and secondary investigators and a group of medical students. A subset of manuscripts reviewed by students was concurrently reviewed by the principal or secondary investigator to establish reliability of the student investigators' work.

Results: Fifty-five manuscripts met our inclusion criteria: empirical studies of interventions in undergraduate medical pathology education. Data extracted from each manuscript related to sample size, instructional aim, type of intervention, outcome measurement, significance of results, and strength of evidence.

The majority of the studies focused on interventions in the basic science phase

Basic Science Phase	43
Clinical Science Phase	8
Both	4

The instructional interventions described in these manuscripts focused on medical knowledge (49), clinical skills (5), attitudes and perceptions (17), laboratory skills (4), and patient and family interaction (2). Four manuscripts were categorized elsewhere, and each study could fit into more than one category.

One study was identified as multi-institutional, and none included analysis of learning in a longitudinal fashion. Sample size ranged from 34 students to 1501 students. Five authors did not indicate their sample size. Thirteen of the studies reviewed for this project utilized randomization of subjects.

Conclusions: The use of satisfaction surveys, pre- and post-tests, and confidence ratings were overwhelmingly used to measure the strength of an intervention. Readers cited difficulty identifying specific design details from the Method section of manuscripts. More rigorous inquiry and stronger reporting of methodology and results are needed to strengthen the body of pathology education research.

566 "Pathology Is Relevant, but We Don't Want to Do It." Medical Student Attitudes to Pathology Teaching and Understanding of Pathologists

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Background: Pathology departments play a key role in medical school teaching and patient care, yet few medical students select pathology as a career. Possible reasons for this include negative pathologist stereotypes, lack of awareness about what pathologists actually do, and trainee perception that pathology is a boring subject. This paper presents comparative findings between second year medical students and practising Canadian pathologists on pre-conceived notions of the working environment, lifestyle and personality of pathologists.

Design: Second year medical students at Western University (Ontario) and pathologists practising in Canada participated in incentivized on-line surveys. Descriptive and mean comparisons were used to understand whether their perceptions were similar or different.

Results: Survey response rates were 85% (145/171) for students and 19% (155/828) for pathologists. The majority of students (83%) stated that teaching in medical school was their main source of knowledge about pathology but only 33% agreed that they had a good understanding of what pathologists do. Seventy-five percent agreed that pathology teaching is as relevant as teaching in other specialties. While 67% thought pathology was an interesting subject, only one student intended to pursue a career in pathology. Comparatively, there were significant differences between pathologists' and medical students' views of the entertainment industry's portrayal of pathology, with students thinking the portrayal was more accurate ($t(295)=-4.679$, $p < .001$, $d=.55$). Pathologists were less satisfied with their careers than students perceived ($t(192.05)=-4.885$, $p < .001$, $d=.56$) although 74% were moderately or extremely satisfied.

Conclusions: Pathologists play a critical role in the health care system and lack of student interest in choosing pathology as a career may have long-term detrimental effects. After 2 years of integrated pathology teaching in our medical school curriculum, the majority of students do not have a good understanding of what pathologists do. It is imperative to understand why this is, and to address students' perceptions and attitudes towards pathology to inform how training can enhance interest in the field.

567 A Feedback-Based Training Module Improves Tumor Cellularity Estimation for Molecular Testing

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Background: Assessment of specimen adequacy for molecular testing is the responsibility of pathologists. Given the therapeutic implications in the era of personalized medicine, accurate determination of the percentage of genetic material contributed by lesional cells is imperative to ensure assay quality and appropriate interpretation of results. It is especially important to avoid overestimation in the setting of low tumor content as this can lead to overconfidence in a false negative result and a missed opportunity for effective targeted therapy. Multiple published studies expose significant variability and poor accuracy in tumor cellularity estimation, highlighting a need for evidence-based standardization and training. We present the results of an educational training module designed to address this problem.

Design: An overview of the importance of estimating tumor percent, key concepts, common pitfalls, pictorial diagrams, and virtual practice cases with immediate feedback on performance were compiled into a computer-based training module. The module was administered to a cohort of 7 pathology trainees and 1 experienced molecular pathologist. Participants completed pre- and post-training tests comprised of 10 H&E glass slides of lung adenocarcinoma from FNA and resection specimens. Duplicate slides (5) were included in each test to assess improvement. As a gold standard, tumor cellularity was directly assessed by manual cell counting on digitized slides. Estimation of tumor purity based on the allele frequencies (AFs) of driver mutations detected in routine next generation sequencing-based testing was performed as an additional objective measure of tumor content and compared to the manual count.

Results: Review of molecular test requisitions revealed overestimation of tumor cellularity by an average of 22%. Pre-training slide set responses overestimated tumor by a mean of 12% (3 to 23%) with individual deviance up to 50%. Post-training responses showed 11% mean reduction and overall mean deviation within 1% (-14 to 13%) of the gold standard. A high concordance between manual cell counts and variant AF-based estimates was observed with a mean deviation of -1% (-17 to 7%).

Conclusions: Estimation of tumor percentage by pathologists is highly variable and demonstrates a strong tendency toward overestimation that could contribute to false negative test results. Our study shows that implementation of a simple standardized training module with immediate feedback yields significant performance improvement as demonstrated by more conservative and more accurate estimations.

568 The Use of Screencasts with Embedded Virtual Microscopy Cases to Teach Pulmonary Pathology in the Era of Subspecialized Residency Education

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Background: Academic pathology departments are increasingly subspecialized at a time when the amount of information that residents are required to learn during 4 years has skyrocketed. Our residents rotate through pulmonary pathology for 4 weeks, providing them with limited and intermittent exposure to cases. Screencasts are digital recording of computer screen output with audio narration. They can be combined with virtual microscopy to provide exposure to pulmonary cases in a structured manner that stimulates learning.

Design: Screencasts from neoplastic and non-neoplastic lung cases were prepared using Camtasia Studio 8 (TechSmith, Okemos, MI) and Powerpoint 2016 (Microsoft, Redmond WA) software. The files were saved in mp4 format and saved on our Intranet, YouTube.com and Screencast.com. They can be viewed using a web brower, a PC or MacOS computer and/or a mobile iOS or Android device. Files saved in screencasts.com require a proprietary viewer. Screencasts include a narrated presentation with clinical history, radiologic images, hyperlink to virtual microscopy slides prepared with Aperio scanner (Leica Biosystems, Buffalo Grove, IL), a quiz, a narrated description of the virtual slide by an attending explaining how to examine the cases and a final quiz. The quiz results are automatically emailed to an attending pathologist. A focus group of 5 residents was asked to examine the screencasts and provide feedback to various questions using a 0-5 scale.

Results: Screencast files are relatively small, up to 50 megabytes, and can be viewed from the departmental website, YouTube.com and Screencast.com using desktop computers and mobile devices. However, only files saved in screencast.com provide the ability to answer quizzes and email the results. The members of the focus group liked the technology and provided an average scores ranging from 4.4-4.8 to various questions. They found the quality of video satisfactory, prefered using computers rather than mobile devices and favored the use of screencasts lasting up to 10 minutes each**.**

Conclusions: Screencasts with embedded virtual microscopy provide an efficient method to supplement the teaching of pulmonary pathology, providing residents with exposure to interesting cases and stimulating their learning with quizzes. The screencasts can be viewed on computers and iOS and Android mobile devices such as cellphones and tablets, providing an attractive learning method to trainees that are skillful at integrating these technologies into their daily routine.

Endocrine Pathology

569 Pediatric Poorly Differentiated Thyroid Carcinoma: A Clinicopathologic Study

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Background: Pediatric thyroid carcinoma is uncommon, comprising less than 3% of all childhood malignancies and 10% of all thyroid carcinomas. The majority are papillary carcinomas (PTC). Poorly differentiated thyroid carcinomas (PDTCs) are extremely rare in this age group with existing literature limited to case reports, most lacking detailed description of tumor histology.

Design: We identified 4 cases of pediatric (age $\leq$ 21 years) PDTC from 2 institutions using the Turin criteria for diagnosis: solid/trabecular/insular growth pattern; absence of papillary nuclear features; and $\geq$3mitoses/10 high power fields (HPF), tumor necrosis or convoluted nuclei. Clinical data was obtained by chart review. A literature review was also performed.

Results: Clinical and pathologic features are shown. Patient age ranged from 4 - 19 years (mean 13.5). The majority were female (M: F ratio of 3:1). One patient had a prior history of radiation exposure for a life-threatening right neck hemangioma at the age of 4 months. The mitotic index ranged from <1-40/10 HPF. Necrosis was seen in 3 of 4(75%). All had lymphovascular invasion (LVI) and lymph node (LN) metastases; extrathyroidal extension (ETE) was present in 3 of 4 (75%). Two of 4 (50%) had associated well-differentiated PTC; the other 2 cases were TTF-1 and thyroglobulin positive.

All underwent total thyroidectomy with radioactive iodine ablation. Two had distant metastases at the time of diagnosis (1 to lung/finger/scalp and 1 to lung and later to brain), both died of disease (DOD) at 8 months and 2 years, respectively. No clinical follow-up was available for the other 2 patients. Literature review identified 16 cases of pediatric PDTC, 11 with follow-up. None died of disease. However, Turin criteria could only be determined for 2 cases both of which lacked clinical follow-up.

Age (years)/ Sex	PTC	Mitosis/10 HPF	Necrosis	LVI+LN	ETE	Distant Mets	Patient status
4/F	Yes	<1	Yes	Yes	Yes	NA	NA
19/F	No	40	Yes	Yes	Yes	Yes	DOD
14/F	Yes	10	No	Yes	No	NA	NA
17/M	No	37	Yes	Yes	Yes	Yes	DOD

Conclusions: Pediatric PDTC may be more clinically aggressive than previous reports suggest. Consistent application of Turin criteria is important to identify high risk patients. Mortality was associated with distant metastases at diagnosis

570 Mixed Adenoma-Well Differentiated Neuroendocrine Tumors (MANETs) of the Colon. Clinico-Pathologic and Molecular Analysis of 6 Cases of a Rare and Recently Recognized Entity

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Background: MANETs are rare neoplasms composed of both adenoma and well-differentiated neuroendocrine tumor (WDNET) and have been described only recently. While the clinico-pathological features of mixed adenoneuroendocrine carcinomas (MANECs) have been investigated and the clonal origin of the different tumor components analyzed, the clinico-pathological profile and the pathogenesis of MANETs are still largely unknown.

Design: The clinico-pathological data for 6 colonic MANETs were retrieved. Immunohistochemistry for synaptophysin, chromogranin A, Ki67 and p53 was performed. Moreover, the neuroendocrine and adenomatous components were microdissected using laser capture microdissection (LCM) technique and direct sequencing was performed to search for microsatellite instability (MSI) (BAT 25-26) and *KRAS*, *BRAF* and *PIK3CA* mutations.

Results: The adenomatous component was tubular in 5 cases (3 with high grade and 2 with low grade dysplasia) and tubulo-villous in one (with low grade dysplasia), ranging in diameter from 3 to 18 mm. In all cases, a grade 1 (< 2% Ki67 index and <2 mitoses x 10 HPF) WDNET component was present: it was limited to the lamina propria in 3 cases (measuring 2 mm, 2 mm and 8 mm, respectively), whilst it involved the submucosa in 2 cases (2.5 and 8 mm, each) and the muscularis propria in 1 case (measuring 16 mm). Immunostaining for p53 was negative in the neuroendocrine component, while it was positive in scattered nuclei of the adenomatous component in all investigated cases. MSI was absent in both components of all MANETs, and no mutations of *KRAS*, *BRAF* and *PIK3CA* were identified. All patients were alive and free of disease after a mean follow-up time of 11.2 years.

Conclusions: Colonic MANETs are small lesions with a benign/indolent behavior. No alterations of *KRAS*, *BRAF* and *PIK3CA* genes have been found in either tumor component. p53 was negative in the WDNET component and focally expressed in the adenomatous one. A common origin from a same progenitor cell may be hypothesized for the two components of MANETs.

571 Benign-Appearing Thyroid Follicles in Cervical Lymph Nodes from Patients with Papillary Thyroid Microcarcinomas: A Histologic and Immunohistochemical/Molecular Study

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Background: Benign-appearing thyroid follicles (BTFs) in cervical lymph nodes (CLN) is intrigue and can pose a challenge diagnostically. Most BTFs studies were performed on neck dissections (ND) for non-thyroid malignancies or autopsies. It is usually overlooked in patients with thyroid carcinomas. The recent increased detection of thyroid microcarcinomas (TMC) with low tumor volumes in primary and metastatic sites provides opportunities to further study this issue. We investigated the incidence, morphologic, and immunohistochemical/molecular features of BTFs in CLNs from patients with TMC.

