Title: Detecting Known Driver Mutations & Levels of Long Non-Coding RNAs in Differentiated Thyroid Cancer

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Background: Thyroid cancer, commonest endocrine malignancy, iscaused by multiple genetic and epigenetic changes leading to alterations in signalling pathways.Ifdiagnosed early and treated surgically prognosis is excellent. However, diagnosis of malignancy and decision of surgical removal guided by Fine-Needle Aspiration Cytology (FNAC) can be problematic due toinconclusive reports as a result ofinadequate sample, classification as atypia/follicular lesion of undetermined significance and Follicular neoplasm/ suspicious for follicular neoplasm. **Objective:**To detect a panel of known driver mutationsand levels of long non-coding RNAsin plasma of suspected patients. **Methodology**:Patients attending Nodule clinics of IPGMER presenting with solitary thyroid nodule and provided consent were recruited. Detailed history, clinical examination and ultrasonographic findings following TIRADS were recorded. About 5 ml blood, FNAC samples and surgically removed tissues, whenever available, were collected. Cell free DNA/RNA was isolated from plasma was isolated DNA/RNA from FNAC samples and tissue was isolated using standard in house methods. Hotspot mutations in BRAF, NRAS and HRAS were detected by allele specific PCR primers. Levels of lncRNA PVT1 were detected by reverse transcriptase mediated PCR. **Results:**We recruited (62) patients, based on FNAC (15)with malignancy of which (6) tumors were removed surgically. Mutations BRAF (V 600 E), NRAS (Q 61 R) and HRAS (G 12 V) were detected in 3 samples; one of them was in non-diagnostic category; in 2 cases had confirmed malignant diagnosis after surgery. A combination of cytology and molecular testing showed significant improvement in the diagnostic accuracy and allowed better prediction of malignancy in the nodules with indeterminate cytology.Besides, levels of PVT1in plasma was identified; levels were absent in most of the non-malignant cases. **Conclusions:**We established proof of concept that mutation detection in plasma can help making decision for the surgeons.