TSHR mRNA Arrives as Thyroid Cancer Marker

BY PATRICE WENDLING

FROM THE ANNUAL MEETING OF THE AMERICAN SURGICAL ASSOCIATION

CHICAGO — Thyroid-stimulating hormone receptor messenger RNA is a clinically useful blood test in the pre- and postoperative management of thyroid cancer, based on results from a prospective validation study in 1,095 consecutive patients.

If detectable preoperatively, when fine-needle aspiration suggests follicular neoplasm, thyroid-stimulating hormone receptor (TSHR) messenger RNA (mRNA) accurately predicts thyroid cancer and guides the extent of surgery, reported Dr. Mira Milas, principal investigator.

"It has a practical role to predict thyroid cancers where other modalities may fall short," she said. In addition, high levels on the first postoperative day alert physicians to persistent disease, while its presence during long-term surveillance aids in identifying recurrence.

"We are encouraged by this performance and the fact that it is a convenient blood test to perform," said Dr. Milas, director of the thyroid center at the Cleveland Clinic. "Our next steps are to search for multicenter trials and [Food and Drug Administration] approval for some of these indications."

No new blood tests for differentiated thyroid cancer have been introduced into routine clinical practice since thyroglobulin. Thyroglobulin is used for cancer follow-up, but not initial diagnosis.

The TSHR mRNA assay was developed 9 years ago at the clinic's pathology department by study collaborator Manjula Gupta, Ph.D.

TSHR mRNA acts as a surrogate marker for circulating thyroid cancer cells, and in initial studies distinguished benign from malignant thyroid diseases.

A recent report suggests that TSHR mRNA is detectable even in thyroid microcarcinomas, and may characterize those with potentially more aggressive histology (Surgery 2009;146:1081-9).

The aim of the current analysis was to validate the clinical use of the marker 1 year after its introduction at the Cleveland Clinic, where the test is now used daily in all patients scheduled for thyroid surgery and those undergoing consultation for thyroid disease in the office.

From October 2008 through September 2009, TSHR mRNA was measured by quantitative real-time polymerase chain reaction from blood drawn in 403 patients undergoing thyroid surgery, postoperatively in 541 patients, and in 151 patients monitored for benign goiters.

Preoperative Use

Preoperative TSHR mRNA greater than 1 ng/mcg as a sole predictor of cancer had a positive predictive value (PPV) of 81% and specificity of 83% in 374 patients with surgically confirmed pathology, Dr. Milas said. Sensitivity was modest at 61%, as was negative predictive value at 64%. However, its PPV was 100% in patients with papillary thyroid cancers greater than 1 cm.

She observed that TSHR mRNA is particularly useful in detecting cancer in patients with follicular neoplasms on fine-needle aspiration. In 54 such patients, TSHR mRNA alone had a PPV of 96%, a specificity of 96%, and accuracy of 85%. The sensitivity of diagnosing cancer improved from 76% to 97% when the blood test was combined with ultrasound. Ultrasound features such as irregular margins, hypervascularity, indistinct borders, and microcalcification are suggestive of cancer in follicular neoplasms, but none are independently diagnostic. The highest risk of a false positive occurs with Hashimoto's disease, Dr. Milas acknowledged.

Postoperative Use

Use of the blood test in 69 paired samples with thyroid cancer revealed that elevated TSHR mRNA levels became undetectable in all patients on postoperative day 1, except in seven who had persistent or recurrent cancer within the year and unfavorable histologic features.

TSHR mRNA had a positive predictive value of 100% in patients with papillary thyroid cancers greater than 1 cm.

DR. MILAS

In contrast, all 40 patients with benign disease had undetectable TSHR mRNA levels on day 1 after thyroidectomy. "This suggests the potential use of TSHR mRNA as an early marker of adequate surgical clearance of disease or future recurrence," Dr. Milas said in an interview.

Long-Term Surveillance

TSHR mRNA also showed merit during long-term follow-up of thyroid cancer, notably in two particularly challenging scenarios: when thyroglobulin antibodies were present, and when patients had residual thyroid tissue from original surgery and detectable thyroglobulin levels between 0.2 and 49 ng/mL that are difficult to interpret, she said.

At a median follow-up of about 2 years in 60 patients with elevated thyroglobulin antibodies, detectable TSHR mRNA was the only blood test to confirm cancer in four patients. Negative TSHR mRNA reassured absence of disease in 54 of the 56 remaining patients whose imaging was also negative.

All 59 patients with residual thyroid tissue because of partial thyroidectomy for cancer had undetectable TSHR mRNA levels and no radiologic evidence of cancer recurrence at follow-up, she said.