Design: The archived thyroidectomy material from 2005 to 2015 was reviewed. The cases with a diagnosis of TMC were identified. H&E slides were reviewed. Tissue blocks were retrieved and immunohistochemistry (IHC) for CK19 and $BRAF^{v600e}$ was performed in a Dako autostainer with prediluted antibodies according to the manufactory's instructions.

Results: We identified 135 thyroidectomy specimens with diagnosis of TMC, of which 48 had ND, yielding 231 lymph nodes. Of the 48 cases, 16 cases (33.33%) were found to have metastasis in 39 of 135 CLNs. BTFs were identified, singly or in small clusters in subcapsular areas or intermingled with carcinomas in 6 CLNs in 5 of 48 cases with ND (10.42%). No BTFs were found in other negative CLNs. CK19 and $BRAF^{v600e}$ IHC were performed on primary and metastatic tumors. All primary and metastatic TMCs were strongly and diffusely positive for CK19. CK19 staining in BTFs was either negative or weak and discontinuous as in normal thyroid tissue. Eight of 16 TMCs (50%) were positive for $BRAF^{v600e}$, indicating presence of BRAF mutation. The $BRAF^{v600e}$ status was consistent in primary and metastatic sites for all cases. Two of 5 metastatic TMCs with BTF were positive and 3 were negative for $BRAF^{v600e}$. The BTFs in these CLNs were negative for $BRAF^{v600e}$.

Conclusions: Our data indicated that BTFs in CLNs may be more common than one might expect. The concordance of BRAF status in primary and metastatic sites supports that carcinomas in CLNs were the result of metastasis from TMCs in thyroid and were unlikely to have arisen from BTFs in CLNs. IHC mutational analysis may help to characterize the BTF-like tissue in CLNs and reduce overtreatment for TMCs.

572 Vasodilator-Stimulated Phosphoprotein (VASP) Immunoreactivity Is Associated with Lymphovascular Invasion and Lymph Node Metastasis of Papillary Thyroid Carcinoma: Role as a Potential Diagnostic Marker and Treatment Target

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Background: Papillary thyroid carcinoma (PTC) represents 80% of thyroid cancers and has a high rate of cervical *lymph node metastasis.* Vasodilator-stimulated phosphoprotein (VASP) is an actin binding protein involved in cellular adhesion and motility that could be associated with tumor metastasis. The role of VASP in thyroid carcinoma pathogenesis has not been previously reported.

Design: A total of 87 tissue samples from 71 patients of PTC were analyzed. 16 of the 71 PTC cases had paired primary PTC and PTC within lymph nodes, 22 cases had no lymph node involvement. Immunohistochemical stains of VASP were performed. VASP immunoreactivity was blindly scored as 0, 1+, 2+ or 3+ in density with a percentage of positive cells. Statistical analysis was performed using Fisher exact test and statistical significance was set at $p < 0.05$.

Results: VASP immunoreactivity was negative in 27/ 29 (93%), focally and weakly positive in 2/29 (7%) cases of benign thyroid tissue. 7/9 (78%) cases of Hashimoto thyroiditis with Hurthle cell changes were negative and 2/9 (22%) were weakly positive for VASP. PTC cells were negative in 3/71 (4%), weakly positive (1+) in 10/71 cases (14%), moderately positive (2+) in 38/71 cases (54%) and strongly and diffusely positive (3+) in 20/71 (28%) cases. 8/22 (36%) of nonmetastatic PTCs were negative or weakly positive, and 14/22 (64%) were moderately or strongly positive. 12/13 (92%) cases of PTCs present in lymphovascular spaces showed a strong and diffuse positive (3+) VASP. 15/16 (94%) PTCs with foci present within lymph nodes showed strongly and diffusely positive VASP. VASP is significantly upregulated in the PTC cells as compared to the adjacent benign thyroid tissue or lesions ($p<0.0001$). High level of VASP immunoreativity is significantly associated with regional lymph node metastasis of PTCs ($P=0.030$). The sensitivity for VASP as a marker of lymph node metastasis in PTC was 92% and specificity 36%. VASP had a positive predictive value of 62% and a negative predictive value of 80%.

Conclusions: VASP is significant upregulated in majority of PTCs but not in benign thyroid lesions. A strong and diffuse VASP immunoreactivity is strongly associated with lymphovascular invasion and may be a highly sensitive marker of lymph node metastasis and potential treatment target of PTCs.

573 Prognostic Roles of CD15 and Ki67 Immunohistochemistry in Medullary Thyroid Carcinoma

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Background: There are only a few morphologic prognostic variables for medullary thyroid carcinomas (MTCs) with TNM stage being the most useful factor. Recently, increased CD15 immunoreactivity was associated with unfavorable outcome in patients with MTCs. CD15 or SSEA4 has been reported to be a marker of cancer stem cells (CSCs). High Ki67 index and/or decreased calcitonin expression have also been linked to aggressive MTCs. It remains unclear whether CD15-positive tumors also tend to have higher Ki67 index and/or decreased calcitonin expression. This study was done to clarify the relationship between the three markers and validate their associations with MTC outcomes.

Design: Tissue microarrays (TMAs) were constructed with formalin-fixed paraffin-embedded (FFPE) tissues of normal thyroid (n=39), primary tumors (N=39) and metastases (N=18) from a total of 42 MTC cases diagnosed from 1987 to 2016. Immunohistochemistry stains for CD15, Ki67, calcitonin, chromogranin A and synaptophysin were performed and graded by intensity of staining (0 to 3+) and the percentage of positive tumor cells: rare (<5%), focal (5-25%) and diffuse (>25%).

Results: There was diffuse immunoreactivity for CD15 in 12 (30.8%) cases and Ki67 in 2 (5.1%). All primary tumors had strong expression of calcitonin, chromogranin A and synaptophysin. Small cell or anaplastic variant morphology was not present in any cases. In univariate analysis, CD15 immunoreactivity was significantly associated with post-thyroidectomy persistent disease (P=0.02). In addition, cases with distant metastases at presentation (n=2; P=0.07) and/or MTC-related mortality (n=2; P=0.07) showed diffuse CD15 immunoreactivity. Among the two cases with a very high Ki67 index (>75%), both also showed diffuse CD15 immunoreactivity. Tumors from both patients had disseminated metastatic disease at initial presentation involving liver, vertebrae, along with bulky retroperitoneal and pelvic tumors.

Conclusions: Our findings suggest that CD15 and Ki67 immunoreactivity may be helpful in distinguishing a more aggressive subset of MTC with conventional MTC morphology. Interestingly, tumors with a very high Ki67 index (>75%) tend to be very aggressive and were concurrently positive for CD15. Routine immunohistochemical staining for CD15 and Ki-67 may be useful in detecting more aggressive variants of MTCs with conventional morphological features.

574 MicroRNAs miR-21 and miR-885 Are Associated with More Aggressive Behavior in Medullary Thyroid Carcinomas

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Background: Non-coding RNAs, including microRNAs (miRNAs), are well-recognized post-transcriptional regulators of gene expression. Recent studies have led to the discovery of multiple aberrantly expressed miRNAs in medullary thyroid carcinomas (MTCs). As a crucial mediator in oncogenic RAS-induced cell-cycle deregulation, the upregulation of miRNA-21 (miR-21) has been previously associated with postoperative

persistent MTC. Another novel miRNA, miR-885, was previously found to be highly expressed in oncocytic follicular thyroid carcinoma, but has not been studied in MTCs. This study was designed to investigate the expressions and prognostic implications of miR-21 and miR-885 in MTCs.

Design: Tissue microarrays (TMAs) were constructed with formalin-fixed paraffin-embedded (FFPE) tissues of normal thyroid (n=39), primary tumors (N=39) and metastases (N=18) from a total of 42 MTC cases diagnosed between 1987 and 2016. In situ hybridization with probes for miR-21 and miR-885 (Exiqon) was performed and graded by intensity of staining (0 to 3+) and percentage of cells staining positively. A medullary thyroid carcinoma cell line (MZ) was used to evaluate the effects of miR-21 on cell proliferation and invasion by using transfection of small interfering RNA (siRNA) targeting miR-21.

Results: There was strong (2+ to 3+) expression of miR-885 in the primary tumors in 16 (42.1%) cases. Univariate analysis showed that miR-885 expression was significantly associated with increased tumor size ($P<0.05$). A total of 17 (43.6%) cases demonstrated strong expression of miR-21. In addition, 8 (20.5%) cases of metastatic MTCs showed strong miR-21 expression, even though the primary tumors showed negative or weak expression of miR-21. Interestingly, two cases which had distant metastases at initial presentation showed strong expression of both miR-21 and miR-885. In both of these cases, the patients had a high disease burden involving liver, vertebrae, as well as bulky retroperitoneal and pelvic tumors. The Ki67 index was also high (>75%) in both of these cases. The siRNA experiments showed effectively inhibited miR-21 expression in the MTC cell line, which resulted in a significant decrease in cell proliferation ($P<0.05$) and invasion ($P<0.05$).

Conclusions: Given the associations with increased tumor size and early metastases, these findings suggest that miR-21 and miR-885 function as oncogenes in MTCs, and that these two microRNAs may have important regulatory roles in the development and progression of MTCs.

575 Non-Coding RNAs and Phosphorylated Mammalian Target of Rapamycin (p-MTOR) Expression in Follicular and Oxyphilic Thyroid Neoplams

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Background: Oxyphilic and follicular neoplasms are related thyroid tumors, but there are differences in the molecular findings, biological behavior and response to radioactive iodine treatment in these two groups of neoplasms. We examined the expression of the long non-coding RNA (lncRNA) Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1), the microRNA (miR)-885, and p-MTOR protein in a series of follicular adenomas (FAs), follicular carcinomas (FCs), oxyphilic or Hurthle cell adenomas(HAs) and oxyphilic or Hurthle cell carcinomas (HCs) to determine some of the biological differences in these related neoplasms.

Design: A tissue microarray (TMA) was constructed using triplicate cores of formalin-fixed paraffin-embedded (FFPE) tissues of normal thyroid (NT, n=12), FAs (n=25), FCs (n=25), HAs (n=25) and HCs (n=24). In situ hybridization(ISH) for MALAT1 was done with the RNAScope method, ISH for miR-885was done with a probe from Exiqon and immunohistochemistry(IHC) for p-MTOR was done with a monoclonal antibody (Cell Signaling). Staining on the TMA was evaluated using a scale of 0 to 3+ for the intensity of staining and the percentage of tumor cells showing staining. qRT-PCR analysis of a subset of the tumors (n=12) was also performed.

Results: There was increased expression of MALAT1 and miR-885 in all neoplastic groups compared to the normal thyroid tissues ($p< 0.05$). MALAT1 was more highly expressed in HCs compared to FCs, although the differences were not statistically significant ($p=0.06$). MiR-885 was expressed at similar levels in FCs and HCs. p-MTOR protein was more highly expressed in FCs than in HCs ($p< 0.001$). qRT-PCR analysis of non-coding RNAs supported the ISH findings.

Conclusions: These results indicate that the non-coding RNAs MALAT1 and miR-885 show increased expression in neoplastic follicular and oxyphilic thyroid neoplasms compared to normal thyroid tissues. HCs had the highest levels of MALAT1 while FCs had the highest levels of miR-885, suggesting that these non-coding RNAs have regulatory roles in follicular and Hurthle cell neoplasms. Although p-MTOR protein was most highly expressed in FCs, the presence of p-MTOR in HCs suggests that drugs targeting this pathway may be useful for treatment of patients with HCs which are unresponsive to conventional therapies.

576 Clinicopathologic Features of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Features (NIFTP) with Imaging and Molecular Data: The Weill Cornell Medicine Experience

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Background: Recently, the term noninvasive follicular thyroid neoplasm with papillary-like features (NIFTP), has been proposed to replace noninvasive follicular variant of papillary thyroid carcinoma, due to the indolent behavior of this tumor. Since this proposed change, little information is available about NIFTP. In this study, we reviewed the clinical, fine needle aspiration cytology (FNAC), imaging, and molecular findings of histologically proven NIFTPs in our institution.

Design: Thyroid resections from NYPH/Weill Cornell, during an 11-year period (2005-2016), with a histologic diagnosis of follicular variant of papillary thyroid carcinoma (FVPTC), were retrospectively reviewed to identify NIFTP. The ultrasonographic appearance, FNAC findings, and molecular data were reviewed. All tumors <1 cm were excluded.

