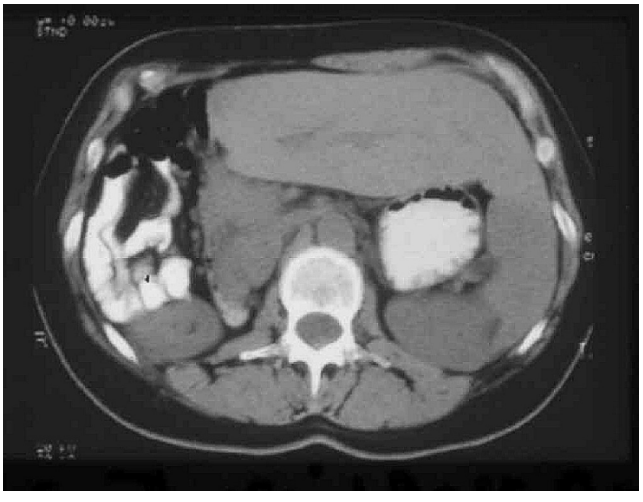

Figure 1. False positive ^{131}I WBS. **A**. ^{131}I WBS showing uptake in a bowel loop simulating uptake in right lobe of the liver. The loop was displaced due to previous right liver lobectomy; **B**. CT showing upward displacement of bowel.

Gamma camera imaging

A great proportion of studies relates to ^{99m}Tc-MIBI. Almeida-Filho et al [24] evaluated 99 patients with DCT, while on suppressive thyroxine treatment, with whole-body ^{99m}Tc-MIBI and compared the results with ^{131}I, using Tg as a gold standard. They found whole-body ^{99m}Tc-MIBI to be concordant with Tg in 96% and discordant in 4% of cases. Such high sensitivity has not been shown by other studies, and some authors recommend combination with US [25] for better yield. Some have highlighted better sensitivity for metastatic disease but lower sensitivity in detecting remnant thyroid tissue and lung metastases [26, 27].

In general, ^{99m}Tc labelled radiopharmaceuticals have better resolution than ^{201}Tl but head to head comparison between ^{99m}Tc-MIBI and ^{201}Tl showed very similar results with sensitivity of 53%, high specificity of 100% and an overall accuracy of 69% for both [28]. This comparative study employed planar images that missed residual cancer in high cervical lymph nodes adjacent to salivary gland activity, in small nodes of < 1 cm deep in the neck or chest, and diffuse pulmonary micro metastases. A similar comparative study between ^{201}Tl and ^{99m}Tc-tetrofosmin [29] revealed identical sensitivity of 79.4% in detecting metastatic lesions compared to 67.6% for ^{131}I. However, sensitivity for detecting lung metastases was equally lower at 68.8%.

Imaging with ^{201}Tl and ^{99m}Tc-tetrofosmin was similar to that with ^{99m}Tc-MIBI in showing reduced sensitivity for detecting thyroid remnants but higher sensitivity in metastatic disease. However, some studies have shown good results with ^{201}Tl in the pre-ablative states. Carril et al [30] found at least one lesion that was ^{131}I negative but ^{201}Tl positive in 31 patients (15 pre-ablative and 16 post-ablative) out of a cohort of 116 patients with DCT. When discordant results were analysed, ^{201}Tl positive-^{131}I negative lesions were more likely to be associated with high Tg levels, while ^{131}I positive-^{201}Tl negative lesions were associated with normal Tg levels.

As is the case with ^{99m}Tc-MIBI, imaging with ^{201}Tl and ^{99m}Tc-tetrofosmin showed no difference in sensitivity when patients were on or off thyroxine replacement therapy [31].

There is limited experience with ^{111}I-octreotide [32] and ^{99m}Tc-MDP [33], but the available data suggests lower specificity and confirms their role in complementing rather than replacing ^{131}I WBS.

^{18}F-FDG-PET imaging in DTC

Metabolic imaging was based on early observation by Warburg that tumours utilise more glucose than normal cells [34] and was made possible by using positron emitters that match the internal biological milieu. Experience with ^{18}F-FDG-PET, with its superior resolution and sensitivity, has shown it to be an effective modality in the management of patients with a wide variety of cancers [35]. Most importantly, it is a good marker of proliferative potential and aggressiveness in lung cancer, lymphoma, brain and soft tissue tumours [36–39].

