clinicopathologic data were obtained through retrospective chart review. We identified 49 *PTEN* mutation-positive nodules from 48 patients. Patients were 57 years old on average (range 14-88) and 80% female. Cytology was predominantly indeterminate (73% atypia of undermined significance, 18% follicular neoplasm). There were 18 (29%) frameshift, 6 (10%) splice site, and 39 (62%) single nucleotide variant *PTEN* mutations. Fourteen (29%) nodules had two *PTEN* mutations, 5 (10%) had copy number alterations, and single cases had concurrent *BRAF K601N*, *EZH1*, and *NRAS* mutations. Surveillance was pursued for 27 (56%) and surgery for 21 (44%) patients (16 lobectomies, 5 total thyroidectomies). There were 14 follicular adenomas (FA), 4 oncocytic FA's, 1 oncocytic hyperplastic nodule, and 1 encapsulated follicular variant papillary thyroid carcinoma (EFVPTC). The EFVPTC had two low-frequency *PTEN* mutations, *PTEN* locus loss, an *NRAS* mutation, and was a low-risk tumor with capsular but no angiolymphatic invasion. Four (8.3%) patients had confirmed or suspected PHTS, all with multiple nodules. Two had surgery finding no malignancies (2 FA). One PHTS patient had a prior thyroidectomy for a *MET* mutation-positive nodule that was follicular carcinoma. On US, the mean nodule size of patients who had surgery was larger than the surveillance group (3.2 cm vs. 2.3 cm, p=0.02) but there was no difference in TI-RADS level (p=0.54). There was no difference in mean nodule size (3.5 cm vs. 2.6 cm, p=0.35) or TI-RADS level (p=0.81) between PHTS and non-PHTS patients. Among surveillance patients, follow-up US was done at 1 year in 13/19 (68%) and 2 years in 3/6 (50%) of eligible cases. Only 1/19 (5%) underwent repeat FNA for increased nodule size. No thyroid malignancy was found with a mean of 1.75 years of follow-up (range 1.00-2.78). The EFVPTC patient had no recurrence after 1.05 years of follow-up. In summary, thyroid nodules with isolated somatic *PTEN* mutations are primarily benign and can be safely followed with serial imaging. Nodules with multiple *PTEN* mutations were only associated with malignancy when accompanied by an additional *NRAS* mutation. About 8% of patients with *PTEN* mutations may be PHTS patients who may be at greater risk for malignancy.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Comparative Analysis of Different International Criteria (ACMG-AMP vs. TENGEN) Applied to Classification of Missense Germline Allelic Variants in Patients With Multiple Endocrine Neoplasia Type 1 or Suspected to this Syndrome.

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Context: Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant genetic syndrome caused by germline pathogenic allele variants (PAV) in the *MEN1* tumor suppressor gene, which predispose *MEN1* carriers to the increased risk of several endocrine neoplasms throughout life. The *MEN1* gene (11q13), contains 10 exons encoding the MENIN protein. About 600 different PAVs have been reported, with 25% of them being missense variants. Of value, the definition of pathogenicity can be challenging, especially for missense variants. Thus, international guidelines for improving the classification of allele variants were recently defined by the ACMG-AMP (2015). Recently, applying ACMG-AMP criteria with inclusion of clinical features the TENGEN French group suggested modifications aiming to refine the classification of variants in MEN1 syndrome. **Objective:** To classify missense allelic variants found in the *MEN1* gene by the ACMG-AMP guideline using VARSOME and by the TENGEN group to support a comparative analysis of the results obtained with these two methodologies (ACMG-AMP; TENGEN). **Methods:** the classification of 16 different missense allele variants identified in 17 index cases with or suspected to MEN1 syndrome was conducted according to ACMG-AMP criteria using the VARSOME software followed by the analysis defined by the TENGEN group. **Results:** Of the 16 variants, 6 were new, 1 was recurrent (2 unrelated index cases) and 9 of them occurred in codons with previous reports of different amino acid exchanges in the same region. Differences observed in the classification by ACMG-AMP and TENGEN were: pathogenic variant (6% vs. 65%); probably pathogenic (88% vs. 12%) and variants of uncertain significance (VUS) (6% vs. 23%). The four VUS classified by TENGEN (one of them for ACMG-AMP) were of sporadic cases without clinical diagnosis of MEN1 (2, for one MEN1-related tumor in early age; 1, for suspected MEN1) or with high risk of phenocopy (1, HPT + acromegaly). **Conclusion:** The difference observed in the classification of the pathogenicity of these variants, especially due to the higher occurrence of VUS in TENGEN, indicates that the criteria adopted by ACMG-VARSOME would have to be refined for clinical features. By other side, TENGEN apparently reinforce the classification of pathogenicity in cases with clinical diagnosis of MEN1 and reduce the definition of pathogenicity to variants found in MEN1-suspected cases without clinical criteria for the MEN1 diagnosis. These protocols apparently need to be investigate, validated and, probably, improved in other cohorts to reduce risks of misinterpretations and classifications that can, lately, interfere in genetic counseling and in the clinical management of patients. Finally, long-term outcome of cases classified as VUS, functional studies and, familial segregation may reinforce the initial impressions obtained with TENGEN classification.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Comprehensive Analysis of Clinical Features in Index Cases With Multiple Endocrine Neoplasia Type 1 Refine the Risk Rate for Detection of Mutation Distinguishing Negative-Mutation (Phenocopies) and Positive-Mutation Cases.

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