Results: Of 244 cases of FVPTC identified, 76 (31%) were re-classified as NIFTP. The patients were predominantly female (M:F-1:3) with an average age of 50 years (range 26-77 years). The mean tumor size was 2.5 cm (range 1-6 cm). Twenty-four patients (32%) underwent total thyroidectomy and 52 (68%) had lobectomy. Of 34 patients (45%) with a lymph node dissection, none had lymph node metastases. On imaging, 37 NIFTPs (49%) showed vascularity and 25 (33%) were isoechoic to hypoechoic. Calcifications were identified in only 14 cases (19%). Seven (9%) had a hypoechoic rim. FNAC results were available in 75/76 cases (99%) (Table 1) with most showing an indeterminate cytology. Of the total 76 cases, 46 (61%) had molecular data, 8 with NRAS mutations, two with BRAF *V600E* mutations, and one with a variant BRAF mutation. The remaining cases were either negative for BRAF *V600E* or had no identifiable molecular alterations.

	Bethesda Grading on Thyroid FNA					
	Nondiagnostic (I)	Benign (II)	Atypia (III)	Follicular neoplasm (IV)	Suspicious for malignancy (V)	Malignant (VI)
NIFTP cases (75)	2 (3%)	19 (25%)	23 (31%)	11 (14%)	12 (16%)	8 (11%)

Conclusions: A significant percentage of tumors that were previously diagnosed as FVPTC were reclassified as NIFTP. This tumor cannot be reliably diagnosed preoperatively on FNAC, and should be included in the differential diagnosis of all indeterminate categories of thyroid cytology. In general, NIFTP had a low suspicion of malignancy on ultrasound imaging. BRAF *V600E* mutation is infrequent in NIFTP. Clinical outcome studies are being conducted and will be reported.

577 Efficient Immunostaining Panel to Distinguish Poorly Differentiated/Undifferentiated Thyroid Carcinoma from Follicular and Papillary Carcinoma

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Background: Poorly-differentiated/undifferentiated (anaplastic) thyroid carcinoma (ATC) is a rare, highly malignant tumor accounting for 1-9.8% of thyroid tumors. Histologically, it may present as a minor component in the background of thyroid papillary or follicular carcinoma (FTC and PTC), thus identification of ATC component is a challenge. Tumor suppressor *p53* gene mutation is the most common genetic alteration in ATC. Alteration in expression level of thyroid lineage biomarkers including thyroglobulin, TTF1 and PAX8 is identified in ATC. Our study aims to 1) analyze the frequency of ATC based on the past 10 years of large thyroid cancer cohort, and 2) establish an efficient diagnostic biomarker panel for identifying ATC.

Design: A single institution thyroid cancer cohort with total 2106 thyroid tumors including 10 ATC was identified within the last 10 years at our institution. A large panel of biomarkers including p53, ki-67, thyroid lineage biomarker (thyroglobulin, TTF-1, PAX8) and synaptophysin were immunohistochemically analyzed for ATC and selected PTC and FTC with appropriate controls. The positive staining was evaluated based on the intensity and % positive cells, and scored as 0, negative, 1, weak/moderate in <10% tumor, 2, moderate in 10 – 50% tumor, and 3, moderate/strong in >50% tumor cells.

Results: Retrospective analysis over the past 10 years revealed that the frequency of ATC in total thyroid cancers was 0.5% (10/2,106) with an average age at diagnosis of 74 years and male to female ratio of 1:1. The IHC biomarker studies showed that 1) for thyroid cell lineage biomarkers, all ATC lost TTF-1 and thyroglobulin expression (0/9) and PAX-8 expression was identified in 45% of ATC (4/9), while these 3 biomarkers were retained in all FTC and PTC. 2) Strong/diffuse nuclear staining of p53 (mutant) was seen in all ATC (9/9), while only weak/focal staining (wild-type p53) was identified in FTC or PTC. 3) Synaptophysin was lost in all ATC cases (0/9), but was weakly expressed in 80% of FTC (4/5), and weakly present in 20% of PTC (1/5). 4) Ki-67 staining was ≥20% in all ATC (9/9), while showing variable staining patterns <20% in all FTC and PTC cases.

Conclusions: Our data analyzing a large thyroid cancer cohort indicates that the frequency of ATC is rare (only 0.5% of total thyroid cancers). The large diagnostic IHC panel indicates that the loss of thyroid cell lineage biomarkers (TTF-1, thyroglobulin) and synaptophysin with retained PAX-8 expression, and strong/diffuse mutant p53 accumulation is an efficient biomarker panel to identify ATC.

578 Biologic and Genetic Basis of a Histological Risk Assessment of Early Recurrence/Metastasis in Paragangliomas

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Background: Mid-term outcome information in risk stratified patient cohort is needed to inform prognosis in individual patients with paragangliomas (PGL), adjuvant therapy choice and future research. The objective is to define the genetic features setting a PGL histological risk stratification scheme of early recurrences/metastasis.

Design: A classification scheme for PGLs was devised, and specimens were assessed for invasion capacity (infiltrative edges, extra-adrenal extension, capsular and peritumoral vascular invasion), tumorigenic expansion, necrosis, and mitogenic activity. Patients were prospectively stratified as low histological risk (LHR) or high risk (HHR, presence of at least one feature of invasive capacity and two features of tumorigenic expansion). Patients underwent regular treatment and follow-up for their PGLs in a tertiary referral center.

Whole-exome sequencing was performed on tumor and normal tissue samples, using a Random Forest machine learning approach to compare LHR vs. HHR for early recurrence/metastasis. Predictive Model Analysis Pipeline and Methods ► Functional somatic mutations unique to tumors were identified and represented as a samples x genes mutation matrix (mutated=1, non-mutated=0). ► Pairwise Random Forest

models were built for each diagnostic category ► Variable selection was conducted using Fisher's Exact test with 5x10 fold cross validation design, measuring predictive accuracy in independent test sets.
Results: Disease-free survival was significantly lower in HHR patients 0% vs 78.4% (p=0.004). Histological risk stratification predicts DFS with AUC of 0.8 (95% CI: 0.69-0.90; p<0.01). 7/37 HHR patients had a synchronous diagnosis of malignancy based on other criteria and four patients suffered a local recurrence.
The HHR-predictive genes included ARID1A (P=5.13E-09), AKT3 (P=3.57E-08), MAX gene associated (P=6.86E-11), PIK3CA (P=1.35E-09), ELK3 (P=8.03E-16), MAP3K12 (P=4.17E-21), and TP53 (P=3.12E-40), being the accumulation of genetic abnormalities the best predictor.
Conclusions: Histologic risk stratification of early recurrence/metastasis is genetically defined by the accumulation of alterations in the proliferation and cell survival pathways. A high-risk status is associated with high risk of malignancy and disease recurrence.

579 Distinctive Metabolic Signatures in Adrenocortical Tumorigenesis

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Background: Enhanced aerobic glycolysis is a well-known metabolic reprogramming phenomenon that occurs in many cancers, although its role remains unclear in adrenal cortical neoplasms. We investigated the metabolic phenotype in neoplastic and normal adrenocortical tissues, using immunohistochemical markers hexokinase (HK1), pyruvate kinases (PKM2, PKM1), succinate dehydrogenase (SDHB), and phospho-S6 (pS6).
Design: We constructed a tissue microarray of 42 adrenocortical carcinomas (ACC), 50 adenomas (ACA) and 45 normal samples, and stained the slides for HK1, PKM2, PKM1, and pS6. A minimum of 3 cores for each case was used. Individual cores were scored by multiplying the percent positive cells by intensity scores (0-3), and each case received an average score (max: 300) for HK1, PKM2, PKM1, and pS6. Additionally, case-matched Ki67 and p53 labeling index, nuclear β-catenin and SDHB expression status were available for 40 ACCs and all 50 ACAs.
Results: Expression of HK1 and PKM2 were significantly higher in ACC (HK1: score 146.20; PKM2: score 203.24) than in ACA (HK1: score 58.62; PKM2: score 156.56) (p<0.001; p=0.014) and normal tissue (HK1: score 22.52; PKM2: score 100.20) (p<0.001; p<0.001). Moreover, expression of HK1 and PKM2 were significantly higher in ACA than in normal tissue (p<0.001; p<0.001). Moderate-to-high intensity staining of HK1 and PKM2 was more frequent in ACC (HK1: 62%; PKM2: 79%) than in ACA (HK1: 20%; PKM2: 60%) and normal tissue (HK1: 13%; PKM2: 47%) (p<0.001; p=0.001). PKM1 expression was significantly higher in ACC (score 22.44) than in ACA (score 2.82) (p=0.027). Importantly, HK1 expression correlated with both PKM2 and PKM1 expression (p<0.001; p=0.007). HK1 expression significantly correlated with p53 (p=0.001) and Ki67 (p<0.001), but not with nuclear β-catenin expression. Although pS6 expression was significantly lower in ACC (score 26.59) than in ACA (score 72.89) (p=0.003) or normal tissue (score 60.23) (p=0.008), it was not associated with HK1, PKM2 or PKM1 expression. There was no loss of SDHB in any tumor.
Conclusions: Our data suggest that aerobic glycolysis is implicated in adrenocortical tumorigenesis. In particular, overexpression of HK1 and PKM2 differed significantly between ACC, ACA and normal cortex with multi-step increase towards malignancy. HK1 was a significant predictor of PKM2 and PKM1 expression, along with p53 and Ki-67. Aberrant HK1 overexpression may serve as a novel biomarker and a potential therapeutic target for ACC.

580 The Impact of Reclassification of Encapsulated Follicular Variant of Papillary Thyroid Carcinoma on the Risk of Malignancy in the Bethesda System for Reporting of Thyroid Cytopathology

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Background: The indolent behavior of non-invasive, encapsulated follicular variant of papillary thyroid carcinoma (niEFV) has led to its proposed reclassification as non-invasive follicular tumor with papillary like nuclear features (NIFTP). The impact of this change in classification on the malignancy rates within the Bethesda System for Reporting of Thyroid Cytopathology (TBS) is unclear. We studied a series of thyroid fine needle aspiration biopsies (FNA) and corresponding surgical pathology results to calculate malignancy rates in each TBS category.
Design: After obtaining IRB approval, we searched our institutional databases and identified all patients who had thyroid FNA with subsequent thyroidectomies from June 2014 to June 2016. Thyroidectomy slides from all cases of niEFV were reviewed by two pathologists and included in the study if the tumor capsule was entirely submitted for histologic evaluation. Cases were reclassified as NIFTP provided none of the following exclusion criteria were present: tumor capsular/vascular invasion, necrosis, >1% papillae, psammoma bodies, greater than 3 mitoses per 40x field or an infiltrative border. The risk of malignancy (ROM) for each TBS category was calculated before and after the niEFV were reclassified.
Results: A total of 468 thyroid FNAs from 316 patients (67 males, 249 females) had corresponding surgical specimens. A summary of results, TBS categories and ROM before and after reclassification is shown in table 1.

TBS category	Cases n=468	Malignant cases n=126	ROM without NIFTP(%)	NIFTP cases	ROM with NIFTP(%)
1. Nondiagnostic	22	0	0	0	0
2. Benign	171	7	4	1	4
3. Atypical	149	38	26	7	21
4. Follicular neoplasm	53	18	34	1	32
5. Suspicious for malignancy	29	20	69	7	45
6. Malignant	44	43	98	0	98

The majority of NIFTP FNA were diagnosed as either follicular lesion/atypia of undetermined significance (TBS-3) or suspicious for malignancy (TBS-5). The largest change in ROM was seen in the TBS-5 category, decreasing from 69% to 45%.
Conclusions: Reported ROM in TBS-5 has been sufficiently high enough to warrant surgical intervention. The current study suggests that under the NIFTP terminology, there is a decreased risk of malignancy in TBS-5. This change in ROM may have an impact on clinical management of these nodules. Further study of NIFTP and its impact on cytodiagnoses and management will be needed to accurately risk stratify for optimal patient care.

581 Should Subcentimeter Non-Invasive Encapsulated, Follicular Variant of Papillary Thyroid Carcinoma (NI-EFV PTC) Be Diagnosed as Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP)?