"This assay has come of age," remarked Dr. Collin Weber, the invited discussant and chief of endocrine surgery at Emory University Hospital in Atlanta.

He questioned whether total thyroidectomy is performed at the Cleveland Clinic on all indeterminate lesions when the assay is positive and whether its accuracy is good enough to recommend observation of TSHR mRNA-negative follicular neoplasms greater than 2.5 cm in size.

Dr. Milas responded that total thyroidectomy would be advised based on abnormal TSHR mRNA levels because a positive predictive value of 96% is reassuring and has held up in daily practice since the analysis was closed.

She said the assay is not accurate enough, however, to recommend observation in sonographically suspicious, 2.5-cm or greater tumors with undetectable TSHR mRNA levels, but "is possibly and cautiously" enough when combined with an informed discussion with the patient when smaller lesions lack concerning ultrasound features and in patients with medical comorbidities who face increased risk during a diagnostic thyroidectomy. ■

Disclosures: *Dr. Milas and Dr. Weber stated they had no relevant disclosures.*

Papillary Thyroid Cancer Survival 2% Better With Treatment

BY MARY ANN MOON

FROM THE ARCHIVES OF OTOLARYNGOLOGY AND HEAD AND NECK SURGERY

Patients with papillary thyroid cancers that are limited to that gland are likely to have a favorable outcome regardless of whether they undergo rapid definitive treatment or are simply observed for disease progression, researchers reported.

In an epidemiologic study using Surveillance, Epidemiology, and End Results (SEER) data on more than 35,000 papillary thyroid cancers (PTCs) diagnosed in 1973-2005, 20-year survival was 97% in patients who did not receive definitive treatment within 1 year, compared with 99%—"only 2% better"—in those who did, wrote Dr. Louise Davies of Veterans Affairs Medical Center, White River Junction, Vt., and her associates.

"Papillary thyroid cancers of any size that are confined to the thyroid gland, have no lymph node metastases at presentation, and do not show extraglandular extension are unlikely to result in death due to the cancer. Thus, clinicians and patients should feel comfortable considering the option to observe for a year or longer cancers that fall into this category," the investigators said.

In an editorial, Dr. Erich M. Sturgis and Dr. Steven I. Sherman of the University of Texas M.D. Anderson Cancer Center, Houston, strongly disagreed with this conclusion, emphasizing that observation "should only be cautiously considered in the most carefully selected cases." They added, "We would wonder whether the six people who died of their thyroid cancer in this real yet very selected … 'no treatment' group would have agreed that a statistically significant 2% difference in survival was not clinically relevant."

Dr. Davies and her associates examined the natural history of untreated PTC using SEER data because the number of thyroid cancers detected using new technologies has tripled in the past 30 years, and there is still great uncertainty about whether and how to treat these mostly subclinical lesions.

They identified 35,663 cases of microscopically confirmed, localized PTC diagnosed during the 32-year study period. Only 440 patients (1.2%) did not undergo hemithyroidectomy or total thyroidectomy, with or without irradiation, within 1 year of diagnosis.

The reasons for the decision to forgo treatment were not available. In 216 of the 440 patients, definitive treatment was recommended but not done, and in 165 it was not recommended and not done. Treatment recommendations were not documented for the remaining 59 patients.

After mean follow-up of approximately 8 years for the treated group and 6 years for the untreated group, there was no significant difference between the proportion of thyroid cancer deaths that occurred in the treated group (161 of 35,223 patients, or 0.5%) and the untreated group (6 of 440 patients, or 1.4%). Long-term thyroid cancer–specific survival rates "were nearly identical" at 99% and 97%, respectively, the investigators said.

Survival was not affected by whether treatment had been recommended or not, Dr. Davies and her colleagues said (Arch. Otolaryngol. Head Neck Surg. 2010;136:440-4). In addition, cancer-specific survival was essentially the same whether patients underwent hemithyroidectomy or total thyroidectomy.

For patients with this form of cancer, "survival is so good that it is appropriate to consider whether the risk of complications outweighs the benefits of treatment during discussions about when and how to treat the disease. The risk of permanent hypoparathyroidism and significant damage to laryngeal function have been reported to range from 3% to 5% in large case series," they noted.

In their invited commentary, Dr. Sturgis and Dr. Sherman disputed these conclusions, noting that readers will be "poorly informed and perhaps misinformed" by the authors' interpretation of their data (Arch. Otolaryngol. Head Neck Surg. 2010;136:444-6). ■

Disclosures: *This study was supported in part by the Department of Veterans Affairs and the Robert Wood Johnson Faculty Scholars Program. No financial conflicts of interest were reported.*