Cancer Guidelines (ATA Guidelines) and the 2017 ACR TIRADS system (ACR Guidelines). The nodules were divided into benign or malignant categories based on surgical pathology. Noninvasive follicular thyroid neoplasms with papillary like nuclear features (NIFTP) were categorized as benign. **Results:** A total of 22 nodules were identified to have a RAS mutation. NRAS mutated nodules, all with the same point mutation (pQ61R c.182A>G), were most common 14/22 (63.6%). There was no significant difference in clinical features, ultrasonographic appearance or histopathologic outcomes between NRAS- and HRAS-mutated nodules. 12/22 (54.4%) were low risk by ATA Guidelines and 11/22 (50%) were TIRADS 4 (moderately suspicious) by ACR Guidelines. There was no significant difference in predictive value of ATA Guidelines vs ACR Guidelines. The prevalence of malignancy was 45.4% (only slightly lower than the general risk for a suspicious GSC). Invasive follicular variant papillary thyroid cancer (FVPTC), was the most common malignancy, 4/10 (40%). 6/10 (60%) were classified as low risk of recurrence post-operatively. All malignant RAS-mutated nodules (10/10) had at least one other non-cystic nodule present on ultrasonography whereas only 4/9 (44%) of RAS-mutated benign nodules did [P=.006]. RAS-mutated malignant nodules had significantly more nodules with irregular borders compared to RAS-mutated benign nodules (4/10 and 0/10, 40% and 0% respectively) [P=.03]. **Conclusions:** This is the first study to observe higher rates of malignancy in RAS-mutated indeterminate nodules when other non-cystic nodules are present. A lobectomy is the preferred surgical approach for RAS-mutated nodules, however a total thyroidectomy may be considered in patients with other non-cystic nodules or irregular nodules borders. Overall, RAS-mutated nodules have a low risk of recurrence post-operatively.

Thyroid

THYROID CANCER

Interobserver Variability in Ultrasound Reporting - Tertiary Hospital Radiologists Do Better

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Introduction: Thyroid Imaging Reporting and Data System (TI-RADS) was developed to provide a standardized risk-stratification system for patients with thyroid nodules. Single-center studies have demonstrated an acceptable level of interobserver agreement in applying TI-RADS in clinical practice, however data regarding consistency among different centers is limited. In Israel, thyroid nodules are initially evaluated by ultrasound performed by radiologists at the health maintenance organization (HMO) and then patients are referred to tertiary hospitals for ultrasound-guided fine needle aspiration (FNA) biopsy when indicated. **Objective:** To evaluate the interobserver concordance in TI-RADS classification system reporting between the HMO and a tertiary hospital. **Methods:** We performed a retrospective analysis of the sonographic features of 370 thyroid nodules TI-RADS category 2 or higher, from 350 patients evaluated by ultrasound at the HMO and at Hadassah Medical Center from January 1, 2018 to December 31, 2019. The primary outcome was concordance between the TI-RADS classification at the HMO compared to the hospital. Additional endpoints included correlation of TI-RADS to the Bethesda category following FNA, and correlation of TI-RADS with malignancy on final pathology. **Results:** Of 370 nodules, only 73 (19.8%) demonstrated concordance between the HMO and the hospital. The level of agreement was poor, with 277 (74.8%) nodules demonstrating higher TI-RADS at the HMO compared to the hospital, and 20 (5.4%) with lower TI-RADS at the HMO compared to the hospital ($p<0.001$, weighted Kappa = 0.120). Of the nodules referred to the hospital, 241 (65.1%) were selected for FNA. A strong correlation between the hospital TI-RADS and Bethesda category was demonstrated ($p<0.001$). Furthermore, 60 (16.2%) nodules were surgically removed. A strong correlation was identified between the hospital TI-RADS and malignancy on final pathology ($p<0.001$), yet there was no correlation with the TI-RADS of the HMO ($p=0.346$). **Conclusions:** There is poor concordance between TI-RADS classification on ultrasound performed in the HMO compared to a tertiary hospital. In patients who underwent FNA and eventually surgery, the hospital TI-RADS strongly correlated with Bethesda category and final risk of malignancy. Standardization of thyroid ultrasound terminology and dedicated training in thyroid imaging are needed to improve the interobserver concordance in clinical practice.

Thyroid

THYROID CANCER

Is Metformin Use Associated With Decreased Thyroid Cancer Risk in Patients With Acromegaly?

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Context: Acromegaly has long been blamed to portend an increased risk for benign and malignant thyroid neoplasia. Growth hormone (GH) and consequent insulin-like growth factor 1 (IGF-1) hypersecretion are implicated in cancer promotion. Metformin, a biguanide derived from the French lilac, is gaining considerable interest because of its plausible anti-tumor properties. Besides, metformin has been shown to inhibit somatotroph proliferation and decrease GH secretion in *in vivo* studies. Patients with acromegaly have high incidence of diabetes and were thereof treated with metformin. We hypothesized metformin use may be linked to decreased thyroid cancer incidence in patients with acromegaly. **Study Design and Methods:** The medical records of 508 patients with acromegaly followed at our tertiary referral center between 1969 and 2019 were retrospectively reviewed. The inclusion criteria were having a follow-up duration for at least 12 months and being regularly screened for nodular thyroid disease and thyroid cancer by ultrasonography as indicated in respective guidelines. Patients with acromegaly were evaluated based on ongoing or prior history of metformin use or thyroid cancer diagnosis. Metformin exposure was defined

