

## Review Article

# Management of Differentiated Thyroid Cancer Patients with Elevated Serum Thyroglobulin Level but Negative Radioiodine Scan

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### Abstract

After undergoing the initial therapy for differentiated thyroid cancer of surgery and radioiodine, a patient is considered in remission when a follow-up radioiodine scan is negative, serum thyroglobulin is undetectable and there is no clinical or radiological evidence of the disease. However, cases with elevated serum thyroglobulin, but negative radioiodine scan are occasionally seen. Management of these patients is controversial, particularly the role of alternative radionuclear imaging studies, empiric radioiodine therapy and other treatment options.

**Keywords:** Differentiated thyroid cancer, thyroglobulin, radioiodine scan, radioiodine therapy.

(*J Med J* 2012; Vol. 46 (2):171- 175)

Received

June 8, 2009

Accepted

February 14, 2012

### Introduction

Differentiated thyroid cancer (DTC) originates from follicular epithelial cells and accounts for the majority of cases of thyroid cancer. About 85% of the cases are papillary, 10% follicular and 3% Hurthle cell tumors.<sup>1</sup>

Usually the initial therapy of DTC includes a near total thyroidectomy followed by the radioiodine ablation of thyroid remnants. This permits a more accurate evaluation of the persistent disease and a long term surveillance for recurrence with the use of a whole-body radioiodine scan and measurement of serum thyroglobulin (Tg).<sup>2</sup>

A patient is considered in remission when a radioiodine scan is negative, serum Tg is < 2ng/ml while the patient is off l-thyroxine and there is no clinical or radiological evidence of the disease.

In the study of Samman et al,<sup>3</sup> the remission rate was 80 % with a follow-up period of about 11 years. Also, other large studies show nearly similar results. For an assessment of risk, a three level stratification can be used.<sup>4</sup> High risk is if there is a macroscopic tumor invasion, incomplete resection, or distant metastases. Intermediate risk is if there is a microscopic tumor invasion, lymph nodes metastases or variants with aggressive histology, e.g. tall cell, columnar cell or insular. Low risk is if the mentioned risk factors are absent.

Because of the broad heterogeneity of the clinical characteristics of patients with DTC and the lack of sufficient data from well-controlled prospective studies, the management of patients with DTC continues to be controversial. One aspect of this controversy is the management of patients with negative radioiodine scan and increased serum Tg.

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## **Serum Thyroglobulin**

The measurement of serum Tg in patients with DTC is used to monitor for the residual or recurrent disease and is considered the cornerstone in a long-term follow-up. Serum Tg levels principally integrate three variables: the mass of the thyroid tissue (benign or malignant), the degree of TSH receptor stimulation, and the tumor's intrinsic ability to synthesize and secrete Tg.<sup>5, 6</sup> Two methods can be used for the measurement of serum Tg: immunometric assay or radioimmunoassay. Most laboratories currently use immunometric assays that are calibrated against the CRM-457 international standards, but immunometric assays are prone to interference from Tg autoantibodies which commonly cause a false low level of serum Tg.<sup>7</sup> Serum Tg measurements after l-thyroxine withdrawal or stimulation using recombinant human (rh)TSH injections are much more sensitive than during TSH suppression. However, even TSH stimulated Tg may fail to identify patients with residual disease which may be due to the presence of anti-Tg antibodies or less commonly, defective or absent production and secretion of immunoreactive Tg by tumor cells.<sup>8</sup> In addition, Tg levels should be interpreted in the light of pretest probability of clinically significant residual tumor.

