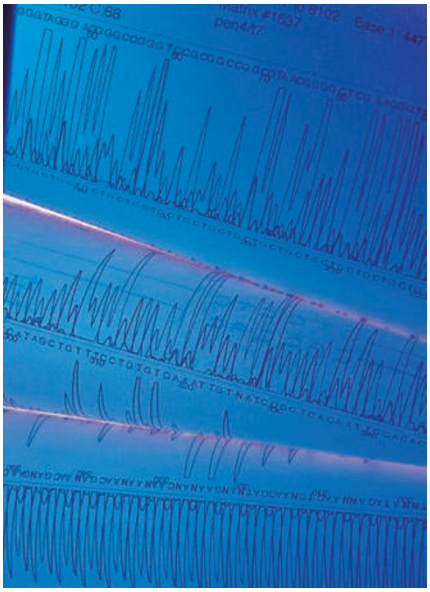
DIAGNOSIS

Molecular analysis assists differential diagnosis of thyroid nodules

Analysis of gene mutations in fine-needle aspiration biopsies could help improve the diagnosis of cancer in patients with thyroid nodules, say researchers from the University of Siena, Italy. "Oncogene mutation is strongly correlated with the final diagnosis of thyroid cancer, with better sensitivity and specificity compared to traditional cytology," explains lead investigator Furio Pacini. "Furthermore, the combination of the two tests increased the sensitivity and specificity, with diagnostic accuracy near to 95%."

Thyroid nodules have become a frequent (and often incidental) finding over the past few years; however, only a small fraction of these nodules are actually cancerous. Fine-needle aspiration cytology is considered the gold standard for evaluating the malignant potential of thyroid nodules. This approach benefits the patient in that it is minimally invasive, reasonably safe and allows rapid diagnosis of the nodule. However, because the total number of thyroid cells in each aspirate is small, some biopsies can be insufficient for analysis. In addition, an appreciable number of samples return indeterminate results. Given these limitations, many researchers are actively engaged in finding ways to improve the diagnostic accuracy of fine-needle aspiration cytology.

One potential method to increase the reliability of traditional cytology is to perform molecular tests on the nodule aspirates. Somatic point mutations and rearrangements of a number of genes have previously been identified in patients with differentiated thyroid cancer. The aim of the study performed by Cantara and colleagues was, therefore, to evaluate the diagnostic utility of screening aspirates for mutations in a panel of genes—*BRAF*, *RAS*, *RET*, *TRK* and *PPARγ*—known to be associated with thyroid cancer.



The study group included 174 consecutive patients scheduled for thyroid surgery after undergoing fine-needle aspiration cytology; 138 of the participants were female and the mean age was 51.2 years (range 20–83 years). The cytological indications for surgery included probable cancer (48 patients), suspicion of cancer (22 patients), indeterminate result (50 patients) and compressive symptoms in the presence of benign or inadequate cytology (54 patients). Ultrasound-guided, fine-needle aspiration biopsy was repeated before surgery in 235 thyroid nodules; one-third of each aspirate was used for the molecular analysis, the remainder being reserved for traditional cytology. Cantara *et al.* took this approach to evaluate whether their method could be performed in routine clinical practice without the need for additional sampling of the nodules. Tissue samples were taken at surgery to validate the molecular analysis of the aspirates.

The investigators detected mutations in 67 of the cytology samples (28.5%). *BRAF* was found to be the most frequently mutated gene (33 samples); *RAS* mutations were detected in 23 aspirates and *RET* rearrangements (*RET–PTC*) in 11 aspirates. Most aspirates harboured mutations within a single gene. The mutation detected in the cytology sample was confirmed in the corresponding tissue sample in 88.2% of cases. A total of 78 thyroid cancers were confirmed by histology after surgery. Detection of mutations in the aspirates was associated with the presence of thyroid cancer in 91.1% of cases and with follicular adenoma in the remainder of cases. *BRAF* mutations and *RET–PTC* were always associated with thyroid cancer, whereas *RAS* mutations were associated with thyroid cancer in 74% of cases. The combination of molecular analysis and traditional cytology led to improved diagnostic accuracy when compared with the use of either technique alone.

The next step for the research group is to enlarge the number of cases studied. In addition, they plan to refine the technique by defining the amount of cytological material that should be collected in order to maximize the number of informative results. Finally, the investigators hope to explore the possibility of developing a 'gene chip' platform that would allow the entire panel of gene mutations to be analyzed at once.

"The implications for diagnosis are very important," states Pacini. "Refining the diagnosis of malignancy will save many unnecessary thyroid surgeries and will allow better planning of the best surgical procedure in those patients where surgery is advisable."

Vicky Heath

Original article Cantara, S. *et al.* Impact of proto-oncogene mutation detection in cytological specimens from thyroid nodules improves the diagnostic accuracy of cytology. *J. Clin. Endocrinol. Metab.* **95**, 1365–1369 (2010)