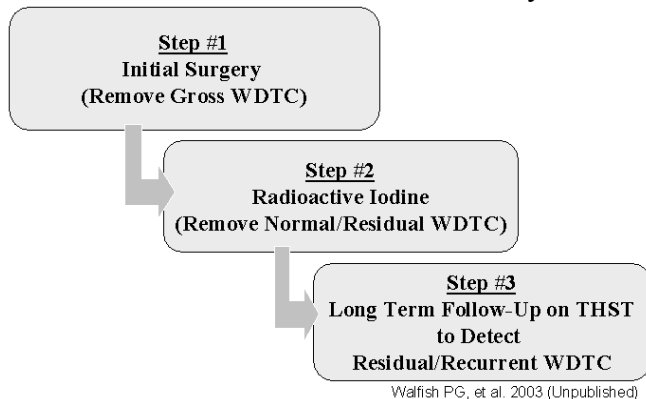


Thyrobuletin of the Thyroid Foundation of Canada  
**Advances in the Early Detection and Treatment of Residual/Recurrent Papillary-Follicular Thyroid Cancer**

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**Introduction\*:**

Well-differentiated papillary-follicular thyroid carcinoma (WDTC) is the most frequent cancer treated by endocrinologists. Although its prevalence has been increasing in many geographic regions, advances in early detection and treatment have improved survival and lessened the chance of recurrent or residual WDTC. These improvements have resulted from the increasing recognition that to optimize long-term results, there is a need to systematically administer adequate treatment to every affected WDTC patient during three successive management steps (Fig. 1). Step #1 mandates a total to near total thyroidectomy



**Figure 1. Management steps for WDTC treatment.**

surgical procedure and the removal of abnormal cervical lymph nodes. Step #2 requires adherence to specific protocol preparations and precautions (Fig. 2) and an adequate dose of radioactive iodine <sup>131</sup>I (RAI) ablation therapy to remove any remnants of residual thyroid cancer. Once these two steps have been properly completed, Step #3 long-term follow-up on thyroid hormone suppression therapy (THST) follows to monitor by clinical and laboratory assessments for the earliest possible detection and

treatment of any residual/recurrent thyroid cancer (Fig. 3).

- Previous Total/Near Total Thyroidectomy
- 8-12 weeks Post-surgery
- Low iodine diet 7-8 days before RAI therapy
- No previous Iodine Contrast Material for 4-6 months
- Avoidance of pregnancy for 3-6 months
- Withdrawal from L-T3 THST for 14-18 days
- Pre-RAI therapy serum TSH and Tg
- Post-RAI therapy WBS 5-7 days after treatment

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**Figure 2. Requirements for satisfactory Step #2 RAI therapy.**

The methods used over the past several decades to monitor WDTC patients in Step #3 have included various combinations of neck ultrasound and an isotopic diagnostic whole body scan (WBS), as well as serum TSH, free T4 and serum thyroglobulin (Tg) blood tests (Fig. 3). However, much confusion has occurred in the literature as to the utility of these tests in the early detection of residual disease and their impact the quality of life for WDTC patients. In this article, the strategies currently available for the earliest detection and prompt management of residual/recurrent thyroid cancer will be reviewed and the limitations of previously recommended diagnostic screening methods such as radioisotopic whole body scanning (WBS), with its associated morbidity and inconvenience, will be re-evaluated.

**An estimated 10-20% of patients have residual/recurrent disease on follow-up over 10-20 years, with the highest risk of recurrence in the first 10 years**

\* Abbreviations used in this publication are listed in the Appendix.

### What are the best strategies for detecting and managing residual/recurrent WDTC?

The increasing recognition that the serum thyroglobulin test can be a useful diagnostic method for detecting high-risk compared to low-risk recurrent/residual WDTC for most affected patients has greatly assisted in Step #3 follow-up management. As demonstrated in the current report, routine serum Tg testing on either thyroid hormone suppression therapy (THST) or after TSH stimulation, and the advances in tumor localization by neck ultrasound, CT, MRI, and FDG-PET have greatly improved the long-term outlook and quality of life for the vast majority of WDTC patients.

