CLINICAL THYROIDOLOGY **FOR THE PUBLIC**

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THYROID CANCER

Use of BRAF and RET/PTC molecular tumor markers in thyroid cancer biopsies showing papillary thyroid cancer

BACKGROUND

Thyroid nodules are very common. When a thyroid nodule of sufficient size is found, a biopsy of the nodule is usually performed to suggest whether it is benign (non-cancerous) or malignant (cancerous). While the biopsy results are usually clear, sometimes it can be difficult to clearly identify a cancer and surgery is required to make the diagnosis. Recent advances have made molecular marker testing (mutation testing of thyroid cancer genes) of the biopsy sample available; these represent additional tests that can be used to guide management of the nodule. Two genes in particular are associated with thyroid cancer: BRAF and RET/PTC.

Two studies were recently done to report the frequency of the BRAF and RET/PTC mutations in patients with thyroid nodule biopsies who underwent thyroid surgery. Although it is controversial, some researchers think that having a BRAF mutation suggests that the cancer (usually papillary thyroid cancer, the most common form of thyroid cancer) will be more aggressive, particularly when the initial nodule is large.

These two studies report the relationship between how often these thyroid cancer genes were initially positive and the aggressiveness of thyroid cancer through longterm monitoring. The goal of both studies was to see how useful testing for these molecular markers can be in patients in whom thyroid cancer is suggested by biopsy results.

THE FULL ARTICLES' TITLES

Walczyk A et al The BRAF V600E mutation in papillary thyroid microcarcinoma: does the mutation have an impact on clinical outcome? Clin Endocrinol (Oxf). December 13, 2013 [Epub ahead of print].

Guerra A et al Concomitant BRAF(V600E) Mutation and RET/PTC rearrangement is a frequent occurrence in papillary thyroid carcinoma. Thyroid 2014;24:254-9. Epub August 25, 2013; doi: 10.1089/thy.2013.0235.

SUMMARY OF THE STUDIES

Walczyk and colleagues studied how often the BRAF mutation was positive from 113 samples from patients seen at a Polish hospital during 2012. All patients had been diagnosed with micropapillary thyroid cancer (cancers that are <10 mm in size) following thyroid surgery. Since BRAF mutations have been found usually in larger cancers, this study is novel in that it was studied only in these smaller cancers. The researchers found that surprisingly, a large percentage (78 of 113) of the micro-papillary cancers contained the BRAF mutation, although none of the patients showed persistence or recurrence of the cancer after the patients were followed up on average for 4.8 years.

Previous studies have reported that having both the BRAF and RET/PTC gene mutations in a single tumor is quite rare. In the second study, Guerra and researchers reported how often both mutations were found in 72 Italian patients with papillary thyroid cancer to show whether having dual mutations may carry a unique prognosis. The BRAF mutation was found in 44.4% of the cancers, of which 36.1% also had the RET/PTC mutation. The RET/PTC was found in 69.5% of the cancers, of which 30.5% also had the BRAF mutation. Positive mutations of both genes were not more common in the patients with Stage IV thyroid cancer. The main conclusion is that although both the BRAF and RET/PTC mutations were more frequently found in this group of papillary thyroid cancer patients, this does not necessarily indicate a worse prognosis.

WHAT ARE THE IMPLICATIONS OF THESE STUDIES?

These two studies report on the frequencies of two common thyroid cancer gene mutations, BRAF and RET/PTC in patients with papillary thyroid cancer living in Poland and Italy. Published literature has reported that these mutations usually signal more aggressive disease at initial diagnosis and during longterm monitoring. The main findings from these current studies were that the

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BRAF mutation in patients with micropapillary thyroid cancers and both the BRAF and RET/PTC mutations in patients with all sizes of papillary thyroid cancers do not necessarily suggest more aggressive disease. Further research is needed to show whether these findings are similarly applicable for papillary thyroid cancer patients living in the U.S. using larger groups of patients with longer follow-up.

— Angela M. Leung, MD, MSc

ATA THYROID BROCHURE LINKS

Thyroid cancer: http://www.thyroid.org/cancer-of-the-thyroid-gland

ABBREVIATIONS & DEFINITIONS

Thyroid nodule: an abnormal growth of thyroid cells that forms a lump within the thyroid. While most thyroid nodules are non-cancerous (benign), ~5% are cancerous.

Thyroid fine needle aspiration biopsy (FNAB): a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or cancer. The doctor uses a very thin needle to with-draw cells from the thyroid nodule. Patients usually return home or to work after the biopsy without any ill effects.

Papillary thyroid cancer: the most common type of thyroid cancer.

Papillary microcarcinoma: a papillary thyroid cancer smaller than 1 cm in diameter.

Molecular markers: genes and microRNAs that are expressed in benign or cancerous cells. Molecular markers can be used in thyroid biopsy specimens to either to diagnose cancer or to determine that the nodule is benign.

Cancer-associated genes: these are genes that are normally expressed in cells. Cancer cells frequently have mutations in these genes. It is unclear whether mutations in these genes cause the cancer or are just associated with the cancer cells. The cancer-associated genes important in thyroid cancer are BRAF, RET/PTC and RAS.

BRAF gene: this is gene that codes for a protein that is involved in a signaling pathway and is important for cell growth. Mutations in the BRAF gene in adults appear to cause cancer.

Mutation: A permanent change in one of the genes.