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Background: In 2016, NI-EFV PTC was renamed as NIFTP in order to reduce overtreatment of this indolent tumor. However, as the study cohort did not include subcentimeter tumors (i.e. papillary thyroid microcarcinoma (mPTC) with NI-EFV morphology), such lesions are still labelled and staged by many pathologists as mPTC. Despite the recommendations of various medical societies, a substantial number of physicians offer radioactive iodine (RAI) therapy to patients with unifocal and especially multifocal mPTC. It is therefore crucial to evaluate the clinical outcome of mPTC, NI-EFV in order to assist therapeutic decision making.
Design: A stringent clinico-pathologic review was conducted in four tertiary hospitals for cases with a diagnosis of mPTC. A total of 48 patients with unifocal mPTC NI-EFV who had at least one year clinical follow up (FU) without post-operative RAI administration were examined.
Results: The mPTC, NI-EFV included in this study predominantly affected women (F: M ratio = 7:1) and patients in their 50s (median = 52, range: 27 – 81). The median tumor size was 0.39 cm (range: 0.1 - 0.9 cm). There were no distant or lymph node metastases at diagnosis in all patients including all cases (n=17, 35%) with nodal tissue available for microscopic examination. Twenty-one patients (44%) underwent lobectomy alone, while the remainders were subjected to total thyroidectomy. No recurrence was observed in the entire cohort (n=48) including all 34 patients with at least 2 years of FU (median FU: 5.8 years). Among patients with ≥ 5 years of FU, all 21 individuals did not recur with a median FU of 9.6 years (range 5.2 - 18 years).
Conclusions: Papillary thyroid microcarcinoma, NI-EFV, when stringently selected for, lacks metastasis at presentation and follows an extremely indolent clinical course even when treated conservatively without RAI therapy. Consideration should be given to diagnose mPTC, NI-EFV as NIFTP in order to avoid overtreatment of these highly indolent tumors.

582 Pathologic Reporting of Tall Call Variant of Papillary Thyroid Cancer: Have We Reached Consensus?

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Background: Tall cell variant (TCV) is widely believed to be a more aggressive subtype of papillary thyroid carcinoma (PTC). Despite the significance of TCV with respect to risk stratification and therapeutic decision making, its pathologic reporting is subject to interobserver variability. We aim to determine the level of agreement among expert pathologists in the identification and reporting of TCV.
Design: 39 cases of PTC were selected and digitalized using a Pannoramic 250 Flash II scanner. 13 expert pathologists evaluated the scanned cases for the presence of TCV. The criteria that the reviewers used to make a diagnosis of TCV were also assessed. Data were collected and analyzed.
Results: The overall strength of agreement for identifying TCV was fair (Fleiss kappa 0.27) and the proportion of observed agreement was 0.68. It was noted that four different definitions (A,B,C,D) were used based on the combination of cell height to width (H:W) ratio and the percentage of tumor cells showing that specific ratio.

Definition	H:W	Tumor percentage	Number of pathologist using the definition
A	2:1	≥30%	1/13
B	2:1	≥30%	2/13
C	3:1	≥50%	5/13
D	3:1	≥50%	5/13

When pathologists using definition D were analyzed, the inter-observer agreement improved (Fleiss kappa 0.49, moderate).

Conclusions: Pathologic reporting of TCV varies among pathologists. This disagreement is a result of the lack of unanimous diagnostic criteria and variation in individual pathologists' interpretations. These discrepancies lead to over- and under-diagnosis of TCV, which has significant implications in patient management. Interestingly, inter-pathologist variability improves when definition D is used. It is imperative for clinicians to understand this variability in interpretation and lack of concordance in reporting, as well as the implications for interpreting clinical studies related to this histologic subtype of PTC.

583 Absence of PTEN Predicts Aggressive Behavior in Low Grade Neuroendocrine Tumors

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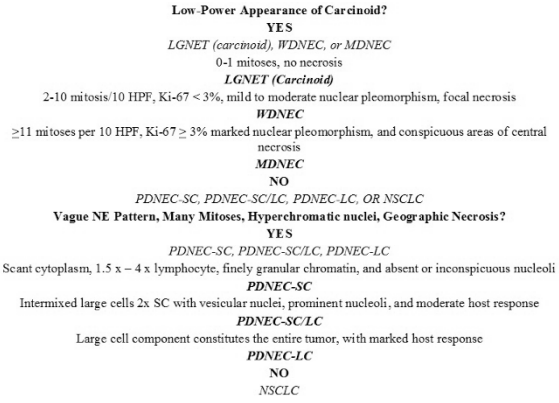
Background: There are no known morphologic or molecular parameters to predict the biologic behavior of low grade neuroendocrine tumors (LGNET, carcinoid) in various organ systems. The phosphatase and tensin homologue (PTEN), a tumor suppressor gene that negatively regulates the PI3K-AKT-mTOR pathway, is also a neuroendocrine differentiation marker highly expressed in neuroendocrine tissues as well as LGNET; and is frequently lost or decreased in high grade neuroendocrine carcinomas. We hypothesize that PTEN may be a useful marker in predicting the biologic behavior of LGNET.

Design: Twenty (20) neuroendocrine neoplasms (lung=8, gastrointestinal tract=10, endometrium=1, thymus=1) were retrieved from our archives. H & E, Synaptophysin, Chromogranin and Ki-67 stained tissue sections were reviewed and the tumors were classified utilizing a specific diagnostic algorithm (Figure 1). Representative sections were immunostained with PTEN (Santa Cruz Biotechnology, Santa Cruz, CA) and pAKT murine MAbs (Cell Signaling Technology, Danvers, MA) and results scored as follows: 0 – 10% - 0; 11- 25% - 1+; 26 – 50% - 2+; 51 – 75% - 3+; 76 – 100% - 4+. Follow up was obtained for five years on all patients.



HPF, high-power field; LGNET, low grade neuroendocrine tumor (carcinoid); WDNEC, well differentiated neuroendocrine carcinoma; MDNEC, moderately differentiated neuroendocrine carcinoma; NE, neuroendocrine; PDNEC-LC, poorly differentiated neuroendocrine carcinoma, large cell type; PDNEC-SC, poorly differentiated neuroendocrine carcinoma, small cell type; SC/LC, small cell, large cell; NSCLC, non small cell lung carcinoma.

Results: The neuroendocrine neoplasms were classified as, LGNET (carcinoid,N=10), well differentiated neuroendocrine carcinoma (WDNEC, N=3), moderately differentiated neuroendocrine carcinoma (MDNEC, N=2), large cell neuroendocrine carcinoma (LCNEC, N=2) and small cell neuroendocrine carcinoma (SCNEC, N=3). Four (4/10) LGNET showed 4+ expression of PTEN and no aggressive behavior. PTEN was lost/decreased in six (6/10) LGNET (0 to 2+ expression), four of which showed aggressive behavior (recurrence/metastasis) on follow up. All cases of LCNEC, SCNEC and MDNEC had loss/markedly decreased PTEN. Loss of PTEN correlated significantly with aggressive behavior of the tumor (P=0.0189) and increased pAKT expression (P=0.0002). A trend of decreased disease free survival is observed in cases with loss of PTEN and further studies are underway to establish the same.

Conclusions: PTEN loss and elevated pAKT expression are predictive markers of aggressive behavior (recurrence and/or metastasis) in LGNET. PTEN and pAKT assessment in neuroendocrine tumors may also be useful as a prognostic marker.

584 Prognostic Implication of Histological Features Associated with EHD2 Expression in Papillary Thyroid Carcinoma

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Background: Papillary thyroid carcinoma (PTC) is a heterogeneous tumor with various histological and molecular subtypes. EHD2 is involved in endocytosis and endosomal recycling. This study aimed to investigate the prognostic significance of EHD2 expression in PTC and develop a new model for predicting persistent/recurrent disease after thyroidectomy.

Design: Pathologic slides of 512 consecutive patients with PTC ≥ 1 cm were retrospectively reviewed. *BRAF* mutation analysis and immunohistochemistry for EHD2 was performed. Clinical significance of *EHD2* mRNA expression was analyzed in 388 PTC patients using The Cancer Genome Atlas dataset.

Results: The presence of dyscohesive cells and psammoma bodies were found have significant association with persistent/recurrent disease (p= 0.049 and p= 0.038, respectively). The best discrimination of disease-free survival was found by dividing patients into three prognostic groups based on the following two risk factors according to the size category: psammoma bodies ≥ 4 and dyscohesive cells (≥ 1% and ≥ 20% in PTCs of < 2.0 cm and ≥ 2.0 cm, respectively). In PTCs of ≥ 2.0 cm, patients with the two risk factors had a hazard ratio of 13.303 (p= 0.005) compared to those without risk factors. High expression level of EHD2 was associated with *BRAF* V600E (p< 0.001), presence of dyscohesive cells (p= 0.010), and absence of psammoma bodies (p= 0.001). Increased *EHD2* mRNA expression level was associated with extrathyroidal extension (p< 0.001), pT3-4 (p< 0.001), lymph node metastasis (p< 0.001), higher risk of recurrence (p< 0.001), and *BRAF* V600E (p< 0.001).

Conclusions: Our prognostic model is useful for predicting persistent/recurrent disease after surgery of PTC. *EHD2* mRNA expression could be a novel prognostic marker for PTC patients.

585 Neuroendocrine Site of Origin Immunohistochemistry in Medullary Thyroid Carcinoma

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Background: 10-20% of neuroendocrine tumors (NETs) present as metastases of occult origin. We routinely perform site of origin immunohistochemistry (IHC) in these cases, which may include TTF-1 (for lung origin), CDX2 (midgut), and Islet 1 and PAX6 (pancreas). For NETs presenting above the diaphragm, we are often asked to exclude medullary thyroid carcinoma (MTC). Calcitonin is considered the gold-standard marker for this tumor. We sought to validate the specificity of calcitonin as an MTC marker, as well as examine expression of other NET site of origin IHC in this tumor type. We also examined somatostatin receptor subtype 2A (SSTR2A) IHC, as high-level expression may predict response to somatostatin-analogue (SA)-based therapies.

Design: Tissue microarrays were constructed from the following 358 tumors: 37 MTC (14 primary, 23 metastatic), 218 other NETs (46 lung, 8 duodenum, 67 pancreas, 93 jejunoileum, 4 appendix), and 103 NECs (37 lung, 21 extrapulmonary visceral, 45 Merkel cell). All tumors were stained for calcitonin, and the MTCs were also stained for TTF-1, CDX2, Islet 1, PAX6, and SSTR2A. Cases were assessed for extent (%) and intensity (0-3+) of staining and an H-score calculated (extent*intensity).

Results: Calcitonin was diffusely, strongly expressed by 100% of MTCs (mean H-score of 281 and 253 in primaries and metastases). 20% of lung and 25% of duodenal NETs were positive, with expression typically moderate (mean H-score of 76 and 72); 1.5% and 2% of pancreatic and jejunoileal NETs were weakly expressing (mean H-score of 15 and 1.5), while no appendiceal NET was positive. NECs were uniformly calcitonin-negative. The vast majority of MTCs were TTF-1 and ISL1-positive (typically strongly so), a rare tumor expressed PAX6 weakly, and CDX2 was uniformly negative. Up to 30% expressed SSTR2A, though typically at a low level. Detailed MTC data are presented below.

	Primary MTC		Metastatic MTC	
	% Positive	Mean (median) H-score, if positive	% Positive	Mean (median) H-score, if positive
TTF-1	86%	137 (140)	91%	181 (210)
Islet 1	100%	166 (202)	96%	181 (223)
PAX6	0%	NA	9%	2.8 (2.8)
SSTR2A	29%	17 (3.8)	30%	32 (10)

Conclusions: Diffuse, strong calcitonin expression is exquisitely sensitive and fairly specific for MTC, though other foregut-derived NETs are sometimes moderately to strongly expressing. MTCs nearly always express TTF-1 and Islet 1, while rarely to never expressing PAX6 and CDX2. Unlike most other NETs, MTCs are only occasionally SSTR2A-expressing, and typically not at levels expected to respond to SA-based therapies.

586 Has the Noninvasive Follicular Thyroid Neoplasm with Papillary Like Nuclear Features Been Seen in the Pediatric Age Group?

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Background: The most common malignant thyroid neoplasm in children is papillary thyroid carcinoma (PTC). In 2015 the Endocrine Pathology Society introduced the terminology "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) to replace the noninvasive follicular variant of papillary carcinoma. In this study we aimed to evaluate the previously diagnosed PTC in our pediatric population and reappraise it for NIFTP.

Design: The electronic medical database of our institution was searched for all thyroidectomy specimens in patients <19 years of age from 06/01/2001 through 06/01/2016. The patient's age, sex, diagnosis, previous fine needle aspiration cytology (FNA) diagnosis and follow up information were tabulated. All available thyroidectomy slides were reviewed.