- Clinical Examination & Neck Palpation
- Blood Tests while on THST or after TSH stimulation:
  - TSH, FT4, Tg, TgAb
- Structural Imaging
  - Neck US
  - Neck CT or MRI (with or without contrast)
  - Chest CT (without contrast)
- Radioisotopic Imaging
  - Post-RAI therapy WBS
  - FDG-PET (with or without TSH stimulation)
  - Some centers do a diagnostic WBS after TSH-stimulation

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### Figure 3. Summary of Step #3 management for detecting residual/recurrent WDTC.

#### What are the clinical features of high-risk versus low-risk WDTC?

Clinical features at WDTC presentation that contribute to an increased risk of residual/recurrent disease and mortality include: > 45 years of age, primary lesion size > 4 cm, local invasion into adjacent extrathyroidal structures, extension into regional neck lymph nodes, cancer cell histology of tall/columnar > Hürthle > follicular > papillary, as well as a delay of WDTC treatment in Steps #1 and #2 for > 1 year. Patients of the male sex, inadequate previous Steps #1 (surgery) and #2 (radioactive iodine treatment) as well as inadequate thyroid hormone suppression therapy (THST) during Step #3 can also increase the risk for WDTC recurrences and death. Delay in the treatment of residual disease may contribute to an unfavorable outcome.

The extent of WDTC documented at the time of surgery (Step #1) using a staging classification can

also assist in predicting high vs. low risk for residual/recurrent disease. **Stage 1** is when the WDTC is confined to the thyroid gland; **Stage 2** when cervical regional lymph node metastases are observed; **Stage 3** has evidence of extrathyroidal extension to adjacent structures at the time of surgery; and **Stage 4** has spread to distant sites such as the lung and bone. The clinical risks and staging of WDTC disease at presentation can be applied to each affected patient to determine the indications for aggressive radioactive iodine ablation therapy (Step #2) and intensity of follow-up care (Step #3). Thus, low-risk Stage 1 disease confined to the thyroid bed at initial presentation and adequately treated with surgery and radioactive iodine will have a lesser risk for recurrence and the need for further treatment than WDTC patients with a Stage 2, 3 and 4 staging classification.

#### Serum thyroglobulin as a marker for determining residual/recurrent WDTC.

It has been estimated that 10-20% of WDTC patients are at risk for residual/recurrent disease within 10-20 years after initial diagnosis and treatment. Since the highest risk occurs in the first ten years, it has been of importance to determine the best screening methods for providing the earliest detection and prompt treatment of residual/recurrent WDTC. In the past, the “gold standard” for long-term care had been to routinely perform a radioactive iodine (RAI) whole body scan (WBS). However, a diagnostic WBS requires a withdrawal from thyroid hormone suppression therapy for 4-6 weeks and the imposition of severe symptomatic hypothyroidism every 6-12 months. Concurrently, there has been increasing recognition over the past decade that the measurement of serum thyroglobulin (Tg) can also be a useful screening test for detecting residual WDTC. Providing that Steps #1 and #2 have been correctly performed and there is no anti-thyroglobulin antibody that could interfere with the Tg assay, it has been well established that the serum Tg becomes an excellent marker for the risk for residual disease. Unfortunately, approximately 15% of WDTC patients have concurrent autoimmune (Hashimoto’s) thyroiditis with the release of an anti-thyroglobulin antibody into the circulation that interferes with the accurate measurement of serum

Tg levels. Depending upon the commercial detection method employed, Tg antibody interference results in either a false low or false high serum Tg. Fortunately for the remaining 85% of WDTC patients who do not have Tg antibody interference, the serum Tg test can be utilized as a more convenient and cost-effective diagnostic test than a diagnostic WBS for detecting residual/recurrent WDTC. Observations in our center and others have documented the very frequent occurrence of a negative WBS result when the serum Tg has been positive. Interestingly, we have also shown that a serum TSH-stimulated Tg test taken just prior to Step #2 RAI ablation therapy can also be a useful predictor of the risk for either an unfavorable or good long-term outcome during Step #3. Based upon these experiences, we and others have concluded that whenever initial surgery (Step #1) and RAI ablation therapy (Step #2) have been correctly performed, the serum Tg becomes the “platinum standard” for detecting residual/recurrent thyroid cancer (Fig. 4).