Early observation in DTC showed that metastases could accumulate only ^{18}F-FDG, only ^{131}I, or both with higher ^{18}F-FDG in progressive metastases [40]. Feine et al [41] confirmed this "flip flop" phenomenon in a series of 41 patients and described alternating behaviour in metastases (those trapping ^{131}I showing no ^{18}F-FDG uptake and vice versa) in 30 patients. They found that metastases with positive ^{131}I and negative ^{18}F-FDG uptake represent better differentiation and tumour grade, while those with neg-

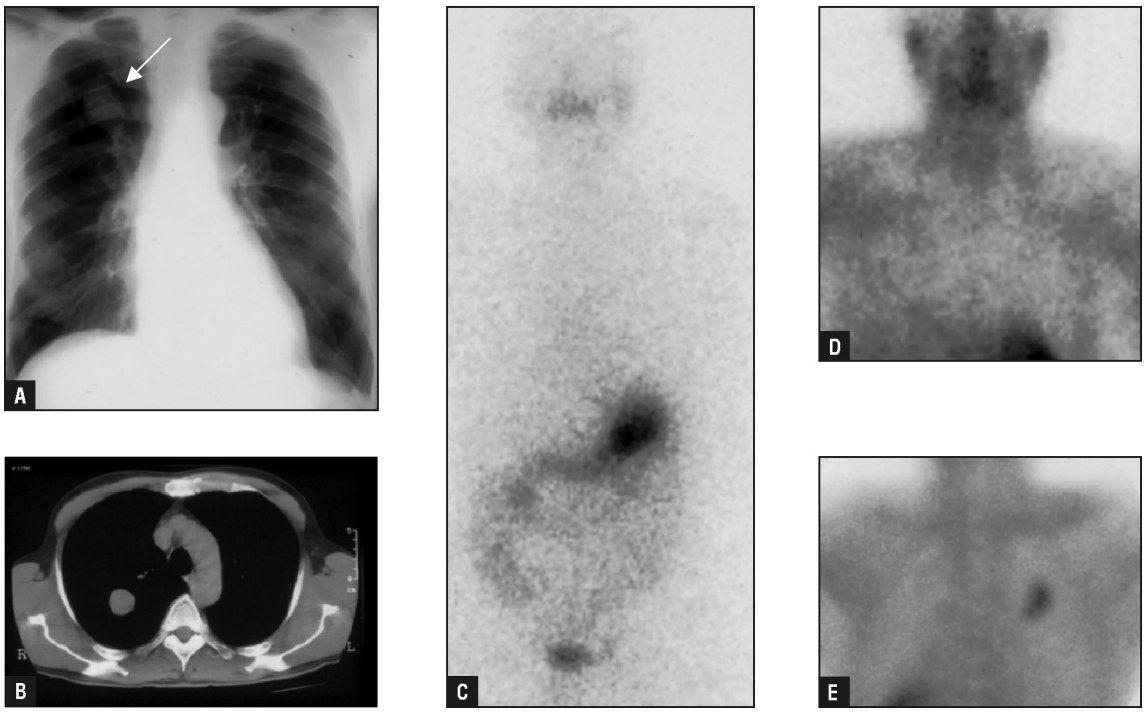

Figure 2. Alternative imaging in DCT. **A**. Chest X ray of a 52-year-old male with follicular carcinoma of the thyroid presented with rising Tg and RUL shadow (arrow); **B**. CT scan confirmed presence of a well--defined rounded mass in the same area thought to be a benign hamartoma; **C**. Whole-body ^{131}I scan was negative as was ^{201}Th scan **D**; **E**. Posterior chest ^{99m}Tc--MIBI scan demonstrated uptake in the lesion that was shown on biopsy to be metastatic disease.

ative ^{131}I and positive ^{18}F-FDG uptake were regarded of higher malignancy, a view shared with others [18, 40, 42, 43]. The results of a multicentre study in 222 patients with DTC showed a sensitivity of 85% and specificity of 90% for patients with negative ^{131}I WBS [42]. When the results of ^{18}F-FDG PET and ^{131}I WBS were considered in combination, tumour tissue was missed in only 7% of lesions.