Results: The study included 28 patients (24 female (85.7%); 4 male (14.3%)) with ages ranging from 9-18 (mean: 15.6 years). Of all thyroidectomy cases 6 (21.4%) were benign and 22 (78.6%) were malignant. The benign cases included multinodular goiter (4/6, 33.4%) and Graves' Disease (2/6, 66.6%). The malignant cases included PTC (18/22, 81.8%), follicular carcinoma (2/22, 9.2%), follicular neoplasm with hürthle

cell features (1/22, 4.5%) and poorly differentiated carcinoma (1/22, 4.5%). Upon review, none of the PTC was reclassified as NIFTP. FNA was performed on 22 cases. Four out of 6 benign cytology cases were correctly classified as benign on surgical follow up, one each were diagnosed as PTC and follicular carcinoma. Out of the 22 malignant cases, 16 had a preoperative FNA, of which 15 were correctly classified (13 PTC, 2 follicular neoplasms). One case that was diagnosed as "follicular neoplasm" on FNA was found to be poorly differentiated carcinoma on thyroidectomy. Follow up of the malignant lesions showed that only one patient had recurrence of classical PTC in lymph nodes after 12 years.

Conclusions: In our small series of pediatric patients we did not find NIFTP on reappraisal. Perhaps NIFTP is a disease of older individuals?

587 Significant Predictive Biomarkers Expression Through Immunohistochemistry and Analysis of microRNA in Gastroenteropancreatic Neuroendocrine Tumors

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Background: Molecular basis of Gastroenteropancreatic Neuroendocrine tumors (GEP-NETs) involves cell signaling pathways PI3K/AKT/ mTOR, Notch1, and Wnt (activated constitutively in 80% of cases), genes involved in these pathways (HES1, NOTCH1, MTOR, VEGFR2, PDGFRβ, and ATRX) have been found with an abnormal expression. Epigenetic factors like microRNAs (miRNAs) could be involved in post-transcriptional regulation, we use a bioinformatic approach to select a group of miRNAs that might regulate the expression of those genes and have been previously reported

Design: Retrospective evaluation of the total samples diagnosed as GEP-NETs (period 2003-2016) was conducted, clinical and pathological characteristics were evaluated in all cases. Biomarkers expression was assessed trough immunohistochemistry using tissue microarrays. Simultaneously, microRNAs that were possibly regulating biomarkers expression in small intestine and colon were identified applying a bioinformatic approach. For the 5 microRNAs identified we measured the expression by qRT-PCR

Results: 143 cases of GEP-NET mainly from ileum/jejunum (23,8%), appendix (19.6%), colon/cecum/rectum (16,8%), pancreas (15,4%) and stomach (14%) were included. Average age was 55(11-83 years-old). Expression was positive: Hes1 (95.8%), Notch 1 (91.6%), ATRX (89.5%), VEGFR2 (74.8%), PDGFR-β (62.9%), mTOR (39.9%), and MGMT (23.8%). VEGFR was more commonly expressed in jejunum/ileum (p: 0.00; OR: 0.24 IC95% 0.10-0.57), cecum/colon/sigmoid (p:0.02; OR: 5.84; IC95%:1.06-31.98) and in grade 2 GEP-NETs (p = 0, 01). MGMT lost expression more commonly in appendix (p: 0.00; OR: 0.13 IC95% 0.02-0.76). A significant loss of expression of MTOR in colon/sigmoid/cecum (p: 0.03; OR: 0.34 IC95% 0.12-0.95) was identified. We also found 4 microRNAs upregulated (miR-96, miR-145, miR-182 and miR-200a) and one downregulated (miR-19a) in tumor compare with normal tissue. The high expression of ATRX was correlated with the loss of miR-19a expression and the downregulation of MTOR and VEGFR2 with the upregulation of miR-96 and miR-200a respectively

Conclusions: Our results must conduct to new studies focused on follow up of specific therapies (alkylating agents, oxaliplatin-based chemotherapy, growth factor and protein kinase inhibitors) to evaluate a possible improve in survival rates of this patients. Epigenetic factors such as microRNA expression regulated key cell signaling pathways involve in GEP-NETs

588 Examination of PHOX2B in Adult Neuroendocrine Neoplasms Reveals Relatively Frequent Expression in Pheochromocytomas and Paragangliomas, Rare Expression in Neuroendocrine Carcinomas, and No Expression in Neuroendocrine Tumors

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Background: Paired-like homeobox 2b (PHOX2B) is a transcription factor with expression restricted to neurons and chromaffin cells of the autonomic nervous system (ANS). Germline mutations cause congenital central hypoventilation syndrome and predispose to neuroblastoma (NB) and Hirschsprung disease. Among pediatric small round cell tumors, PHOX2B is NB-specific. Two studies of adult ANS tumors (i.e., pheochromocytoma, paraganglioma), including only 62 tumors, produced conflicting results, with all tumors staining in one and expression restricted to 40% of paragangliomas in the other. We examined PHOX2B expression in a large cohort of pheochromocytomas and paragangliomas, as well as neuroendocrine tumors (NETs) and carcinomas (NECs).

Design: Tissue microarrays were constructed from 609 tumors: 111 pheochromocytomas, 146 paragangliomas (112 head and neck, 34 thoracoabdominal), 250 NETs (32 thyroid, 46 lung, 8 duodenum, 67 pancreas, 93 jejunoileum, 4 appendix), and 102 NECs (36 lung, 21 extrapulmonary visceral, 45 Merkel cell). PHOX2B immunohistochemistry was scored for extent (%) and intensity (0-3+) and an H-score (extent*intensity) calculated. Two-sided Fisher's exact and Kruskal-Wallis tests were used, as appropriate, with $p<0.05$ considered significant.

Results: PHOX2B expression was seen in 32% of pheochromocytomas and 47% of paragangliomas (p=0.015), including 52% of head and neck and 32% of thoracoabdominal tumors (p=0.052). Mean/median H-scores for these tumor types were in the 30-55 range (i.e., weak to moderate staining) (p=0.798). No NETs and only 7% of NECs were positive, the latter often strongly so. Detailed data are presented below.

Tumor type	n	% positive	Mean (median) H-score, if positive
Pheochromocytoma	111	32%	48 (33)
Paraganglioma (all)	146	47%	52 (30)
Paraganglioma (head and neck)	112	52%	55 (30)
Paraganglioma (thoracoabdominal)	34	32%	34 (27)
Neuroendocrine tumor	250	0%	NA
Neuroendocrine carcinoma	102	7%	140 (210)

Conclusions: We found weak to moderate PHOX2B expression in a significant minority of pheochromocytomas and paragangliomas and no expression in NETs, which could potentially be diagnostically useful in the distinction of these tumor types. High-level expression in a fraction of NECs likely reflects the transcription factor lineage infidelity characteristic of this class of tumors.

589 Adrenal Gland Myelolipomas with Plasma Cell Neoplasms

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Background: Rarely, lymphomas have been described in adrenal gland myelolipomas; however, no plasma cell neoplasms have been documented in myelolipomas to date. We aim to report the presence and evaluate the frequency of plasma cell neoplasms within adrenal gland myelolipomas.

Design: 23 adrenal gland myelolipomas were retrieved from a single institution's archive from 1999 to 2016. All slides were reviewed and clinical information was recorded. Immunohistochemistry for CD138 and in-situ hybridization for kappa and lambda light chains were performed to assess for the presence of a monotypic plasma cell population.

Results: Two of the 23 cases (9%) demonstrated involvement by a plasma cell neoplasm while the remaining 21 cases showed polytypic plasma cells. The myelolipomas involved by plasma cell neoplasms were from patients aged 71 and 81 years old, 1 female and 1 male, both right sided, with tumor sizes 7 cm and 8.5 cm, respectively. Histologically, the tumors contained multiple large aggregates of plasma cells occupying at least 10x fields that consistently were highlighted by CD138 and demonstrated either kappa (1 case) or lambda restriction (1 case). One patient had an established diagnosis of multiple myeloma prior to adrenalectomy while the other did not.

Conclusions: Plasma cell neoplasms in adrenal gland myelolipomas are rare phenomena. Prominent plasma cell aggregates (~10x field) should prompt evaluation for potential involvement by a plasma cell neoplasm utilizing CD138 and kappa and lambda light chain stains. Although this most commonly will reflect secondary involvement by a systemic plasma cell myeloma, a complete clinical workup is necessary to distinguish such involvement from a solitary plasmacytoma.

590 The Utility of FH and SDHB Immunohistochemistry (IHC) in Patients with Clinical Suspicion for Hereditary Paraganglioma-Pheochromocytoma (PGL/PCC) Syndromes

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Background: The majority of PGL and PCC occur sporadically, however, up to 30% may be associated with hereditary syndromes. Genes with germline mutations implicated in hereditary PGL/PCC syndromes include candidates like *fumarate hydratase* (*FH*) and *succinate dehydrogenase* subunits (*SDHA*, *SDHB*, *SDHC*, and *SDHD*). In addition, patients with inherited genetic syndromes, including multiple endocrine neoplasia (MEN) types 2A and 2B and von Hippel-Lindau (VHL), may present with multiple PGL and/or PCC. SDHB IHC has emerged as an effective ancillary tool to identify SDH-deficient tumors (including PGL and PCC). While FH IHC has been previously utilized to identify FH-deficient tumors in patients with hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome, it has not been widely explored in PGL and PCC.

Design: Patients with clinical suspicion for hereditary PGL/PCC syndromes were identified retrospectively at a large tertiary academic institution. For all patients with available PGL or PCC specimens, IHC for SDHB and FH was performed on full sections of representative formalin-fixed paraffin-embedded tissue and evaluated qualitatively (retained, lost, indeterminate, and failed) via concurrent review by two experienced pathologists. Available germline sequencing data was reviewed for all patients.

Results: Overall, PGL/PCC from 47 patients were identified and analyzed by FH and SDHB IHC, including: 24 with *SDH* mutations, 3 with *VHL* mutations, 1 with an *FH* mutation, 1 with a *RET* mutation (MEN type 2B), and 18 without known mutations. Of the PGL/PCC specimens from patients with *SDH* mutations, SDHB IHC results were: lost (19), retained (1), indeterminate (1), and failed (2). Of the PGL/PCC specimens from patients without known mutations, SDHB IHC results were: lost (2), retained (14), indeterminate (1), and failed (1). Of the PGL/PCC specimens from patients with known non-*SDH* mutations, SDHB IHC results were: lost (2) and retained (3); the two patients with loss of SDHB staining by IHC have *VHL* mutations and are related. FH staining was lost in the PGL/PCC from the patient with an *FH* mutation but retained in all other specimens (FH IHC failed in one PGL/PCC).

Conclusions: When applied to a large group of PGL/PCC specimens from patients with clinical suspicion for hereditary PGL/PCC syndromes, SDHB IHC has a high sensitivity and specificity for *SDH* germline mutations. In addition, FH IHC can be utilized to detect rare cases of FH-deficient PGL/PCC occurring in patients with germline *FH* mutations.

591 MicroRNA Expression in Gastrointestinal Neuroendocrine Neoplasms

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Background: Grading of gastrointestinal neuroendocrine neoplasms (GI-NENs) relies mainly on mitotic activity and Ki-67 index. It is often difficult to predict metastatic potential in these neoplasms. Recent studies have shown that GI-NENs express a wide spectrum microRNAs. We examined two microRNAs (miR-96 and miR-133) that were recently identified in GI-NENs to determine if they could assist in evaluating the biological behavior of these neoplasms.

Design: A tissue microarray (TMA) was constructed with 52 primary GI-NEN mainly from the small intestine and metastatic tumors from the same cases including liver metastasis (LVM, N=20) and lymph node metastases (LNM, N=33). In situ hybridization (ISH) was done with probes from Exiqon. Staining on the TMA was evaluated using a scale of 0 to 3+ for the intensity of staining and the percentage of tumor cells showing positive staining. Quantitative RT-PCR (qRT-PCR) was also performed on all the same cases (N=105).

Results: ISH analysis showed that miR-96 expression was significantly higher in the liver and lymph node metastatic neoplasms compared to the primary NENs ($p<0.05$). qRT-PCR showed that miR-96 levels were increased during progression from the primary tumors to metastases in the liver. qRT-PCR showed a significant decrease in miR-133 in the liver metastases compared to the primary tumors($p< 0.05$), although the ISH analysis did not detect significant differences in miR-133 expression levels between the primary and metastatic tumors. Appendiceal carcinoids without metastases had low levels of miR-96 and high levels of miR-133 by qPCR.