<u>“High-Risk”</u>	<u>“Low-Risk”</u>
Detectable Tg on THST	Undetectable Tg on THST
→ Localize by imaging recurrent WDTC for potential surgical removal	→ Exclude residual/ recurrent disease by a stimulated Tg test

\* The utility of serum Tg as a guide to management depends upon:

- 1) previous total or near-total thyroidectomy and at least one dose of radioactive iodine ablation therapy
- 2) Tg antibody interference is absent

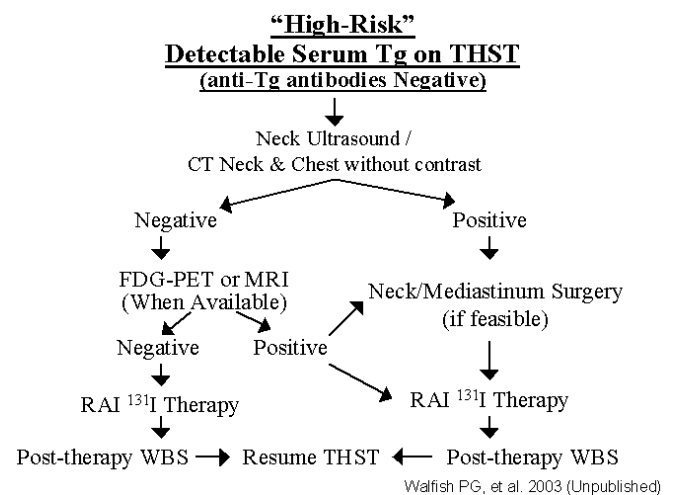
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**Figure 4. Serum Tg is the “Platinum Standard” Screening Test\* for establishing high- versus low-risk residual/recurrent WDTC.**

**A detectable serum thyroglobulin while on thyroid hormone suppression therapy indicates a “high-risk” for residual/recurrent WDTC.**

Patients with “high-risk” by either clinical features and/or a detectable serum thyroglobulin despite thyroid hormone suppression therapy require intensive investigation to localize the site of residual disease (Fig. 5). Imaging methods can be used for diagnostic confirmation and tumor localization. Such tests include neck ultrasound (US), magnetic resonance imaging (MRI), computerized tomography (CT) of the neck and chest. Additional functional imaging for patients who are WBS negative, but

thyroglobulin positive, includes a radioactive fluorodeoxyglucose labelled positron emission tomography (FDG-PET) test. Although PET imaging is not yet routinely available in Ontario, it may assist in localization of the thyroid cancer cells by detecting increased glucose uptake in cancer cells. The goal of these localization imaging studies is to determine whether residual cancer can be detected and amenable to surgical removal before another radioactive iodine (RAI) treatment is administered. Since radioactive iodine therapy may only effectively ablate small volumes of residual disease (i.e. not readily seen with imaging techniques), preference is given to surgical resection of WDTC whenever possible prior to another RAI treatment. Should a post-I<sup>131</sup> therapy WBS fail to demonstrate uptake in any site (i.e. negative result), RAI is no longer a feasible treatment option for the future management of such WDTC patients. For “high risk” WDTC patients with a negative post-therapy WBS, the goal of future Step #3 follow-up would be to localize by structural imaging procedures residual disease which is accessible to removal. To this goal, periodic neck ultrasound, CT, MRI and/or an FDG-PET imaging studies may assist in the identification of metastatic deposits that can be surgically resected.



**Figure 5. Schematic outline of the management strategy for high-risk WDTC patients.**

### What are the recommended management strategies for those “low-risk” patients who have undetectable serum thyroglobulin while on thyroid hormone suppression therapy?

Although an undetectable serum Tg when the serum TSH is **suppressed** on thyroid hormone suppression therapy, indicates a “low risk” for residual WDTC and a potentially favorable long-term outcome (particularly for Stage 1 WDTC patients), it has been established that stage 2 to 4 WDTC patients with an undetectable serum Tg on THST can have approximately a 20% risk for residual/recurrent lymph node metastases and 5% risk for distant metastases. It has therefore become essential to obtain a serum Tg after TSH stimulation particularly in those with previously identified clinical and pathologic evidence indicative of a “high risk” to facilitate the earliest detection and treatment of residual disease in Step #3 follow-up monitoring.

