# Thyroid Carcinoma Recommendations Updated

BY DAMIAN McNAMARA

HOLLYWOOD, FLA. — The National Comprehensive Cancer Network has updated its thyroid carcinoma guidelines to add consideration of small molecule kinase inhibitors in metastatic disease treatment, refine diagnosis and treatment strategies based on fine-needle aspiration, and provide new information on thyroid-stimulating hormone suppression.

The panel of 26 physicians noted increasing off-label use of small molecule kinase inhibitors in patients with thyroid carcinoma. They said these agents can be considered to treat papillary, follicular, Hürthle cell, or medullary carcinoma, if a clinical trial is unavailable or inappropriate.

Although it's a drug class recommendation, "we specifically mention sorafenib and sunitinib as options," Dr. Steven I. Sherman said at the annual conference of the National Comprehensive Cancer Network (NCCN). Best supportive care also remains a consideration for these patients with clinically progressive or symptomatic disease.

Neither kinase inhibitor is indicated for thyroid cancer. The Food and Drug Administration has approved sorafenib (Nexavar) in advanced renal cell carcinoma and hepatocellular carcinoma, and sunitinib (Sutent) in gastrointestinal stromal tumors and metastatic renal cell carcinoma. Both are under investigation in other tumors.

The NCCN revised procedures for evaluating thyroid nodules, especially follicular or Hürthle cell neoplasms and follicular lesions of undetermined significance that cannot be diagnosed by fine-needle aspiration (FNA). For an undetermined lesion, if the thyroid-stimulating hormone level is high or normal, repeat FNA and consider surgery based on clinical findings concerning growth or suspicious findings on ultrasound. If the TSH is low, perform a thyroid scan, and repeat FNA based on the same factors if the scan is cold; if it is hot, evaluate and treat for thyrotoxicosis. A follicular lesion of undetermined significance still carries a 5%-10% risk of cancer, Dr. Sherman said.

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**Treat undetermined lesions according to TSH level, Dr. Steven I. Sherman said.**

Diagnostic categories based on FNA findings have been updated. One category, for example, is patients who have or are suspected of having papillary, medullary, or anaplastic thyroid carcinoma. These patients have a 99% risk of cancer, and should go directly to primary treatment, said Dr. Sherman, department chair and professor of endocrine neoplasia and hormonal disorders at the University of Texas M.D. Anderson Cancer Center, Houston.

If the FNA indicates thyroid lymphoma, refer to NCCN Non-Hodgkin's Lymphoma Guidelines. If the FNA comes back as an insufficient biopsy or as nondiagnostic, treatment is dictated by whether it is cystic or solid. "An insufficient biopsy still carries a 1%-7% risk of cancer," Dr. Sherman said.

For a benign thyroid nodule, the risk of cancer is 1% or less, Dr. Sherman said, and observation is recommended. However, if there is nodule growth, repeat the FNA or consider surgery.

Patient age over 45 years is no longer a factor that should raise clinical suspicion with a solitary thyroid nodule greater than 1 cm in diameter in the setting of an unknown TSH level, according to the new guidelines.

For patients with a positive FNA finding, the panel provides a less stringent recommendation for a chest radiograph: "Consider chest x-ray" instead of "chest x-ray, if not recently done." There is greater consensus now behind the panel's recommendation to perform a lateral neck ultrasound in this group of patients.

The NCCN also added recommendations for the use of levothyroxine for TSH suppression in papillary, follicular, and Hürthle cell carcinomas. The use of levothyroxine is considered optimal to maintain low TSH levels and minimize risk of stimulating the growth of cells derived from thyroid follicular epithelium, but there are insufficient data to recommend serum TSH targets. Instead, the guidelines say, "in general, patients with known residual carcinoma or at high risk for recurrence should have TSH levels maintained below 0.1 mU/L, whereas disease-free patients at low risk for recurrence should have TSH levels maintained either slightly below or slightly above the lower limit of the reference range." Patients who remain disease free for several years can probably have TSH levels maintained within the reference range.

The guidelines advise balancing risks and benefits of suppressive levothyroxine therapy for each patient. There is potential for cardiac tachyarrhythmias, bone demineralization, and thyrotoxicosis caused by TSH-suppressive doses. Also, patients on long-term suppression need an adequate intake of calcium (1,200 mg/day) and vitamin D (800 U/day).