Conclusions: There is increased expression of miR-96 and decreased expression of miR-133 during progression from primary to metastatic GI-NENs. These results suggest that analysis of these two microRNAs by qRT-PCR may be useful in detecting metastatic disease and that ISH analysis may also assist in the evaluation of patients with GI-NENs.

592 Phospho-Akt (p-Akt) Expression in Thyroid Neoplasms Including the Non-Invasive Follicular Neoplasm with Papillary-Like Nuclear Features (NIFTP)

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Background: The PI3K/Akt/mTOR pathway has been linked to thyroid cancer pathogenesis. This pathway controls major cellular processes such as cell growth, proliferation and survival. Aggressive thyroid cancers including certain variants of papillary thyroid carcinomas (PTCs) and anaplastic thyroid carcinomas (ATCs) often respond poorly to conventional thyroid cancer treatment, and targeting this pathway may provide additional therapeutic options for these patients. The intracellular distribution of Akt and its phosphorylated form (p-Akt) in benign and malignant thyroid lesions remains controversial. We analyzed a large series of benign and neoplastic thyroid tissues by IHC for p-Akt and examined its intracellular distribution and compartmentalization with Vectra imaging technology.

Design: Tissue microarrays (TMAs) were constructed with formalin-fixed paraffin-embedded tissues of normal thyroid (NT, n=10), nodular goiter (NG, n=10), follicular adenoma (FA, n=32), follicular carcinoma (FCA, n=28), papillary thyroid carcinoma (PTC, n=28), follicular variant of papillary thyroid carcinoma (FVPTC, n=29) and anaplastic thyroid carcinoma (ATC, n=10). FVPTC were divided into invasive (I-FVPTC, n=16) and NIFTP (n=13). NIFTP tumors were defined as recently published (JAMA Oncology, 2016). IHC was performed on a Ventana stainer with p-Akt (S473) rabbit monoclonal antibody (Cell Signaling) and cytoplasmic and nuclear staining were analyzed with Vectra imaging technology, Nuance® and inForm ® software.

Results: ATC showed the highest total cellular expression levels of p-Akt, which was significantly higher than in NG, FA, FC, PTC and I-FVPTC ($p<0.05$). PTC expressed higher levels of p-Akt than FA and FC ($p<0.001$), while NIFTP tumors expressed higher p-Akt levels than FA and FC ($p<0.05$). Analysis of nuclear and cytoplasmic distribution showed that the highest levels of p-Akt were within the cell nucleus, which was consistently higher than cytoplasmic expression levels in all groups. There were no significant differences in p-Akt expression levels between clinicopathologic parameters such as tumor size, lymph node metastasis, and angioinvasion.

Conclusions: Phospho-Akt shows a predominantly nuclear distribution in benign and malignant thyroid tumors. The highest expression levels were measured in ATCs followed by PTCs, I-FVPTCs and NIFTPs. These findings suggest that the presence of papillary-like nuclear features (as in NIFTPs) is associated with higher p-Akt expression compared to more aggressive tumors such as FCs.

593 Pituitary Adenoma Immunohistochemical Characterization: Refining an Algorithm

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Background: Absent gold standards and diagnostic algorithms complicate pituitary adenoma classification. We previously generated an algorithm for classifying pituitary adenomas using statistical learning methods on immunohistochemical (IHC) data from 136 adenomas. Challenges remain, particularly in resolving Pit-1 family members. IHC for cytokeratin 20 (CK20), E-cadherin and estrogen receptors (ER) reportedly assist in making distinctions among several adenoma classes. Fibrous bodies, identified by a prominent globular pattern of low molecular weight cytokeratin (often CAM5.2) staining, have also been used to distinguish between sparsely- (SGGH) and densely-granulated growth hormone (DGGH) adenomas.

Design: Clinical data and archived formalin-fixed, paraffin-embedded tumor tissue from 143 patients with pituitary adenomas were collected retrospectively. A gold standard diagnosis was established based upon IHC for SF-1, Pit-1, alpha subunit and standard anterior pituitary hormones in conjunction with clinical and serological information. We apply IHC for CK20, E-cadherin, ER and CAM5.2 and consider what refinements might be made to these diagnoses and what limitations subset analysis puts on our conclusions. In particular, we consider the ability of these additional stains to designate SGGH adenoma (CK20, CAM5.2 globular pattern), DGGH adenoma (E-cadherin), and prolactin (PRL) producing adenoma (ER).

Results: Although limited by sample size, CK20 and E-cadherin did not assist in the distinction between SGGH and DGGH adenomas in our series. Globular CAM5.2 staining was observed only in Pit-1 family members, but this pattern was not restricted to GH adenomas. Strong, diffuse ER staining was most commonly observed in PRL adenomas with no other hormone immunoreactivity, but was also, to a lesser degree, in gonadotroph adenomas and in mixed PRL-GH adenomas.

Conclusions: CAM5.2 IHC pattern and ER staining may add value to the IHC workup of pituitary adenoma by helping to distinguish between certain members of the Pit-1 family of adenomas.

594 Ki67 Alone Is the Best Prognostic Predictor in Pancreatic NENs, Irrespective of Their Size

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Background: Surgical approach for well-differentiated pancreatic neuroendocrine neoplasms (pNENs) depends on tumor size and Ki67, with size <2 cm and Ki67≤2% indicative of benign behavior. However, the influence of liver metastasis and/or other factors of disease progression is poorly explored. We investigated the factors predisposing to disease progression in 80 pNEN patients with prior surgery.

Design: 76 patients had Ki67 <20%; 45 had no liver metastasis (24 with Ki67 ≤2%; 21 with Ki67 2-20%). We evaluated disease progression and predisposing factors by univariate Cox proportional Hazard regression. The concordance between Ki67 values on pre-surgical biopsy and on surgical specimens was assessed.

Results: Taking patients with Ki67 <2% and no metastasis as reference, the hazard ratio (HR) for disease progression was 3.34 for those with Ki67 2-20% and no metastasis (95% CI 1.18-9.50), 5.91 (2.42-14.4) for metastatic patients and 28.8 (7.31-113) for the 4 patients with Ki67 >20%. No patient with Ki67 <2% and no metastasis progressed in the 12 months after surgery.

In the whole population, liver metastasis (HR 3.63; 95% CI 1.98-6.64), lymph node metastasis (HR 1.90; 1.07-3.36), parenchymal invasion (HR 2.23; 1.11-4.39), perineural invasion (HR 1.98; 1.11-3.53) and Ki67 >2% (HR 2.67; 1.44-4.97) were associated with disease progression. Similar findings were reported when excluding patients with Ki67 >20%. In patients with Ki67 ≤2% and no metastasis and in those with Ki67 2-20% and no metastasis, the only factor associated with disease progression was perineural invasion (HR 7.30; 1.19-43.6 and HR 5.19; 1.04-25.9, respectively). Tumor size (<20 vs ≥20mm) was not associated with disease progression at any analysis. Ki67 was available both on pre-surgical biopsy and surgical specimen for 35 patients. The correlation between Ki67 values was 0.99; Ki67group (<2, 2-20, >20%) was correctly classified on biopsy in 91% of cases (32/35).

Conclusions: Ki67 alone can be considered as a major determinant of prognosis in pNEN patients. The evaluation of Ki67 and the presence of hepatic metastasis identify groups of patients at various risk of disease progression. Delayed surgery might be investigated for patients with Ki67 <2% and no distant metastasis, regardless of tumor dimension.

595 Microenviroment Features Drive the Prognosis of G3 GEP-NENs

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Background: Gastroenteropancreatic (GEP) neuroendocrine neoplasms (NEN) are divided into different prognostic categories according to Ki67. Treatment strategies based on this classification are not fully effective. Immunotherapy showed remarkable results in several neoplasms, but no information is available as to whether GEP-NEN have a microenvironment allowing the use of this therapy. To this end, the presence of T-cell infiltrate, activation/exhaustion markers (PD1), inhibitory receptor ligands (PDL1), immune-related (HLA-class) and inflammation-related (COX-2, beta-catenin) molecules must be investigated. Moreover, it is not known whether those markers could have a prognostic role in GEP-NENs.

Design: We characterized by immunohistochemistry primitive tumor lesions and stroma from 136 GEP-NENs patients. A validated quantitative score combining expression and intensity was used.

Results: Overall, stromal cells express CD3, CD4, CD8, PD1, PDL1, HLA1 and HLA-DR. Tumor cells prevalently express COX2, NGFR, pS6 and nuclear beta-catenin (NBcat). Statistical analysis showed that NBCat score ($p<0.001$) in tumor and pS6, CD8, NGFR, PDL1, HLA1, and COX2 ($p<0.05$ for all assessments) in stroma cells are independent prognostic factors. Their prognostic ability was summarized by a model linear predictor. NBcat showed a weak negative correlation with stromal pro-inflammatory factors (CD3, CD4, CD8, PD1, PDL1, HLA1 e HLADR), supporting a WNT/BCat-driven suppression of the T-cell infiltrate.

Ki67 had a poor correlation with pro-inflammatory markers - in particular with HLADR - and a strong correlation with the expression of NBcat. A significant interaction

between Ki67 and the above-mentioned linear predictor was disclosed in the G3 group (p=0.034), indicating that the prognostic effect of the markers was different in G3 versus G1/G2.
G3 group was further stratified in three subgroups with different prognosis which were defined by different rates of survival at 5 years (≤30% , 30-70%, >70%; log-rank test, p=0.005).
Conclusions: Factors contributing to aggressive tumor behavior, including Ki67, PDL1, inflammatory cytokines, pS6 and NBcat, are increasingly expressed in tumor microenvironment of GEP-NENs. Protective factors – namely CD8, HLA-Class I and HLA-DR – have a reduced expression. Importantly, the combined analysis of those markers and Ki67 allows to stratify G3 patients in three subgroups according to prognosis.

596 Novel Molecular Markers in Adrenocortical Tumors

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Background: Adrenocortical carcinoma (ACC) is a rare malignancy with poor prognosis and lack of effective therapeutic options. In spite of recent studies on the genetics and molecular biology of this neoplasm, its pathogenesis is still not completely understood and novel biomarkers as well as potential targets are actively sought to enhance patient care.
Design: By means of immunohistochemistry (IHC) and Western blot (WB) analysis, a series of ACCs and adrenocortical adenomas (ACAs) were investigated to assess the diagnostic and prognostic value of Aldehyde-dehydrogenase-6-A1 (ALDH6A1) and Fascin-1, previously identified through proteomic analysis as differentially expressed between ACC and normal adrenals.
Results: Expression of ALDH6A1 and Fascin-1 was evaluated by IHC and WB in tissue samples from a consecutive series of n=36 ACCs and n=37 ACAs operated at our University Hospital. A statistically significant positive correlation between the two techniques was found for both ALDH6A1 (r=0.883, p=0.000) and Fascin-1 (r=0.764, p=0.000) in ACC, but only for Fascin-1 (r=0.417, p=0.013) in ACA. ALDH6A1 was expressed in 47% of ACCs and in 37% of ACAs, whereas Fascin-1 was detected in 73% ACCs and 36% of ACAs (χ^2=15.6, p=0.000). However, the PPP and NPP values of Fascin-1 to discriminate between ACC and ACA were low (57% and 78%, respectively). Interestingly, in the ACC group, positivity for ALDH6A1 was associated with tumor stage (r=0.290, p=0.043), whereas positivity for Fascin-1 was correlated with recurrence/mortality (r=0.437, p=0.002). No significant correlation was found with the other clinico-pathologic parameters considered (i.e. tumor size, Weiss score, Ki-67 index and hormonal activity).
Conclusions: In this series, ALDH6A1 and Fascin-1 failed to differentiate benign from malignant adrenocortical tumors. However, our findings suggest a putative prognostic impact of these biomarkers in ACCs.