### What are the methods available to increase serum TSH levels?

Four previously applied protocol options recommended in Step #3 WDTC management to increase the serum TSH to levels greater than 25 mIU/L before either a diagnostic WBS and/or a serum Tg test have been reported (**Fig. 6**). In **Option #1**, levothyroxine (L-T4) therapy is abruptly discontinued for four to six weeks. Unfortunately, this protocol leads to severe hypothyroid symptoms by the 4<sup>th</sup> week that greatly impair the quality of life and limit employability. In **Option #2**, levo-triiodothyronine (L-T3) is substituted immediately for L-T4 for four weeks before its complete withdrawal for two weeks. Because L-T3 is a very short acting thyroid hormone compared to L-T4, this approach also induces severe symptomatic hypothyroidism and also markedly impairs the quality of life during the last 7-10 days of this protocol. In **Option #3**, the L-T4 dose is reduced by 50% for two weeks and then completely withdrawn for four weeks. This method also induces symptomatic hypothyroidism with a concomitant increase in morbidity and loss of employment time.

Option #1: L- T4 is discontinued abruptly for 6 weeks

Option #2: L-T4 changed to L-T3 for 4 weeks and then discontinued for 2 weeks

Option #3: L-T4 is ↓ by 50% for 2 weeks and then discontinued completely for 4 weeks

Option #4: Recombinant Human TSH (rhTSH) for WBS and Tg Monitoring without discontinuing L-T4 therapy

Walfish PG, et al. 2003 (Unpublished)

### Figure 6. Summary of Options #1-4 for TSH stimulation in treated WDTC patients.

**Option #4** has become available within the past several years to completely avoid any risk of symptomatic hypothyroidism by injecting human recombinant thyroid stimulating hormone (rhTSH) on two successive days while continuing THST. **Option #4** requires adherence to a five-day (Monday-Friday) protocol, as well as the ability to purchase the rhTSH Thyrogen® (Genzyme) at a cost of approximately \$1,300. This medication is not routinely funded by universal health care plans in Canada and is available only to those fortunate to have a private health insurance plan that will pay the costs of this option (**Fig. 7**). To further simplify **Option #4**, the need for a Day 3 RAI 4 mCi <sup>131</sup>I tracer dose for WBS and low iodine diet preparation may be eliminated. Although **Option #4** does induce high serum TSH levels (i.e. over 100 mIU/L), THST is maintained and the metabolic clearance of thyroglobulin from the serum remains increased. Consequently, the stimulated Tg levels observed using **Option #4** may be lower or no different than those obtained using thyroid hormone withdrawal protocols which may have lower TSH stimulation effects (see **Option #5** below).

Day 1: blood test (TSH, Tg) and first injection of rhTSH (0.9 mg)

Day 2: second injection of rhTSH (0.9 mg)

Day 3: (optional) RAI tracer dose for diagnostic WBS

Day 5: blood test (TSH, Tg) and optional WBS

#### **Advantages:**

- High TSH levels
- No hypothyroid symptoms

#### **Disadvantages:**

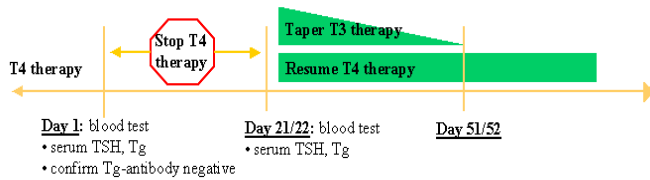
- Logistics & Time commitment
- High cost: ~\$1300 CAD

Walfish PG, et al. 2003 (Unpublished)

### Figure 7. Option #4: Protocol for rhTSH administration.

To minimize morbidity and cost in obtaining a TSH-stimulated serum Tg test, I have administered over the past several years a new protocol – a shortened 3-week T4 withdrawal, **Option #5** (**Fig.**

8). The effectiveness of **Option #5** in not only stimulating an adequate rise in serum TSH, but also detecting residual/recurrent WDTC by a serum Tg test without the need for a routine WBS test has subsequently been confirmed. From a quality of life questionnaire administered to WDTC patients during the **Option #5** protocol, it was documented that a 22-day interval of L-T4 withdrawal resulted