Approximately 20% of patients who are clinically free of disease with serum Tg levels < 1ng/ml during hormonal suppression of TSH will have serum Tg > 2ng/ml after TSH stimulation 12 months after the initial therapy with surgery and radioiodine.<sup>9</sup> One third of these will have identification of persistent or recurrent disease and the other two-thirds will remain free of clinical disease with stable or decreasing levels of Tg.<sup>10</sup> There is good evidence that a Tg cutoff level above 2ng /ml following TSH stimulation is highly sensitive in identifying patients with persistent disease.<sup>9, 11</sup> However, the results on the same serum specimen differ significantly according to assay methods among medical centers and laboratories so that the Tg cutoff may differ.<sup>7</sup> Further, the clinical significance of minimally detectable Tg levels is unclear,

especially if only detected following TSH stimulation. But a rising serum Tg level overtime is important to identify patients with clinically significant residual disease.<sup>10</sup> The presence of anti-Tg antibodies, which occur in approximately 25% of thyroid cancer patients and in 10% of the general population, will falsely lower serum Tg in immunometric assays. The use of recovery assays in this setting to detect significant interference is controversial.<sup>12, 13</sup>

Decreasing antibody levels are correlated with a disease-free status, while increasing levels suggest persistent disease. These patients are a challenge to manage and one cannot be certain of their disease status.<sup>14</sup>

An alternative test for the presence of anti-Tg antibodies is the measurement of Tg-mRNA in the blood, but this is still not completely standardized.<sup>15</sup>

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he recommendations of the American Thyroid Association, in the management guidelines of DTC,<sup>16</sup> are as follows:

- Serum Tg should be measured in the same laboratory and using the same assay during the follow-up of patients with DTC. Also, Tg antibodies should be quantitatively assessed with every measurement of serum Tg.
- In low-risk patients, who have had remnant ablation, negative cervical ultrasonography and undetectable TSH-suppressed Tg the first year after treatment, serum Tg should be measured after thyroxine withdrawal or rhTSH stimulation approximately 12 months after the ablation to verify the absence of disease. Low risk patients with undetectable TSH stimulated Tg can be followed primarily with yearly Tg measurements while on l-thyroxine therapy, and do not require a routine diagnostic radioiodine whole-body scan.
- A diagnostic radioiodine whole-body scan 6-12 months after radioiodine ablation is of value in follow-up of patients with high or intermediate risk.

### **Management of Patients with Elevated Serum Thyroglobulin and Negative Radioiodine Scan**

If the unstimulated Tg is or becomes detectable while on l-thyroxine therapy or if a stimulated Tg level rises to greater than 2 ng/ml with a negative radioiodine scan and no evidence of disease by radiological studies including neck US and chest CT, then a search for persistent disease with the use of other alternative radionuclear imaging studies should be carried out.<sup>17</sup> However, first it is necessary to find a cause for a possible false negative radioiodine scan such as an inadequate TSH elevation, stable iodine contamination (e.g. contrast media, diet, etc.), dispersed micrometastases too small to be detected, or dedifferentiation of the tumor so that it can still produce Tg but has lost its ability to trap radioiodine mainly due to a decreased expression of sodium/iodine symporters.

Examples of these alternative imaging studies are Tc99m-tetrofosmin and Tc99m-sestamibi which, according to some studies, are found to be more sensitive than a radioiodine scan for the detection of lymph nodes metastases and local recurrence with the advantage of not having to withdraw TSH suppression l-thyroxine therapy.<sup>18</sup> Identification of lesions by these methods would allow earlier intervention by surgical excision or external radiotherapy.

Also FDG-PET imaging has an important role in the management of these cases. With dedifferentiation, the growth rate of cancer increases and, subsequently, glucose utilization increases so that it becomes more detectable by FDG-PET imaging. In the meta-analysis of several studies, the sensitivity and specificity of FDG-PET/CT imaging in patients with recurrent cancer but negative radioiodine scan are 0.83 and 0.84, respectively.<sup>19,20</sup> However, it is less clear whether stimulation with intrinsic TSH or rhTSH improves the sensitivity of a FDG-PET scan in thyroid cancer. While some early studies suggest an improved detection rate, some recent studies are more equivocal.<sup>21</sup> According to the American Thyroid Association Guidelines,<sup>16</sup> whole-body FDG-PET imaging may be obtained

if serum Tg > 10 ng/ml. PET imaging with the use of Ga68 DOTA peptides that bind to somatostatin receptors are also being evaluated.<sup>22</sup> If these alternative imaging studies are negative then empiric therapy with radioiodine 131 (100-200 mci) should be considered for the localization of lesions and the therapy for surgically incurable disease.