597 Diagnostic Utility of FoxA1 in Medullary Thyroid Carcinomas

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Background: FoxA1, also known as HNF-3A, regulates a variety of tissues during embryogenesis and early life. FoxA1 is reported to have oncogenic and tumor suppressive roles depending on tumor type. In thyroid, FoxA1 expression has recently been shown in C cells and medullary carcinoma (MTC) but not in follicular cells. FoxA1 has also been proposed as potential oncogene in anaplastic carcinoma (ATC). However, FoxA1 expression has not been extensively investigated in a spectrum of thyroid non-neoplastic lesions and tumors, and their morphologic mimics.
Design: 68 MTCs were stained with anti-FoxA1 antibody (clone 2F53, Merck Millipore), and its expression pattern was compared with those of other conventional markers such as calcitonin and CEA. FoxA1 was also performed on a variety of thyroid tumors, including 52 anaplastic thyroid carcinomas, their morphologic mimics such as parathyroid lesions and paragangliomas, as well as non-neoplastic lesions such as solid cell nests and c cell hyperplasia. The extent of staining was graded as follows: 1+, 1-25%; 2+, 25-50%; 3+, 50-75%; 4+, ≥ 75%.
Results: All 68 MTCs showed diffuse and strong FoxA1 nuclear expression. Expressions of other markers in MTCs were as follows: calcitonin 94.8%, CEA 91.4%, chromogranin 100%, and TTF1 97%, generally in variable intensity. FoxA1 was completely negative in follicular neoplasms, papillary thyroid carcinomas and poorly differentiated carcinomas while FoxA1 was variably expressed in 63.3% of ATCs (32/52). FoxA1 was also strongly expressed in C cell hyperplasia as well as solid cell nests. No FoxA1 expression was seen in thyroid gland with nodular hyperplasia, Hashimoto thyroiditis, and Graves disease. No FoxA1 expression was observed in paragangliomas and parathyorid lesions, including intra-thyroid parathyroid gland, and parathyroid hyperplaisa, adenoma and carcinoma.
Conclusions: FoxA1 discriminates between medullary carcinoma and tumors of follicular derivation with sensitivity and specificity greater than calcitonin and CEA, and its staining pattern is uniformly diffuse and strong. FoxA1 could be a useful ancillary marker for the diagnosis of MTC, including atypical MTC (calcitonin negative MTC), and c cell hyperplasia.

598 Intratumoral Angiogenesis and Lymphangiogenesis, and Peritumoral Vascular Microenvironment in Thyroid Carcinomas

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Background: Different histologic subtype of thyroid carcinoma clinically metastasize differently. While papillary carcinoma (PTC) prefers lymphatic route to regional lymph nodes, follicular carcinoma (FC) prefers hematogenous spread. The goal of this study was to evaluate angiogenesis and lymphangiogenesis inside and outside various thyroid carcinomas.
Design: A total of 92 thyroid carcinomas, including 28 classic PTC, 43 follicular variant PTC, 12 FC and 9 Hurthle cell carcinoma were identified from the archives of Surgical Pathology. Immunohistochemical stains for D2-40 and CD31 were performed on representative sections with tumor
and sufficient peritumoral thyroid tissue. D2-40 positive lymphatics (LV) and CD31 positive angiovasculature (AV) were comparatively assessed inside and outside the tumors.
Results: Table 1.

	N	ITL (D2-40)		ITA (CD31)		Peritumoral vascular network		
DX		Focal	Absent	Inc	No Inc	LV>AV	AV>LV	AV=LV
Classic PTC	28	11 (29%)	17 (61%)	17 (61%)	11 (29%)	20 (71%)	5 (18%)	3 (11%)
FV PTC	43	10 (23%)	33 (77%)	36 (83%)	7 (16%)	27 (63%)	10 (23%)	6 (14%)
FC	12	1 (8%)	11 (92%)	10 (84%)	2 (16%)	5 (42%)	4 (33%)	3 (25%)
HCC	9	2 (22%)	7 (78%)	6 (74%)	3 (37%)	5 (55%)	3 (35%)	1 (10%)
Total	92	24 (26%)	68 (74%)	69 (75%)	23 (25%)	57 (62%)	22 (24%)	13 (14%)

Conclusions: There were more AV than LV inside the tumors while outside the tumors, more LV than AV, particularly classic PTC. Thyroid cancers have poor intratumoral lymphogenesis (ITL), particular FC, and focal ITL(>5 lymphatics in clusters) was seen in 29% classic PTC and only 8% of FC while intratumoral angiogenesis (ITA) was increased in 84% of FC and 61% of classic PTC. LV and AV networks outside classic PTC and FC tended to be the reverse. **For FVPTC and HCC, their ITL was more similar to classic PTC but their ITA is more similar to FC.**
The study is first to compare the ITA and ITL in the context of peritumoral vascular microenvironment (PTVMV) in thyroid cancers. The findings might partially explain the difference of the metastatic behavior of various thyroid carcinomas and provide evidence for future therapy targeting altered vasculatures in thyroid cancers. The pattern of ITA, ITL and PTVMV in thyroid cancers is current under investigation for its prognostic significance.

599 Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP): An Uncommon Diagnosis Lacking BRAF Mutations When Strict Criteria Are Applied

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Background: An international panel of experts recently proposed a nomenclature revision for a subset of encapsulated follicular variant papillary thyroid carcinoma (EFVPTC) to highlight its less aggressive nature and reduce overtreatment. These tumors, termed "noninvasive follicular thyroid neoplasms with papillary-like nuclear features" (NIFTP) have strict diagnostic criteria and are predicted to lack mutations such as BRAF V600E seen in conventional PTC. We retrospectively reviewed cases of FVPTC applying the proposed criteria to reclassify tumors as NIFTP to examine the incidence of this diagnosis and the rate of BRAF V600E mutations.
Design: All FVPTC ≥0.3cm from 1/2014 through 12/2015 were retrieved. Synoptic searches were used to determine overall incidence of all thyroid cancer and PTC over the study period. 52 FVPTC were independently reviewed by all authors and disagreements were reviewed to reach consensus using the proposed criteria for NIFTP. 2 cases were excluded due to lack of slides for review or inadequate sampling of the capsule with no definitive NIFTP exclusion criteria on available slides. Prior BRAF mutational testing performed routinely on PTC at our institution was also collected.
Results: 17 of 50 tumors were reclassified as NIFTP representing 3.7% (17/458) of all thyroid malignancies, 4.0% (17/420) of all PTC and 32.7% (17/52) of all FVPTC over the study period. The table compares tumors classified as NIFTP, noninvasive FVPTC and invasive/infiltrative FVPTC. Reasons for exclusion are also tallied.

	NIFTP	Noninvasive FVPTC	Invasive/Infiltrative FVPTC
N	17	6	27
Mean Age (yrs)	57.4	50.3	50.2
F:M	14:3	3:3	20.7
Mean Size (cm)	2:1	1.1	2:4
BRAF V600E	0/12	1/3	4/20
Other exclusion criteria			
Papillae >1%		4	5
Solid >30%		2	4
Mitoses >3/10HPF		1	0
Psammoma Bodies		0	1
Necrosis		0	1

Conclusions: When proposed criteria are used, NIFTP is not common but accounts for nearly a third of all FVPTC in our institution. Invasion is the most common reason for excluding NIFTP with architectural patterns being much less common. Many cases classified as FVPTC show only focal invasion and this highlights the importance of histologically examining the entire tumor-normal interface for these lesions. BRAF V600E mutations were not detected in cases reclassified as NIFTP confirming that this mutation is not expected in tumors fulfilling NIFTP criteria.

600 Prevalence of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) in Thyroid Tumors with *BRAF K601E* Mutation

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Background: Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a recently recognized entity that encompasses a proportion of tumors formerly classified as encapsulated follicular variant of papillary thyroid carcinoma (PTC). Some of these neoplasms are known to be associated with *BRAF K601E* mutation. The aim of this study is to evaluate the prevalence of NIFTP in *BRAF K601E* mutation positive thyroid tumors.

Design: All thyroid tumors with *BRAF K601E* mutation which had surgical specimens for evaluation over a period of 7 years (June 2009 to June 2016) were retrieved from the archives of the Department of Pathology. Glass slides were independently reviewed by three thyroid pathologists in a blinded manner. If no full agreement in diagnosis was achieved, the diagnosis rendered by two out of three pathologists was accepted.

Results: Thirty-four *BRAF K601E* mutation positive thyroid tumors were identified. This included 32 tumors with isolated *BRAF K601E* mutation and 2 tumors with complex *BRAF* mutations including *K601E*. In 29 (83%) of these cases, blind review by 3 thyroid pathologists yielded a fully concordant diagnosis, and in 5 (17%) a partially concordant diagnosis. Out of these cases, 15 (44%) were reclassified as NIFTP, 12 (35%) were PTC, 4 (12%) were follicular adenomas and 3 (9%) follicular thyroid carcinomas (FTC). The majority of the PTCs were follicular-patterned. Most of the *K601E* mutant nodules were T1 (72%) and T2 (19%) lesions by TNM staging with only 3 (9%) T3 lesions. Two tumors with complex *BRAF* mutations, *BRAF K601E+T599I* and *BRAF V600_K601>E* were both PTC. The median age of the patients was 48.5 years (range 23-86 years). The size of the thyroid nodules ranged from 0.3-4.5 cm (mean, 1.5 cm). Preoperative FNA cytology was done in 11 of these NIFTP cases and yielded the diagnosis of a follicular neoplasm in 8 (73%) cases and atypia of undetermined significance in 3 (27%) cases. 31 (91%) cases underwent total thyroidectomy including 6 completion thyroidectomies following lobectomy. 20 patients received radioactive iodine after surgery. No recurrence or metastasis was noted in any patient with isolated *BRAF K601E* mutated thyroid tumors after a median follow-up of 47.3 months.

Conclusions: In this series of case, NIFTP was the most common thyroid tumor associated with *BRAF K601E*, highlighting a prognostically favorable association of this type of *BRAF* mutation.

601 A French Multicentric Retrospective Clinicopathological Study of 43 Oncocytic Adrenal Tumors

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Background: Oncocytic adrenocortical tumors (OACT) are a rare subtype of adrenal tumors with challenging diagnosis and histoprognostic evaluation and supposed more indolent clinical behaviour. The Lin-Weiss-Bisceglia (LWB) system is the most widely accepted classification for OACT but have only be validated in a meta-analysis.

Design: We present the largest multicentric retrospective clinicopathologic study of 43 cases of OACT (29 pure and 14 mixed) selected on morphology and intense granular antimitochondrial antibody positivity by centralized review of 94 adrenocortical tumors. Four different prognostic scoring systems were evaluated: Weiss score, revisited Weiss score, "reticulin" algorithm (RA) and LWB score. For all cases clinical data were obtained and analyzed in corelation with pathological data.

Results: ENSAT (European Network Study Adrenal Tumors) stage at diagnosis was II for 38 cases and III or IV for 5 cases. 55 % of tumors were hormonally functioning. A majority of tumors were classified as malignant according to all alternative systems: Weiss 72%, Revisited Weiss 56%, LWB 65% and RA 53%. Major discordances between LWB and the other scores exist when "atypical mitosis" or "large tumor weight and size" was isolated criteria of malignancy in LWB score. The Ki-67 index was >10 % for tumors classified as malignant according to all scores, and ≤10% for tumors classified as benign according to all scores. After an mean time follow-up of 38 month, only 3 cases were clinically malignant. This 3 cases were pure oncocytic tumors considered as malignant according to each score and exhibited Ki67 index >10%. Tumor necrosis was the only other significant feature of malignancy between the clinically malignant and benign groups.

Conclusions: OACT are overdiagnosed as carcinoma wathever the classification systems used. Tumor necrosis and Ki67 proliferation index >10% are the most relevant features of malignancy in our study. Despite a relatively short-term in our study, the clinically confirmed oncocytic adrenal carcinoma does not have more favorable prognosis than conventional adrenocortical carcinoma as previously described.

602 Utility of Insulinoma Associated Protein 1 (INSM1) and Orthopedia Homeobox (OTP) in Uncommon Neuroendocrine and Neuroepithelial Tumors

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Background: INSM1 and OTP are transcription factors that play a critical role in neuroendocrine (NE) and neuroepithelial cell development. In adult tissues, INSM1 has been identified in multiple tumors of NE or neuroepithelial origin; however, its expression in uncommon NE tumors has not been explored. OTP expression is believed to be restricted largely to NE tumors of pulmonary origin and appears to correlate with poorer prognosis in pulmonary carcinoids; however, its expression patterns in other NE/neuroepithelial tumors are still under investigation. Here, we assessed the diagnostic utility of these two markers in uncommon tumors with NE differentiation including breast, tumors of gynecologic origin, prostate, retinoblastoma, esthesioneuroblastoma, pituitary tumors, and medullary thyroid carcinoma (MTC).