**Advantages:**

- Fewer hypothyroid symptoms and lesser duration of hypothyroid state
- Involves only 2 visits over a 3-week period for blood work and resumption of T4/T3 combination therapy dose to rapidly restore THST
- Cost effective

**Disadvantages:**

- ~15% Risk of an “Indeterminate Response” (undetectable Tg but inadequate  $< 25$  mIU/L TSH)

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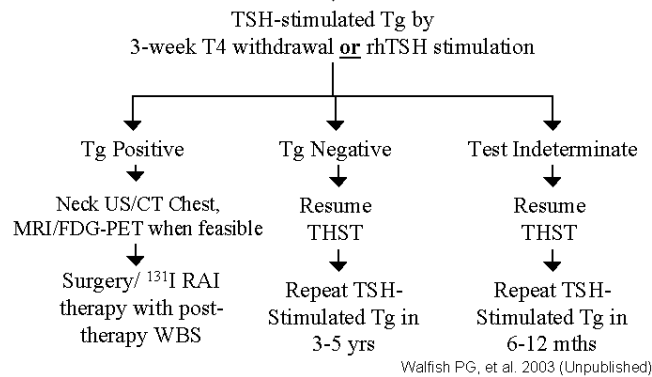
**Figure 8. Option #5 shortened (3-week) T4 withdrawal protocol for obtaining a TSH-stimulated serum Tg test.**

in almost no loss of employment time and only mild hypothyroid symptoms that could be promptly reversed by resuming combined L-T4/T3 therapy (**Fig. 8**). The time commitment for **Option #5** required only one extra office visit 22 days after withdrawal from L-T4 therapy to obtain the blood test and instructions for resuming combined L-T4 and L-T3 therapy. When **Option #5** is administered, three possible serum Tg/TSH outcomes were observed (**Fig. 9**). Among approximately 200 patients screened by **Option #5**, 75% had a negative test result response for **residual/recurrent** WDTC, i.e. a sufficient rise in serum TSH  $\geq 25$  mIU/L and an undetectable serum Tg ( $< 2$   $\mu\text{g/L}$ ). This large subgroup was considered free of disease and was instructed to resume THST management with the possibility that their thyroid hormone dose could be lowered to avoid the consequences of excessive long-term thyroid hormone therapy. This could be relevant to those WDTC patients in older age groups with cardiac disease and menopausal complications. In agreement with other TSH-stimulated Tg protocols, it is also feasible to identify a second small subgroup ( $\approx 10\%$ ) requiring further investigation and treatment who had a “positive test result” for residual/recurrent WDTC on the basis of a

serum Tg test  $\geq 2$   $\mu\text{g/L}$ . Finally, a small ( $\approx 15\%$ ) WDTC third subgroup was identified with an “indeterminate test response” on the basis of an insufficient rise in their serum TSH ( $< 25$  mIU/L) and an undetectable serum Tg. This latter subgroup could be selected for more intensive TSH stimulation by either extending the thyroid hormone withdrawal interval (with its associated morbidity as outlined in Options #1-3) or by using rhTSH Thyrogen® stimulation (with its associated cost and time commitments, as outlined in Option #4). WDTC patients in the third small subgroup with an “indeterminate” TSH stimulated Tg previously identified to have high-risk clinical and pathologic features may require additional TSH stimulation testing and structural imaging tests to more definitively exclude residual/recurrent WDTC. Follow up on low-risk WDTC patients initially screened by **Option #5** with a negative stimulated Tg test result over a subsequent 3-5 year interval by clinical examinations and supplemental serum Tg, as well as non-radioisotopic imaging, has not revealed to date any patient who developed residual/recurrent WDTC.