While most studies support blind radioiodine treatment, others negate this. This approach may identify the localization of persistent disease in approximately 50% of patients with a wide-range of reported success.<sup>23, 24</sup> A cutoff value of Tg above which a patient should be treated with an empiric dose of radioiodine is difficult to determine due to the differences in the Tg levels based on the method used and the degree of TSH stimulation. Recent studies have reported primarily on patients with a Tg level  $\geq 10$  ng/ml after l-thyroxine withdrawal or  $\geq 5$  ng/ml after rhTSH.<sup>25</sup>

Further treatment should be according to the result of a post-therapy scan; while radioiodine therapy is effective for pulmonary micrometastases, surgery is considered for lymph nodes metastases. Radioiodine uptake by thyroid cancer can be improved with the use of retinoids, that are biologically active derivatives of vitamin A, by increasing the expression of the sodium-iodine symporters (NIS) mRNA.<sup>26</sup>

However, if the alternative imaging studies are positive, but non-iodine avid and incurable by surgery, then these cases can be managed with radiotherapy, chemotherapy, radiofrequency ablation or chemo-embolization.

Clinical trials should also be considered such as the use of tyrosine kinase inhibitors, modulators of growth, angiogenesis inhibitors and gene therapy.

Tg levels > 2 and < 10 ng /ml at 9- 12 months following remnant ablation are typically associated with a small volume of tissue and may warrant further therapy. There is no current proof that the aggressive treatment of minimal disease

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improves outcome. This is brought into focus by the fact that only about 5% of all patients die of their disease, yet about 15-20% of low risk patients are likely to have persistent disease based on persistent measurable Tg. Some of these patients demonstrate a subsequent spontaneous fall in Tg overtime.<sup>16</sup>

While radioiodine therapy appears to be reasonably safe, it is associated with an accumulative dose-related low risk of early and late onset of complications such as salivary glands damage, dental carries, nasolacrimal duct obstruction and second malignancy.<sup>27,28</sup> Therefore, it is important to ensure that the benefits of radioiodine therapy outweigh the potential risks.

### Conclusion

In patients with a negative radioiodine scan but elevated serum Tg and no clinical or radiological evidence of disease, alternative radionuclear imaging studies and the use of empiric therapeutic radioiodine dose may localize the active disease in more than 50% of cases. A rising level of serum Tg may warrant more concern for the need for empiric radioiodine therapy. Consequently, further management depends on the result of these imaging studies and findings in post-therapy radioiodine whole-body scan.

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## سرطان الغدة الدرقية المتمايز: الإجراءات الطبية الممكن اتباعها، عندما يكون فحص الجسم باليود المشع سلبياً لكن مستوى الثيروجلوبيولين مرتفع

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### الملخص

بعد علاج سرطان الغدة الدرقية المتمايز في البداية بالجراحة واليود المشع، فإنه يمكن اعتبار المريض قد شفي عندما تكون فحوصات المتابعة سلبية بما فيها فحص الجسم باليود المشع، وقياس مستوى الثيروجلوبيولين في الدم وكذلك الفحوصات الشعاعية. إلا أن هنالك بعض الحالات يكون فيها مستوى الثيروجلوبيولين مرتفع. مع أن الفحص باليود المشع سلبياً. يوجد تباين في الآراء حول هذه الحالات فيما يتعلق بدور الفحوصات النووية البديلة لليود المشع، وكذلك العلاج باليود المشع وخيارات العلاج الأخرى.

الكلمات الدالة: سرطان الغدة الدرقية المتمايز، ثيروجلوبيولين، فحص باليود المشع، علاج باليود المشع.