Changing Concepts in the Management of Differentiated Thyroid Cancer

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- Differentiated thyroid cancer (DTC) is among the most curable of cancers.
- The presence of incidental thyroid micrometastases (diameter 1 cm or smaller) is 5% to 36% of autopsied adults.
- The management of DTC is one of the more debated topics in clinical medicine.

Significant developments in monitoring and treatment during the past decade have changed many of the traditional approaches to the patient with DTC, some of which remain controversial.

Current Approach
After the Diagnosis of DTC

Extent of Surgery

1. Surgery is the primary mode of therapy for patients with DTC.

2. Total thyroidectomy should be performed if the primary tumor is 1 cm or more in diameter or if extrathyroidal extension or metastases are present.

3. If the tumor is less than 1 cm and confined to one lobe, then unilateral lobectomy and isthmectomy are appropriate.

RAI: Is It Always Indicated?

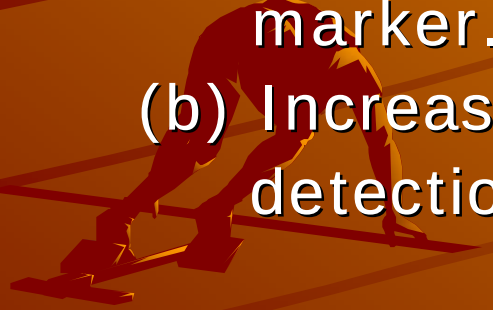
- The most effective nonsurgical treatment for papillary thyroid carcinoma is radioiodine, in the form of I-131.

Radioiodine has 3 main indications in the postoperative management of patients with thyroid cancer: ablation of residual thyroid tissue, imaging for possible recurrent disease, and treatment of residual or recurrent thyroid cancer.

The goals of RAI

1. To destroy any microscopic foci of disease remaining after the surgery.

2. To destroy any remaining normal thyroid tissue to:
   (a) Improve the value of serum Tg as a tumor marker.
   (b) Increase the specificity of I-131 scanning for detection of recurrent or metastatic disease.



Can RAI result in lower recurrence rates and possibly improved overall survival

Published data on this issue are retrospective and not randomized; there remains considerable disagreement about the role of I-131 ablation, especially in patients with low-risk disease (i.e., no soft tissue invasion and no distant metastases).

Combining data from multiple retrospective studies, the relapse rate after RAI may be reduced by as much as 50%, and decreased mortality has been demonstrated in several large retrospective studies among patients whose primary tumors were at least 1 to 1.5 cm in diameter or were muticentric, or who had soft tissue invasion at diagnosis.

At the Mayo Clinic, RAI did not improve mortality or recurrence rates in patients with low-risk papillary thyroid cancer who had undergone complete tumor excision.

It appears that there is less need for RAI in low-risk patients (tumor less than 1–1.5 cm and age younger than 40-45 years at diagnosis) who have had a true total thyroidectomy.

RAI is recommended by:

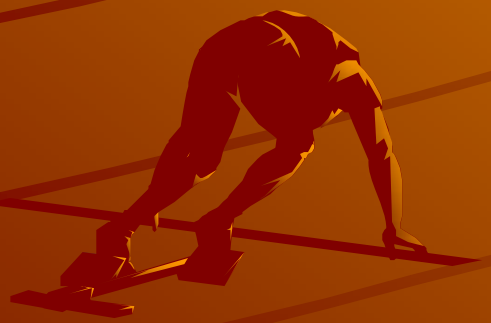
1. any individual with a carcinoma $>$ 1 to 1.5 cm or of any size with obvious lymph node involvement.

2. Extrathyroidal extension

3. Multicentricity

4. Patient 40 to 45 years or older at diagnosis

Recombinant Thyrotropin Versus Thyroid Hormone Withdrawal for Monitoring and Treatment



Periodic diagnostic testing for disease recurrence most commonly includes:

1. Serum Tg measurements reflects the ability of the cells to produce Tg.

2. Diagnostic radioiodine whole-body scanning is dependent on their ability to concentrate iodine.

   Both of these processes are driven by thyroid-stimulating hormone.

