Technical Brief

TSH Receptor mRNA for Thyroid Cancer Diagnosis and Follow-up

Background

Incidence rates of thyroid cancer have been rising, with more than 30,000 new cases now diagnosed annually in the United States. In addition, millions of patients are being followed for recurrence after treatment for thyroid cancer. Current management relies predominantly on fine needle aspiration biopsy (FNA) for the preoperative evaluation of thyroid nodules. Although FNA has good positive and negative predictive values for papillary thyroid carcinoma (PTC), it is unable to differentiate benign follicular lesions from follicular carcinoma. Furthermore, FNA generates indeterminate results in about 15-30% of patients. These patients subsequently require surgery for diagnostic reasons, which might have been avoided if better disease markers were available.

Serum thyroglobulin (Tg) remains the sole circulating marker for the monitoring and detection of recurrent thyroid cancer after total thyroidectomy. It lacks sensitivity and is unreliable in the presence of thyroglobulin autoantibodies (TgAb). These limitations have prompted a search for new disease markers. Among these, a molecular-based assay using quantitative RT-PCR to detect circulating thyroid cancer cells by measuring thyrotropin receptor (TSHR) mRNA in peripheral blood has shown promise as a valuable addition to patient care [1-5].

Clinical Indications

In Preoperative Detection of Cancer in Patients with Thyroid Nodules:

Currently there are no known circulating markers for the detection of thyroid cancer among patients with nodular thyroid disease. Tg cannot be used as a diagnostic marker for thyroid cancer preoperatively.

TSHR mRNA showed a 72% sensitivity and 83% specificity in differentiation of malignant nodules from benign nodules [2,3]. TSHR mRNA combined with FNA had 90% sensitivity and 80% specificity to diagnose thyroid cancer. This test correctly classified 71% of patients with indeterminate FNA, saving some unnecessary diagnostic surgeries.

One of the major limitations of FNA is its inability to differentiate follicular cancer from benign follicular lesions. Combining TSHR mRNA with worrisome nodular features on thyroid ultrasound correctly classified all follicular cancers and could spare some unnecessary surgeries in patients with benign disease [5].

A positive test may be a strong factor for the decision to proceed with surgery in initial evaluation of a patient with nodular disease and indeterminate FNA [1,2].

In Monitoring Patients with Thyroid Cancer:

TSHR mRNA has a short life in circulation. Normalized levels within 24 hours postoperative correlated with disease-free status. Elevated levels predicted residual metastatic disease.

For long-term monitoring, studies have demonstrated a high sensitivity and specificity for TSHR mRNA in detecting recurrent/residual thyroid cancer. This marker is not affected by the presence of thyroglobulin antibodies that are known to interfere in Tg measurement and circumvents some of the other issues currently facing serum Tg measurements, including its low sensitivity while the patient is on TSH suppression.

In patients with known thyroid cancer, a positive test will alert to the high likelihood of persistent or recurrent disease. A negative test may offer reassurance of absence of disease, especially in the presence of thyroglobulin antibodies and negative ultrasound examination of the neck.

Interpretation

TSHR mRNA levels > 1.0 ng /μg total RNA = presence of thyroid cancer (based on receiver operating characteristics [ROC] curve in an in-house study [1]).

Note: TSHR mRNA is not intended to be used as an independent solitary diagnostic test for the initial diagnosis of thyroid cancer among patients with nodular disease preoperatively.

Limitations of the assay

TSHR mRNA measurement should be used and interpreted in the clinical context of the individual patient and other available clinical data [eg. thyroid function tests, fine needle aspiration biopsy and ultrasound] to enhance overall thyroid cancer diagnostic accuracy and with serum thyroglobulin measurement for monitoring.

Proper sample collection and timely processing are necessary for test accuracy. Due to the labile nature of RNA, this sample must be placed on ice immediately after collection and must be delivered or shipped via overnight mail at 4°C. It is important that RNA is isolated within 24 hours of draw. In patients with nodular disease it is recommended to draw blood prior to FNA and/or ultrasound as the effect of these procedures on TSHR mRNA levels are not known at this time.

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Methodology

1. TSHR mRNA levels are determined by a quantitative RT-PCR assay.
2. Total RNA is extracted and reverse transcribed and then subjected to PCR.
3. Samples are normalized for the amount of RNA loaded into each reaction. Absolute quantity is measured against a reference preparation [thyroid cancer RNA].
4. Results are reported in arbitrary units as reference preparation equivalent TSHR mRNA ng/µg of total RNA. The estimated functional sensitivity is 0.14 ng/µg of total RNA.

References:


Test Overview

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<tr>
<th>Test Name</th>
<th>TSHR mRNA</th>
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<tr>
<td>Reference Range</td>
<td>&lt;1.0 ng/µg of total RNA</td>
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<tr>
<td>Specimen Requirements</td>
<td>Two 7 mL whole blood EDTA [lavender] Place and transport on ice.</td>
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<td>Special Information</td>
<td>This is a novel molecular test that detects thyroid cancer cells expressing TSHR mRNA by RT-PCR analysis. Call prior to sending sample 216.445.5104 or Pager 216.464.8410 ext 25064 or via e-mail <a href="mailto:lounsbr@ccf.org">lounsbr@ccf.org</a> or <a href="mailto:guptam@ccf.org">guptam@ccf.org</a></td>
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Technical Information Contact:

Rose Lounsbury
216.445.5104
lounsbr@ccf.org

Scientific Information Contacts:

Manjula Gupta, PhD
216.444.2714
guptam@ccf.org

Mira Milas, MD
216.444.4985
milasm@ccf.org