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 131I 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 131I. This article will review the current management of differentiated carcinoma of the thyroid and the possible causes of the reported inadequacy of thyroglobulin and 131I whole-body scan to detect residual or recurrent disease, and the increasing role of alternative imaging, particularly 18F-FDG PET in the management of this curable malignancy.

Key words: differentiated carcinoma of the thyroid, thyroglobulin, 131I, 99mTc-MIBI, 99mTc-tetrofosmine, 201Tl, 18F-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 (131I);
— suppression of endogenous TSH with life-long thyroxine replacement;
— regular thyroglobulin (Tg) assays;
— periodic 131I whole-body scan (131I 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 131I 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 131I WBS) does not bestow full confidence in ruling out recurrent or metastatic disease. False positive and false negative Tg results [4–7] and 131I WBS [5, 8] are well documented with the potential of missed or needless 131I therapy.

Imaging with 131I
131I 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-
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 131I WBS**

**Low sensitivity**

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

The low sensitivity of 131I WBS can result from one or more of the following:

- 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 131I 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 131I [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 131I 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 131I 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 131I WBS will be noted.

The use of retinoic acids can reverse de-differentiation of DCT and improve diagnostic and therapeutic potential of 131I. Simon et al [13] used 13-cis-retinoic acid in 50 patients with DCT and noted an increase in 131I uptake in 21 patients with an overall response (changes in Tg production, 131I 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 131I WBS who had proven metastasis [5].

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

**Alternative imaging to 131I**

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 131I uptake while retaining their ability to produce Tg [16, 17]. Thus, the entity of ‘Tg positive-131I 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 131I [10, 18, 19] due to higher de-differentiation and growth rate. Some authors have suggested blind 131I 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 201Tl, 99mTc-MIBI, 99mTc-tetrofosmin, 99mTc-MDP, 111In-octreotide and positron emission tomography with 18F-fluorodeoxyglucose (18F-FDG-PET) for the detection of Tg positive-131I 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 131I WBS

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Head and neck</strong></td>
<td>Thymus, dacryocystitis, chronic sinusitis, artificial eye, wig</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td>Tracheostomy, inflammatory disease, carcinoma</td>
</tr>
<tr>
<td><strong>GIT</strong></td>
<td>Meckel’s, gastric adenocarcinoma, constipation</td>
</tr>
<tr>
<td><strong>GU</strong></td>
<td>Poor renal function, cysts, ectopic kidney, cystadenoma, hydrocele</td>
</tr>
<tr>
<td><strong>CVS</strong></td>
<td>Pectus excavatum</td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td>Meningioma</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td>Body secretion, skin burns, psoriasis, lactating breast</td>
</tr>
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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.

**18F-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-
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-
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Review

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

An important aspect of ¹⁸F-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 ¹³¹I WBS. However, the increasing awareness of dedifferentiation requires vigilance and frequent supplementation with ⁹⁹mTc-MIBI, ²⁰¹Tl and morphological imaging.

References