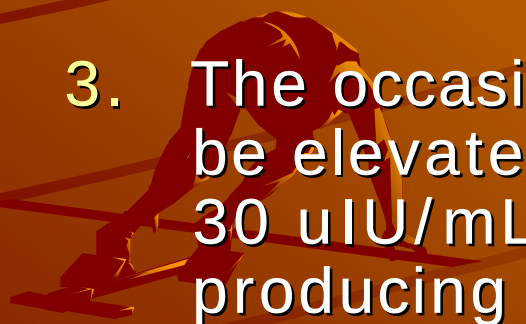
- Maximum TSH stimulation of both normal residual or neoplastic thyroid cells was accomplished by temporary thyroid hormone withdrawal (THW) before testing.

3 potential problems arise from THW:

1. The negative impact of the symptoms of prolonged hypothyroidism, such as fatigue, weight gain, and lack of productivity.

2. The theoretical stimulation and proliferation of DTC cells by the rising TSH.

3. The occasional patient whose TSH level cannot be elevated to the conventional cut-off level of 30 uIU/mL because of large thyroid hormone-producing metastases.



1. After successful clinical trials, rhTSH was approved for use in diagnostic testing by the U.S. Food and Drug Administration (FDA).

2. rhTSH was comparable to THW in terms of sensitivity and specificity with no significant differences.

1. Administration of rhTSH is not indicated in the postoperative period after thyroidectomy and patients at high risk of disease recurrence.

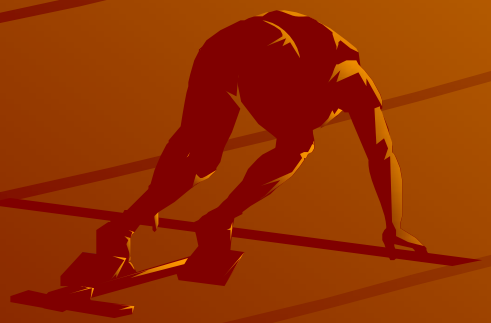
2. rhTSH-stimulated WBS and Tg measurements are appropriate for patients at low risk of harboring a thyroid remnant, disease recurrence, or metastatic disease.

- In practice, “low risk” would be a patient demonstrating a normal WBS and a serum Tg level of 2 g/L or lower while under THW.

1. The use of rhTSH in DTC is FDA-approved for diagnostic testing only, and not for therapy.

2. In early 2005, the European Commission approved the use of rhTSH for therapeutic radioiodine preparation.

Thyroglobulin and Radioiodine Scanning for Long-Term Monitoring



Serum Tg

- Serum Tg is very useful in the follow-up of patients with DTC who are treated with surgery and RAI.

1. The limitation in interpreting Tg levels is the potential for interference by anti-Tg autoantibodies.

2. 25% of patients with DTC have anti-Tg autoantibodies after their initial surgery.

3. The clinical significance of these antibodies is unclear, their persistence for more than 1 year after thyroidectomy and RAI probably indicates the presence of residual thyroid tissue and possibly an increased risk of recurrence.

- In general, the sensitivity of detecting thyroid carcinoma by measurement of serum Tg after discontinuation of thyroxine therapy is 85% to 95%, but may be as low as 50% during therapy.

- The results are most likely to be falsely negative during thyroxine therapy in patients with small nodal metastases of papillary carcinoma and in those with tumor dedifferentiation.

- An undetectable serum Tg during thyroxine therapy can be misleading in a large proportion of patients with residual DTC and therefore a TSH-stimulated serum Tg level should be obtained in the follow-up of patients with DTC.

The use of rhTH-stimulated Tg testing without a diagnostic scan in low-risk patients with DTC

- Who have undergone total thyroidectomy and RAI at least 6 to 12 months ago.
- Who have no clinical evidence of tumor.
- Who have undetectable serum Tg levels during thyroxine therapy; the majority will have had tumors smaller than 4 cm, not of a virulent subtype, which were completely resected with or without nodal metastases, but without distant metastases.

