



THYROID NODULES

Can analysis of a small panel of genetic mutations on samples from thyroid biopsies help us to decide which nodules should be removed?

BACKGROUND

Thyroid nodules are common and are found in over 50% of patients, but thyroid cancer is rare. Thyroid biopsy is an important step in identifying which nodules are benign and which nodules require surgery (suspicious or cancerous on cytology). However, about 30% of the biopsies result in an indeterminate category, meaning that they cannot make a diagnosis based on the cells alone. In the past, many patients with indeterminate biopsies went to surgery, with resulting benign findings. In retrospect, these patients did not require surgery

Further testing has been proposed to categorize these indeterminate nodules into low risk or high risk for cancer. One of the methods used is to analyze the thyroid biopsy specimen for specific genetic mutations, known as molecular markers, which are seen in thyroid cancers. If the biopsy is negative for these mutations, the nodule is considered benign and surgery is not needed. If a mutation is present, the risk of cancer increases anywhere from 40-90%. While several commercially available panels test for a wide range of mutations, the 3 most common mutations associated with aggressive thyroid cancer are BRAF, RAS and TERT. This study evaluated whether analyzing the presence of a limited set of these known mutations could predict which nodules required surgery.

THE FULL ARTICLE TITLE

Macerola E et al 2018 The mutational analysis in the diagnostic work-up of thyroid nodules: the real impact in a center with large experience in thyroid cytopathology. *J Endocrinol Invest*. Epub 2018 Apr 27. PMID: 29704233.

SUMMARY OF THE STUDY

This study looked at a large number of patients (511) in Pisa, Italy who were evaluated by thyroid biopsy of one or more thyroid nodules (total 617 nodules) and performed

genetic testing on all samples looking for mutations in the genes BRAF, RAS and TERT. The genetic testing was not used to determine which patients would go to surgery. They then correlated the frequency and type of mutation to the final pathology in the 167 nodules from 126 patients who ended up having surgery.

The presence of one of the mutations was highly predictive of cancer in the final pathology. In the benign cytology category, 57 of a total of 425 nodules went to surgery and 8 turned out to be follicular variant papillary thyroid cancer. Of these 8, 5 had a RAS mutation. In the indeterminate category, 56 of a total 114 nodules went to surgery, 25 of which turned out to be cancer. In this group, 70% of the nodules with a mutation (1 BRAF, 11 RAS, 1 TERT) turned out to have cancer while only 33% of those without a mutation ended up with cancer. All of the patients in the suspicious or cancerous cytology categories had cancer found at the time of surgery. Of these, 63% of the nodules had mutations (25 BRAF, 2 RAS, 3 TERT).

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study showed that examining thyroid biopsy specimens for a small panel of genetic mutations was highly predictive of cancer on the final pathology. This was most helpful in the indeterminate cytology category, with RAS mutations the most common mutation identified and of those, 80% turned out to be cancer at surgery. Mutation analysis was not helpful in nodules with high-risk cytology categories since all these patients were found to have cancer at surgery. This study adds to the information regarding using molecular testing to further identify patients in whom biopsies are indeterminate that do not need surgery and to target those that would benefit the most from surgery.

— Marjorie Safran, MD





THYROID NODULES, continued

ATA THYROID BROCHURE LINKS

Fine Needle Aspiration Biopsy of Thyroid Nodules: <https://www.thyroid.org/fna-thyroid-nodules/>

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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 biopsy: 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 withdraw cells from the thyroid nodule. Patients usually return home or to work after the biopsy without any ill effects.

Indeterminate thyroid biopsy: this happens a few atypical cells are seen but not enough to be abnormal (atypia of unknown significance (AUS) or follicular lesion of unknown significance (FLUS)) or when the diagnosis is a follicular or hurthle cell lesion. Follicular and hurthle cells are normal cells found in the thyroid. Current analysis of thyroid biopsy results cannot differentiate between follicular or hurthle cell cancer from noncancerous adenomas. This occurs in 15-20% of biopsies and often results in the need for surgery to remove the nodule.

Suspicious thyroid biopsy: this happens when there are atypical cytological features suggestive of, but not diagnostic for malignancy. Surgical removal of the nodule is required for a definitive diagnosis.

Genes: a molecular unit of heredity of a living organism. Living beings depend on genes, as they code for all proteins and RNA chains that have functions in a cell. Genes hold the information to build and maintain an organism's cells and pass genetic traits to offspring.

Mutation: A permanent change in one of the genes.

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. The two most common molecular marker tests are the Afirma™ Gene Expression Classifier and Thyroseq™

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, TERT 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.

Follicular variant of papillary thyroid cancer: one of the subtypes of papillary thyroid carcinoma, which has been classified to three different forms: non-invasive follicular thyroid neoplasm with papillary-like nuclear features, invasive encapsulated and infiltrative FVPTC.