There is general agreement that ^{18}F-FDG-PET offers increased detection and provides information as far as differentiation and grading is concerned [5, 18, 40–50]. Changes in management and prognosis are greatly aided by imaging with ^{18}F-FDG PET. Two recent studies have shown a change of management of 56% and 78% of true positive ^{18}F-FDG PET cases [43, 49]. The prognostic value of ^{18}F-FDG PET is demonstrated in the linear relationship with Tg and higher-grade tumours [40–44, 49, 50] and discordance with ^{131}I WBS [5, 18, 41, 42, 44, 49, 50]. Boerner et al [51] showed that ^{18}F-FDG standard uptake value (SUV) decreased significantly during isotretinoin therapy in association with increased ^{131}I uptake (as a marker of differentiation), but subsequently increased after withdrawal suggesting a tendency towards lower ^{18}F-FDG uptake in tumours with a better outcome.

In addition to its prognostic value, ^{18}F-FDG-PET can be cost effective in limiting unnecessary therapy, as high dose ^{131}I therapy have little or no effect on the viability of ^{18}F-FDG-avid metastatic lesions [18].

^{18}F-FDG-PET can be helpful when Tg is suspected to be false negative. An interesting study by Chung et al [5] on 54 patients with papillary carcinoma and negative ^{131}I WBS showed abnormal ^{18}F-FDG uptake in 31 patients with 94% sensitivity and 95% specificity whereas Tg was elevated in 18 patients with 55% sensitivity and 76% specificity.

Sites of metastasis that demonstrate better ^{18}F-FDG uptake are cervical and mediastinal lymph nodes whereas lung and bone lesions showed less uptake compared to ^{131}I WBS and ^{99m}Tc-MIBI [5, 42, 44, 52]. Figures 3 and 4 are examples of flip-flop phenomenon with discordant uptake of ^{18}F-FDG and ^{131}I.

The issue of performing ^{18}F-FDG PET scanning under TSH stimulation is controversial though Moog et al [53] have shown a convincing improvement in ^{18}F-FDG uptake under TSH stimulation.

Summary

The current strategy of reliance on Tg assay and ^{131}I WBS in the follow-up in DTC is inadequate due to reduced sensitivity and specificity particularly when tumours undergo de-differentiation. In these situations, the tumours become aggressive with higher grade and reduced survival. The difficulty in detecting such recurrences or metastases may result in inappropriate management.

The use of ^{99m}Tc-MIBI or ^{201}Tl, supplemented with CT and US can be helpful in a proportion of cases. However, the detection of de-differentiation requires an improved sensitivity and specificity through the use of a radiopharmaceutical with uptake that correlates well with aggressive and high-grade tumours, and an imaging techniques that provides tomography with higher resolution.

Both criteria are met by employing ^{18}F-FDG-PET. It has a mechanism of uptake that correlates well with higher aggressiveness and grading of tumours and has been shown to detect lesions that are not visible on ^{131}I WBS with excellent specificity. The superb resolution of PET and the facility of whole-body imaging give this technique the edge over cross sectional imaging when provisional localisation of recurrence is not available. The demon-