(1) If serum Tg is detectable on thyroxine therapy, further workup is needed to localize the residual cancer (neck ultrasound, chest x-ray; based on the results, either I-131 scanning/treatment or surgery would be considered).

(2) If serum Tg is undetectable on thyroxine therapy 6 to 12 months after thyroidectomy and RAI, a rhTSH-stimulated Tg alone (without a diagnostic I-131 scan) is performed.

1. A stimulated Tg level more than 2 g/L needs immediate attention and further workup.

2. A Tg level less than 2 g/L could be followed with periodic Tg measurements.

Radioiodine WBS

1. Classically, diagnostic radioiodine WBS are performed periodically (usually once a year) in the follow-up of patients with DTC.

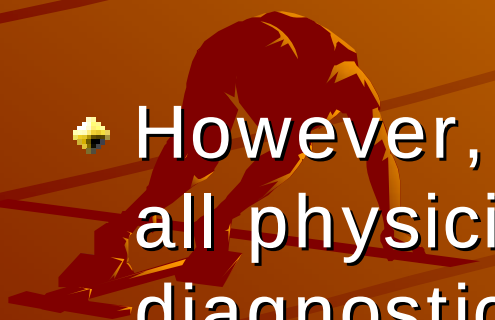
2. WBS are performed after thyroxin withdrawal or after the administration of rhTSH.

3. Two negative annual successive WBS have very good predictive value.

4. Serum Tg concentrations less than 2 g/L after rhTSH administration were rarely associated with evidence of disease in one study, suggesting that the diagnostic WBS could be eliminated in this clinical scenario.

5. However, in a study by Robbins and coworkers, 13% of patients with stimulated serum Tg concentrations less than 2 g/L had evidence of residual thyroid cancer.

- The consensus published in 2003 advocated that a rhTSH-stimulated Tg alone was sufficient for follow-up of low-risk patients with no clinical evidence of disease and suppressed serum Tg during thyroxine therapy.



- However, this approach is not followed by all physicians and many still perform diagnostic WBS in conjunction with stimulated serum Tg levels.

The Use of I-131 Vs I-123 for WBS

Although some institutions are currently using I-123 with success, a few issues have remained controversial.

1. Optimal dose for I-123 remains unresolved.
2. Optimal timing
3. Sensitivity

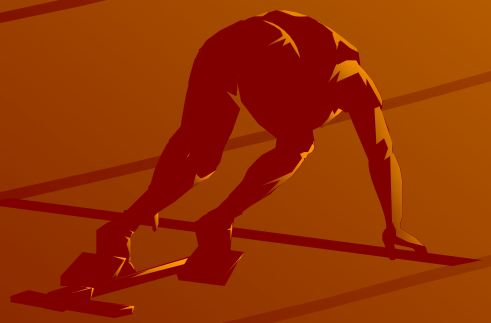
The current data suggests that:

1. I-123 scans using 2 to 5 mCi (74-185 MBq) imaged at 24 hours are comparable but not superior to both I-131 diagnostic and postablation scans.

2. The I-123 diagnostic scans provide an alternative for those who want to avoid the potential for so-called “stunning.”

3. Higher doses and longer scan times have not been sufficiently studied to draw any definite conclusions at this time.

The Stunning Effect: Fact or Fiction?



1. The concept of stunning remains controversial.

2. Although there is evidence that stunning exists at a cellular level, investigations concerning its clinical significance are conflicting and no definitive conclusions can be made at this time.