Dr. Sherman is a consultant for and receives grant and research support from several pharmaceutical companies and the National Cancer Institute, and is on the speakers bureau for Genzyme. ■

## Radioiodine Recommendations Refined

The National Comprehensive Cancer Network changed its recommendations for management of patients with thyroid carcinoma post thyroidectomy, especially concerning the use of radioiodine therapy.

Radioactive iodine (RAI) therapy is now an option for patients with no gross residual disease in the neck after surgery. "Postoperative RAI therapy is to destroy any remaining normal thyroid tissue as a source of thyroglobulin production, to improve accuracy of follow-up testing," Dr. Sherman said.

The guidelines now list RAI as an alternative at 1-12 weeks post thyroidectomy to a total body radioiodine scan.

Clinical indications for RAI are based on pathology, postoperative thyroglobulin, and intraoperative findings.

The recommendations are specific by cancer stage. For example, radioiodine therapy for stage II disease "for the first time is associated with a survival advantage … with total or near-total thyroidectomy," Dr. Sherman said. "Stage I is the problem. This is the largest group of patients, but overall survival is worse with radioactive iodine therapy.

"Clearly there is no evidence of a benefit among stage I patients. This is a very important pullback in terms of the recommendations," he said.

"It is our particular opinion at M.D. Anderson that a total body radioiodine scan should be performed prior to treatment because of its diagnostic usefulness," he added.

# Lower Normal TSH Range May Help Detect Hypothyroidism

BY MITCHEL L. ZOLER

PHILADELPHIA — A lower normal range for thyroid-stimulating hormone would help physicians detect and treat more cases of occult hypothyroidism, Dr. Leonard Wartofsky said at the annual meeting of the American College of Physicians.

Based on common thyroid-stimulating hormone (TSH) levels among U.S. adults, a reasonable normal range is 0.4-2.5 microIU/mL, said Dr. Wartofsky, an endocrinologist and chairman of the department of medicine at Washington (D.C.) Hospital Center.

Although some other experts also endorse this or a similar TSH range as the new normal, it has not yet made its way into official recommendations. For example, the most recent TSH range endorsed by the American Association of Clinical Endocrinologists remained at 0.5-5.0 microIU/mL (Endocr. Pract. 2006;12:63-102). The National Academy of Clinical Biochemistry set an upper limit of normal for TSH at 4.1 microIU/mL in 2003 (Thyroid 2003;13:3-126), Dr. Wartofsky said.

Other experts warn that lowering the threshold for diagnosing hypothyroidism risks identifying and treating patients who have not been proven to face a substantial disease risk or to benefit from treatment (JAMA 2004;291:228-38).

Dr. Wartofsky argued in favor of a lower normal range because of the way TSH levels are distributed among Americans. In the National Health and Nutrition Examination Survey (NHANES) III, which measured TSH levels in about 13,000 U.S. adults who were free from any suggestion of thyroid disorder during 1988-1994, the average TSH level was about 1.5 microIU/mL (J. Clin. Endocrinol. Metab. 2002;87:489-99). Among women, who have a higher risk for hypothyroidism compared with men, the average level was 1.39 microIU/mL in white women and 1.18 microIU/mL in African American women.

Based on the bell-shaped distribution of TSH levels among Americans, statistics showed that about 97.5% of the population has a TSH level of less than 2.5 microIU/mL, Dr. Wartofsky said in an interview. Those patients with higher levels are worth examining further to detect unrecognized hypothyroidism.

He suggested that people younger than 60 years with TSH levels higher than 2.5 microIU/mL get retested a few months later. The second blood draw should also be tested for antithyroperoxidase antibody (anti-TPOAb). People whose TSH level remains high and who are antibody positive should start treatment for hypothyroidism with thyroxine, Dr. Wartofsky said. "They are destined to move on to overt hypothyroidism." In about a quarter of people with initially high TSH, the level will drop on retesting without any treatment.

People with persistently high TSH but without detectable anti-TPOAb fall into a gray area. They could start on thyroxine treatment, or they could defer treatment and get retested in a year. The decision to treat or not would depend on whether the patient had any signs or symptoms of hypothyroidism.

TSH levels seem to normally rise as people age. Among men and women aged 60-80 years, a TSH of 3.0 microIU/mL is reasonable, Dr. Wartofsky said. ■