

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 latency 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  $41.6 \pm 11.7$  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 micro-environment. 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 <sup>18</sup>F-FDG-Avid Thyroid Incidentalomas: Controversies and Limitations*

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**Introduction:** The prevalence of malignancy in thyroid incidentalomas (TI) discovered on <sup>18</sup>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 <sup>18</sup>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 <sup>18</sup>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

examinations and diffuse radiotracer uptake. Of the 476 reports reviewed, 136 cases were included in the study.

**Results:** Common indications included initial staging or restaging of lymphoma (diffuse large B-cell, mantle-cell, T-cell types) (27.9%), lung adenocarcinoma (18.4%), head and neck cancer (16.9%) and breast cancer (11%). Fifty-eight (42.6%) patients had metabolically inactive lesions; five (8.6%) underwent further investigation with thyroid US and 3 subsequently with FNA (5%). All 3 had benign cytology. Seventy-seven (56.6%) patients had metabolically active lesions and 25 (32.5%) underwent imaging with thyroid US. Twelve (15.6%) had FNA; eight (66.7%) had benign cytology, two (16.7%) revealed atypia of undetermined significance and two (16.7%) were malignant. Biopsy for the two patients with malignant cytology showed follicular cell neoplasm of oncocyctic hurtle cell type, and invasive follicular carcinoma with focal insular and papillary features and extensive capsular and vascular invasion. The mean  $SUV_{max}$  in malignant vs benign lesions was 9.05 and 6.41 respectively. **Conclusion:** The malignancy rate was 2.6% amongst all patients with  $^{18}F$ -FDG-avid TI and 8% amongst patients with metabolically active lesions who were investigated with thyroid US +/- FNA. This is significantly lower than malignancy rates previously reported in the literature. The evident inhomogeneity in the literature is likely multifactorial and may be explained in part by a dissimilarity among studies, and an informed decision by some to avoid invasive testing in the context of poor prognosis from underlying non-thyroidal cancer. Research is needed to determine the cohort of patients who could potentially benefit from further evaluation and treatment.

## Thyroid

### THYROID CANCER

#### *Malignancy Risk in RAS-Mutated Cytologically Indeterminate Thyroid Nodules: Real-World Clinical Experience*

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**Introduction:** Fine needle biopsy (FNB) is the standard procedure for thyroid nodules meeting criteria for biopsy according to current national guidelines (ATA and ACR). However, 15-25% of biopsies are categorized as indeterminate in the Bethesda Categories III (Atypical/FLUS) or IV (Follicular/Hurthle Neoplasm). Molecular testing is a common way to further risk stratify these nodules for surveillance versus surgical resection. BRAF-like mutations have a high probability of malignancy while RAS-like mutations have a variable risk of malignancy. This study examines the performance of RAS mutations in identifying malignancy or NIFTP in a real-world clinical setting.

**Methods:** 2,372 sequential thyroid FNBs were performed in our center from July 2014 to June 2020. Of these, 367 were subjected to molecular testing with either Thyroseq V2 or V3. 55 RAS-mutated BCIII or IV cases were identified and retrospectively evaluated. NIFTP was considered malignant in the calculations. ATA and ACR ultrasound classification as well as Doppler grade of the study nodule were assessed.

**Results:** 8 cases were excluded due to lack of follow-up or incomplete data. 40 underwent surgical resection based on the cytology and molecular results. 7 did not undergo surgery based on patient preference or comorbidities and had clinical follow up with stable ultrasound for at least 6 months. Surgical pathology results: 67.5% benign, 7.5% NIFTP and 25% malignant.

All 4 of the Thyroseq "currently negative" RAS nodules were benign. Of the 36 "positive" cases, 6 with additional mutations had a 66.7% ROM and the 30 RAS-only cases had a 30% ROM. Of the 9 RAS-only cases that were not benign, 3 were NIFTP, 5 FVPTC (2 unencapsulated and 3 encapsulated) and 1 was angio-invasive PTC with extensive extrathyroidal extension (this case had high-risk pre-op imaging features). None had lymph node involvement.

Higher allelic frequency, abnormal gene expression (GE) and copy number alterations (CNA) all increased the risk of malignancy/NIFTP; ROM was 50% when both GE and CNA were positive. Nodules that were ATA/ACR moderate and high suspicion had an approximately 40% and 67% ROM respectively with ATA and ACR performing similarly. High intra-nodular vascularity conferred a 46% ROM.

**Conclusions:** RAS mutations represent the most frequent abnormality found in oncogene testing however isolated RAS mutations have a low risk of malignancy and when malignant are generally non-aggressive. When both GE and CNA are positive, the risk increases. US features, including Doppler also contribute to risk assessment. Combining all these features is recommended when counseling patients on active surveillance versus surgical resection of RAS-mutated thyroid nodules.

## Thyroid

### THYROID CANCER

#### *Management of Papillary Thyroid Cancer Metastatic to the Central Nervous System: A Narrative Review of the Literature*

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**Introduction:** Brain metastases (BM) associated with papillary thyroid cancer (PTC) occur with an approximate frequency of 0.15% to 1.3% of PTC cases. There is little evidence regarding the treatment of this association (PTC and BM). A narrative review of the literature is presented. We assessed multiple treatment options and its effectiveness in this vulnerable population. **Methods:** The data were collected using the PubMed search engine and Google Scholar. There were selected all studies that included: << thyroid carcinoma >> << brain metastases >> << radiotherapy >> << surgery >> << iodine-131 >> << papillary carcinoma >>