3. Both qualitative and quantitative analyses have their own pitfalls and both suffer from lack of standardization.

4. Further systemic study will help clarify the impact of stunning from absorbed doses of I-131.

Management of the Tg–Positive/I-131–Negative Patient

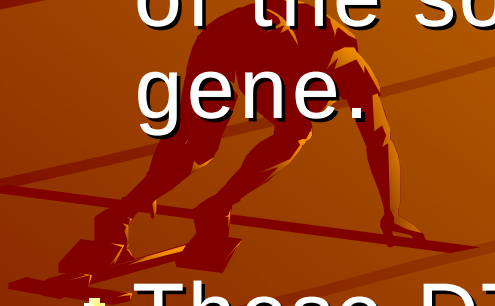
An increased or persistently elevated Tg level indicates recurrent, persistent, or metastatic DTC, even if not visualized on the WBS.

False-Negative I-131 Scan

1. Inadequate TSH stimulation
2. Small tumor size
3. Iodine contamination
4. Tumor dedifferentiation

Tumor Dedifferentiation

- the DTC cells proliferate yet lose their ability to trap, organify, store, and metabolize iodine. The presumed mechanism is an acquired mutation of the sodium-iodine symporter (NIS) gene.



- These DTC cells, however, still maintain the ability to synthesize Tg.

Localization

- Regardless of the capability of the DTC cells to concentrate I-131, any potentially resectable local or metastatic lesion should be surgically removed before consideration for RAI. A tumor localization workup is therefore essential.

- Ultrasound scanning of the neck is the logical first step.
- Anatomic imaging with CT and MRI.
- Functional imaging with FDG PET.

The degree of FDG uptake is directly proportional to:

1. Tg synthesis
2. The degree of tumor dedifferentiation
3. Level of TSH stimulation

Role of FDG-PET

1. The impact of FDG-PET on the management of patients with noniodine-avid DTC was undertaken by Schlutter, yielding a sensitivity of 77% and a positive predictive value of 83%, a negative predictive value of only 25%.

2. The sensitivity of the scan increased as the serum Tg level increased; the true-positive rate was 11% with Tg levels less than 10, 50% with Tg levels 10 to 20, and 93% with Tg levels greater than 100 g/L.

3. FDG uptake indicates tumor dedifferentiation, it does not necessarily indicate a poor prognosis with high mortality, as long as the tumor is completely removed.

4. High-dose RAI had no significant therapeutic impact on FDG-avid metastases.

Approach to the Patient With Localized But Nonresectable Metastases

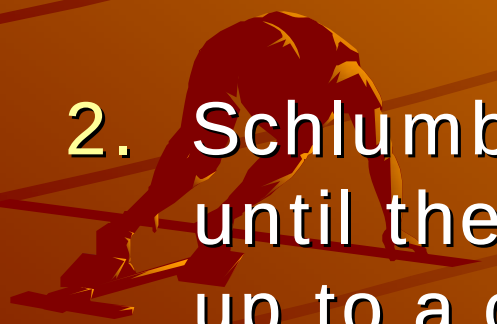
1. If the metastatic lesions are not resectable, the Tg level is elevated, and the WBS is negative, some authors advocate empiric RAI, using doses of 100 to 300 mCi.

2. Fatourechi and Hay showed that most patients in their series with negative WBS undergoing RAI did not demonstrate sufficient I-131 uptake on their postablation scans to warrant such empiric therapy.

3. They advocate the use of external radiation therapy as being the treatment of choice for nonresectable, noniodine-avid DTC metastases.

Approach to the Patient With Nonlocalized Metastases

1. A total of 59 patients with micrometastases underwent empiric RAI, 50 of whom (85%) demonstrated uptake on postablation scans. (75 to 300mCi)



2. Schlumberger advocate repeating RAI until the postablation scan normalizes, up to a cumulative dose of 600 mCi (22.2 GBq) of I-131.

Inpatient Versus Outpatient RAI

1. Before 1997, patients with DTC undergoing RAI in the United States required hospital admission if they received more than 32 mCi of I-131 and were released when their exposure rates at 1m fell to 7 mrem/hr or below.

2. After 1997, patients whose therapeutic doses exceeded 32 mCi need not be hospitalized, provided that their release does not expose the general public to a dose equal to or greater than 500 mrem.

Thank you