test ( $\geq 2 \mu\text{g/L}$ ). Preliminary data from our center

**“Low-Risk”  
Undetectable Serum Tg on THST  
(anti-Tg antibodies Negative)**



**Figure 10. Schematic outline of the management strategy for “low-risk” WDTC patients.**

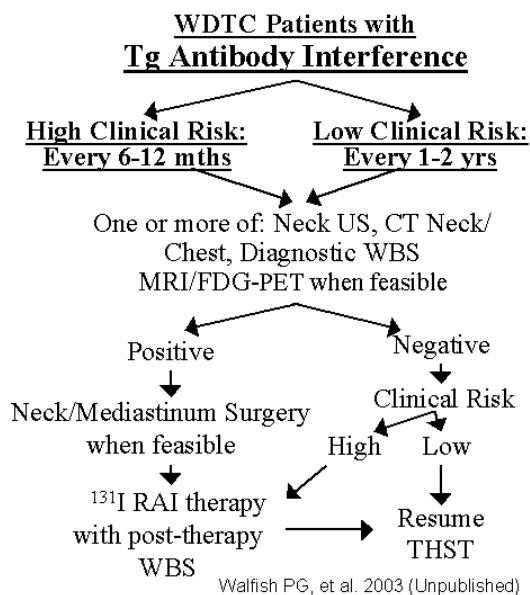
		<u>% of Study Cohort</u>
<u>Negative</u>	1. TSH $\geq 25$ mIU/L, Tg undetectable ( $< 2 \mu\text{g/L}$ ) → considered disease free, resume THST	75%
<u>Positive</u>	2. Tg detectable ( $\geq 2 \mu\text{g/L}$ ) → selected for investigation & treatment	10%
<u>Indeterminate</u>	3. Tg undetectable but TSH $< 25$ mIU/L → consider for rhTSH while on THST or longer T4 withdrawal interval to exclude residual/recurrent WDTC	15%

From Golger A, Fridman TR, Eski SJ, et al. J Endocrinol Invest 2003, In Press

**Figure 9. Summary of possible serum TSH/Tg responses to a 22-day T4 withdrawal TSH-stimulated Tg test.**

Consequently, either Option #5 or #4 protocols can be recommended as the most convenient and effective strategies to guide further management by obtaining a TSH-stimulated serum Tg on “low-risk” WDTC patients followed in Step #3 protocol with an undetectable Tg on THST. As outlined (Fig. 10), those patients who have a positive TSH-stimulated Tg test undergo further imaging to localize the detected residual disease that may be treated by surgery and/or radioactive iodine. Those patients identified to have a negative Tg result can resume THST, whereas those who have an indeterminate result will require repeat TSH stimulation and follow-up. Long-term observations are in progress to determine the precise clinical outcome and significance of a positive TSH-stimulated serum Tg

suggest that low-risk WDTC patients with a TSH-stimulated Tg positive values less than  $20 \mu\text{g/L}$  may not have residual WDTC that can be easily localized by currently available diagnostic imaging technology and could continue to have a favorable long-term prognosis. For those patients who have thyroglobulin antibody interference, the strategies outlined based on serum Tg detection cannot be applied and a greater reliance must be placed on special imaging methods to detect residual/recurrent WDTC (Fig. 11). Those with previously established higher clinical risk for residual WDTC (i.e. those with Stages 2-4 disease), but with negative imaging and/or detected disease not amenable to surgical removal, may be considered for a second RAI treatment and a post-therapy WBS to confirm and attempt to treat unsuspected residual/recurrent WDTC (Fig. 11).



**Figure 11. Schematic outline of the management strategy for WDTC patients with Tg antibody interference.**

In summary, the advances in diagnostic detection and management of residual/recurrent well-differentiated thyroid cancer by the application of a serum thyroglobulin test without a diagnostic WBS test have been outlined. When combined with the established long-term clinical risk factors and recent improvements in structural imaging technologies for localizing residual/recurrent disease, the management of WDTC has greatly improved the quality of life and long-term survival for most WDTC patients.

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**Appendix of Abbreviations:**

WDTC: Well-Differentiated Papillary-Follicular Thyroid Cancer, THST: Thyroid hormone suppression therapy, WBS: Whole Body Scan (diagnostic or post-therapy radioiodine <sup>131</sup>I), Tg: thyroglobulin, US: ultrasound, CT: computed (axial) tomography, MRI: magnetic resonance imaging, FDG-PET: (<sup>18</sup>F)-fluorodeoxyglucose positron emission tomography, RAI: radioactive iodine (<sup>131</sup>I isotope), TSH: thyrotropin, L-T4: levo-thyroxine, L-T3: levo-triiodothyronine, FT4: free thyroxine