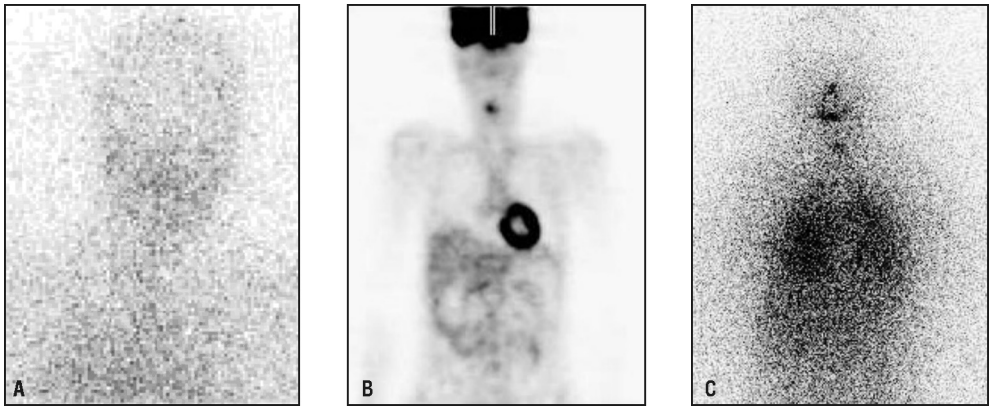

Figure 3. Flip-flop phenomenon — a 38-year-old female with DCT and rising Tg. **A**. Diagnostic ^{131}I WBS appears normal; **B**. Coronal section from an ^{18}FDG-PET showing uptake in thyroid bed, prompting a therapy dose with ^{131}I; **C**. ^{131}I post therapy scan showing similar uptake in thyroid bed but in addition showing diffuse and global uptake in both lungs.

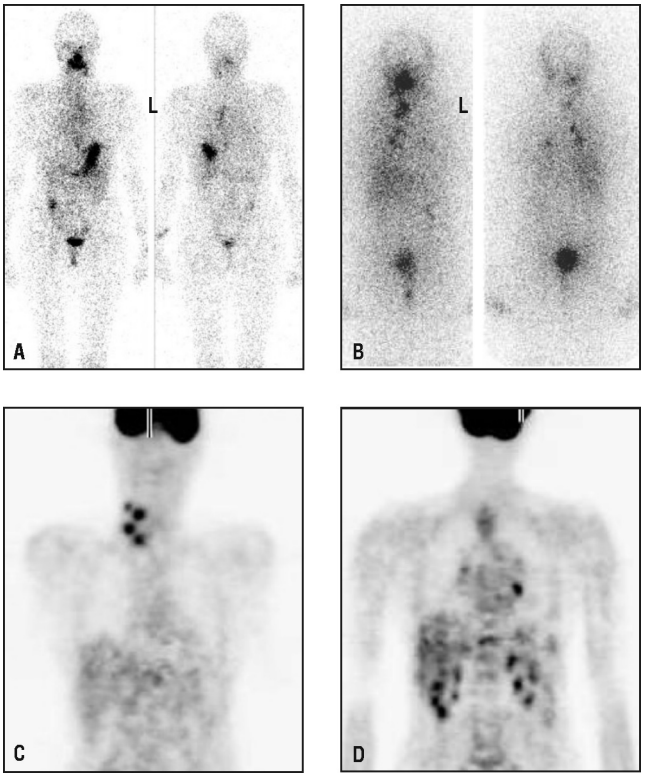

Figure 4. Flip-flop phenomenon A 56-year-old female with DCT and palpable recurrence in right cervical nodes associated with very high Tg. **A.** Anterior and posterior diagnostic ^{123}I WBS done to avoid stunning shows minimal uptake in mediastinum; **B.** ^{131}I post therapy WBS shows higher uptake and more pulmonary and mediastinal disease; **C**, **D.** Selected coronal sections from ^{18}FDG WBS showing mediastinal disease and well defined cervical lymph nodes that were clinically palpable but missed by both ^{123}I and ^{131}I WBS.

stration of flip-flop phenomenon remains a reminder that ^{131}I WBS must continue to be the first line of investigation and that alternative imaging, including ^{18}F-FDG PET, is complementary rather than a replacement, particularly when lung metastasis is suspected.

An important aspect of ^{18}F-FDG PET imaging, compared to other non-iodine imaging, is its ability to provide prognostic information that has helped to change the management of patients with DTC in a large proportion of true positive cases. Likewise, it can help detect tumour foci when Tg is normal due to loss of production caused by de-differentiation.

Unfortunately, there is a worldwide deficiency in the provision of PET scanners and cyclotrons extending to some developed countries such as the UK. Until this is reversed, the management of DTC will continue to depend on the combination of Tg assay and ^{131}I WBS. However, the increasing awareness of dedifferentiation requires vigilance and frequent supplementation with ^{99m}Tc-MIBI, ^{201}Tl and morphological imaging.

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