as use of metformin for at least 12 months on a regular basis between initial date of acromegaly and time prior to cancer diagnosis date. Considering the long patency period of cancer of interest, we excluded exposures in the year immediately prior to index cancer date. We evaluated the effect of metformin exposure on risk of thyroid cancer using Kaplan-Meier analysis. **Results:** Final analysis included 377 patients with acromegaly. Mean age at acromegaly diagnosis was 41.6 ± 11.7 and 60.5% of the patients were female. Three hundred twenty-two patients (85.4%) had undergone transsphenoidal surgery as primary therapy, 73 patients (19.4%) needed radiotherapy and 178 patients (46%) received post-operative medical therapy. Median follow-up duration was 73.5 months (IQR [31.0-137.7]). One hundred twenty patients (31.9%) had an ongoing or prior use of metformin, and total of 19 patients (5%) had thyroid cancer. Age at acromegaly diagnosis, gender distribution, baseline GH and IGF-1 levels, pituitary tumor size and invasiveness, biological aggressiveness, curative therapy options, treatment responses didn't differ between metformin users and non-users, as well as between those having and not having thyroid cancer. Kaplan-Meier estimates for 1 year, 3 years and 5 years of metformin exposure showed decreased probability of thyroid cancer incidence ($p<0.05$ for all). **Conclusion:** Although our results imply decreased thyroid cancer risk upon metformin exposure, prospective study designs with larger cohorts are obliged in order to fully elucidate the effect of metformin use on thyroid cancer.

Thyroid

THYROID CANCER

Macrophage-Tumor Crosstalk in the Pathogenesis of Follicular Thyroid Cancer

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Thyroid cancer is the most common endocrine malignancy and one of the fastest growing cancers in the United States. Follicular thyroid carcinoma (FTC) represents the second most common form of thyroid cancer diagnosed in the US and is most often tied to mutations in the RAS protein family of the MAP kinase pathway. In addition to driver mutations, FTC is characterized by a unique tumor microenvironment (TME) composed of cellular and non-cellular components that impact tumorigenesis and disease progression. Preliminary data from our lab has shown that CD45+ immune cells account for approximately 68% of all cells found in whole tumors collected from mouse models of RAS-driven disease. Macrophages account for the largest portion of known immune cell populations. Further experiments have demonstrated that tumor cell lines isolated from our RAS-driven models secrete cytokines known to impact the recruitment and activation state of cells of the myeloid lineage, particularly macrophages. However, it's unclear what type of functional characteristics are induced by these secreted factors and how the resulting macrophage phenotype affects disease progression. Here, we sought to determine how bidirectional communication between macrophages and thyroid cancer cell lines could contribute to the development of a protumorigenic microenvironment. First, we began by defining how RAS-driven thyroid cancer cell lines affected the functional phenotype of previously unstimulated macrophages. Through gene expression analysis encompassing several markers of macrophage activation states, we determined that tumor cell-secreted factors induced the expression of multiple genes associated with tumor associated macrophages (TAM). In particular, we observed consistent upregulation of IL-10 and TNF-alpha, factors that have been associated with worsening disease. These results were further validated through quantification of protein secretion. In addition, we determined the role of activated macrophages in the progression of thyroid cancer, and specifically the effect of macrophage-secreted factors on tumor cell proliferation. Through direct and indirect assays of proliferation, we determined that factors secreted by classically-activated M1 macrophages inhibited cell proliferation. Surprisingly, secretions from alternatively-activated M2 macrophages reduced in vitro cell growth in some cell lines. Further analysis demonstrated that reduced cell proliferation was not associated with cell death, but rather was a result of delayed progression through the cell cycle. These results help to further define the macrophage phenotype within our model of FTC and will identify potential therapeutic targets to reduce the activity of protumorigenic cell populations.

Thyroid

THYROID CANCER

Malignancy Risk in ^{18}F-FDG-Avid Thyroid Incidentalomas: Controversies and Limitations

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Introduction: The prevalence of malignancy in thyroid incidentalomas (TI) discovered on ^{18}F-FDG-PET or PET/CT varies between 0% and 63.6%. The pooled malignancy rate according to three systematic reviews is 33-35%. The 2015 American Thyroid Association (ATA) guidelines recommend that such nodules, when one centimeter or larger in size, should undergo further investigation with thyroid ultrasound (US) and fine-needle aspiration (FNA) cytology. **Objectives:** The objective of our study was to determine the rate of malignancy amongst TI discovered incidentally on ^{18}F-FDG-PET or PET/CT, examine their clinicopathologic characteristics, and assess the usefulness of maximum standardized uptake values (SUV_{max}) in differentiating benign and malignant lesions. **Methods:** We performed an electronic medical record search looking at all ^{18}F-FDG-PET or PET/CT reports during the study period of 12/01/2015 to 05/31/2019 that included the keyword 'thyroid' in the impression. Exclusion criteria included a history of thyroid disease or malignancy, known lesion(s) detected on previous clinical or radiological