Design: Duplicate cores from 110 formalin-fixed, paraffin-embedded cases of NE tumors were used to construct a tissue microarray (TMA). Immunohistochemistry (IHC) for INSM1 and OTP was performed and scored semi-quantitatively based on intensity and percent of positive immunoreactive nuclei. Scoring results were categorized into 4 different groups based on intensity (0–3) and distribution (focal or diffuse). Positive cases were defined as having a scoring index >1 and negative cases displayed scoring indices ≤1 for nuclear immunoreactivity. IHC for chromogranin A, synaptophysin, and CD56 were used as positive control for NE differentiation in these tumors.

Results: INSM1 was diffusely expressed in 100% of gynecologic tumors with NE differentiation (10/10), retinoblastoma (4/4), esthesioneuroblastoma (8/8), MTC (42/42), and pituitary tumors (34/34). Fifty-seven percent (4/7) of mammary carcinoma and 20% (1/5) of prostate adenocarcinoma with NE differentiation also diffusely expressed INSM1. Diffuse nuclear expression of OTP was detected in 75% esthesioneuroblastoma (6/8); 40% (4/10) of gynecologic tumors and 40% (2/5) of prostate adenocarcinoma with NE differentiation. OTP expression was not detected in mammary carcinoma with NE differentiation, pituitary tumors, retinoblastoma and MTC.

Conclusions: INSM1 is expressed in most of the uncommon NE and neuroepithelial tumors in this study, confirming its diagnostic utility as a new and sensitive marker of NE/neuroepithelial differentiation. The expression of nuclear OTP in some NE and neuroepithelial tumors other than lung indicate that positive staining for this marker in a NE tumor of unknown primary site does not always indicate pulmonary origin.

603 The Utility of Digital Image Analysis on the Evaluation of Thyroid Needle Aspiration Cytology: A Pilot Study

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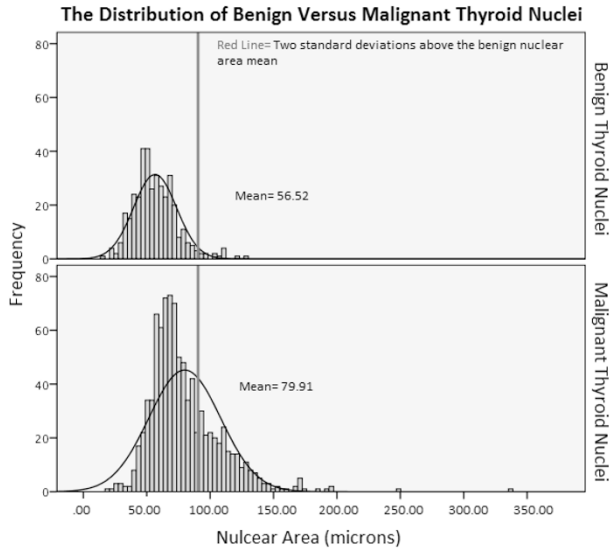
Background: The Bethesda System for Reporting Thyroid Cytopathology was developed to standardize the nomenclature and reporting system of thyroid fine needle aspiration (FNA) cytology. However, this classification is based on qualitative rather than quantitative criteria resulting in significant inter-observer variability. In this pilot study we assessed the feasibility of quantitative digital image analysis (DIA) to differentiate benign from malignant thyroid nodule aspirates.

Design: Ten unique thyroid FNA air-dried Diff-Quick stained smears with histological confirmation, 5 benign and 5 papillary thyroid carcinoma, were identified from Moffitt Cancer Center in line with IRB approval. The slides were scanned using the Aperio ScanScopeAT. A cytopathologist (BAC) segmented the scanned slides into benign or malignant regions, with up to five unique regions per slide. Image Pro Premier was used to perform a semi-automated identification of individual nuclei within each distinct region, for a total of 378 benign cells and 908 malignant cells, followed by an automatic extraction of 14 specific nuclear features.

Results: Statistical analysis found significant differences ($p<0.05$) in 12 of the 14 parameters studied on univariate analysis, including nuclear size, shape and staining characteristics. Nuclear area, the most useful parameter in identifying malignant nuclei, was significantly larger in malignant cells than in benign cells with a mean of 79.91 and 56.52 microns respectively ($p <0.001$). Furthermore, setting the nuclear area threshold at 2 standard deviations above the mean for benign nuclei, DIA correctly classified 83% of the malignant regions as such without misclassifying any of the benign ones (sensitivity=71%, specificity=100%, Figure 1).

Conclusions: This pilot study suggests that DIA could be useful to aid in the characterization of FNA cytology through quantitative criteria, which might improve the reproducibility and reliability of the diagnostic process. Although it is unlikely that any single parameter will be accurate enough to classify thyroid aspirates, an algorithm combining several features may improve accuracy. These promising results should encourage further, larger, studies to identify additional features and/or combination of features that are clinically useful.



604 *cMYC* in Thyroid Follicular Cell-Derived Carcinomas: A Role in Thyroid Tumourigenesis

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Background: It is estimated that *cMYC* regulates 15% of human genes and is involved in up to 20% of all human cancers. Reports discussing *cMYC* protein expression in thyroid carcinomas are limited with controversies pertaining to *cMYC* expression patterns. The aims of the current study were to clarify patterns and intensities of *cMYC* expression in follicular cell-derived thyroid carcinomas across a spectrum of cancer morphologies and disease aggressivities, and to evaluate the potential role of *cMYC* in progression of well-differentiated thyroid carcinomas into less well-differentiated carcinomas.

Design: Immunohistochemical studies using a specific anti *cMYC* monoclonal antibody were performed on tissue microarrays built from a spectrum of follicular cell-derived thyroid carcinomas (25 papillary, 24 follicular, 24 oncocytic, and 21 undifferentiated).

Results: *cMYC* was found to be expressed in a nuclear fashion in thyroid carcinomas and nodular hyperplasia cases.

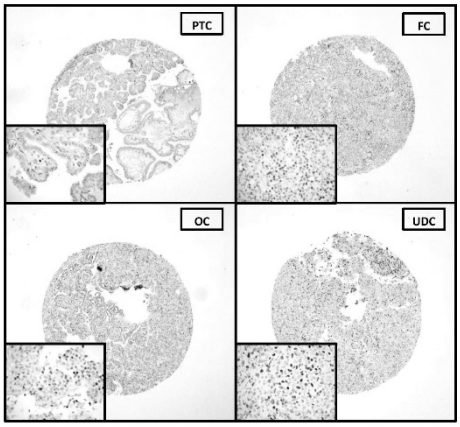

Fig. 1

cMYC expression was weakly positive in nodular hyperplasias and in well-differentiated carcinomas. The majority of undifferentiated carcinomas showed strong *cMYC* positivity.

c-MYC expression	NH (N=25)	PTC (n=25)	FC (n=24)	OC (n=24)	UDC (n=21)
Negative	12	19	18	12	5
Weak positive	11	5	5	7	4
Strong positive	2	1	1	5	12
Total positive	13	6	6	12	16
P value total positives(UDC vs. others)	0.13	0.0009	0.0009	0.12	
P value strong positives(UDC vs. others)	0.0004	0.0001	0.0001	0.02	

Interestingly, there was a correlation between *cMYC* intensity and tumor size in undifferentiated thyroid carcinomas cases.

Conclusions: Our study suggests that nuclear overexpression of *cMYC* correlates with tumorigenesis / dedifferentiation. The *overexpression* of *cMYC* in undifferentiated thyroid carcinomas raises the possibility of *cMYC* contributing to transformation of well differentiated thyroid carcinomas into undifferentiated tumors. Investigations of *MYC* targeted therapies for patients with undifferentiated thyroid carcinomas may be warranted based upon our findings.

605 Expression and Prognostic Significance of Insulinoma-Associated Protein 1 (INSM1) and Orthopedia Homeobox (OTP) Transcription Factors in Pulmonary Neuroendocrine Neoplasms

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Background: INSM1 is a transcription factor expressed in developing neuroendocrine/neuroepithelial tissue and neuroendocrine tumors (NET). In the lung, INSM1 controls differentiation of pulmonary neuroendocrine cells and plays a role in tumorigenesis of small cell carcinoma (SCLC). Diagnostic and prognostic utility of INSM1 expression in other pulmonary NETs has not been studied. OTP expression showed promise in predicting outcomes in pulmonary carcinoid tumors. To further evaluate diagnostic utility and prognostic significance of these markers, we examined the expression of INSM1 and OTP in a large panel of pulmonary NETs.

Design: Formalin-fixed paraffin-embedded pulmonary NETs including 74 typical carcinoids (TC), 19 atypical carcinoids (AC), 24 SCLC and 13 large cell neuroendocrine carcinomas (LCNC) were assembled on a tissue microarray (TMA). Clinicopathologic variables and follow-up were collected. Immunohistochemistry (IHC) with antibodies directed against INSM1 and OTP was performed. Nuclear staining was semiquantitatively assessed based on intensity (0-3) and distribution as focal (<25%) or diffuse. Results were analyzed using Kruskall-Wallis nonparametric test with ordinal values (0-6) assigned to each of six IHC patterns.

Results: INSM1 was expressed in 62/74 TC, 17/19 AC, 24/24 SCLC and 12/13 LCNC. Semi-quantitative INSM1 expression levels were highest in TC and SCC compared to AC and LCNC ($p=0.003$). In either group, INSM1 expression did not correlate with lymph node or systemic metastasis, or disease status. Nuclear OTP was detected in 64/74 TC, 15/19 AC, 5/24 SCLC and 3/10 LCNC, with highest expression in typical and atypical carcinoids and diminished or absent expression in SCLC and LCNC ($p<0.001$). Surprisingly, there was no statistically significant correlation between OTP expression and aggressive behavior in pulmonary carcinoids, including lymph node or systemic metastasis, and disease status.

Conclusions: INSM1 is expressed in a broad range of pulmonary NETs and can serve as an excellent diagnostic marker in these tumors but lacks prognostic significance. We confirmed the sensitivity of OTP expression for well-differentiated pulmonary NETs. However, in contrast to the previous findings, we found no significant association between OTP expression and aggressive behavior in pulmonary carcinoid tumors.

606 Molecular Profile and Cytologic Diagnosis of Non-Invasive Follicular Neoplasm with Papillary-Like Nuclear Features (NIFTP)

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Background: The recent nomenclature revision of encapsulated follicular variant of papillary thyroid carcinoma will have major impact on cytologic evaluation and clinical management. Defining its clinical and biological differences from conventional papillary thyroid carcinoma and infiltrative follicular variant of papillary thyroid carcinoma will help facilitate cytologic diagnosis and stratify patients for surgical management. Correlation of cytologic diagnosis, molecular profile and surgical diagnosis with the new nomenclature can help refine The Bethesda System for Reporting Thyroid Cytology (TBSRTC) and revise the rate of malignancy in various TBSRTC categories.

Design: 228 thyroid aspirates with indeterminate cytologic diagnosis (atypia of undetermined significance AUS, suspicious for follicular lesion SFN, and suspicious for malignancy Susp) performed over 24 months were analyzed for hot spot mutations by next generation sequencing and translocations by targeted PCR. 99 of these cases underwent surgical resection with 70 cases available for histologic review and reclassification to NIFTP.

Results: Of the 228 aspirates (19.5%) submitted for molecular studies 21 had indeterminate results. Surgical resection was performed in 99 cases. Of these, 70 cases that were available for second review, 11 cases fulfilled the criteria for NIFTP. The 11 NIFTP cases had the following histologic (6 PTC , 4 follicular adenoma and 1 benign diagnosis) and cytologic (6 AUS , 4 SFN and one Susp) diagnosis. 8 of the 11 cases (73%) showed mutations with 5 RAS mutations, one P53 G245S,Y220C, one BRAF K601E and one PAX8/PPARg translocation.

Conclusions: This study, although limited by relatively small number of cases, shows that NIFTP is a heterogeneous group with majority of cases having a previous malignant diagnosis. Interestingly, all reclassified cases had indeterminate cytologic diagnosis and most were positive for mutations with no BRAF V600E mutations noted which reinforces the indolent behavior of these neoplasms and supports a conservative approach in management of these lesions.

607 Ancillary Molecular Testing of Cytologic Samples in the Setting of NIFTP

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Background: Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is an indolent thyroid tumor characterized by frequent *RAS* mutations and an absence of the *BRAF* V600E mutation that is commonly seen in classical papillary thyroid carcinoma (cPTC). The ability to differentiate NIFTP from cPTC at the time of fine needle aspiration (FNA) would facilitate conservative management of NIFTPs. The aim of our study was to determine if molecular testing of FNA samples might aid in differentiating NIFTPs from cPTCs.

Design: We previously evaluated whether cytologists are able to prospectively distinguish NIFTP/follicular variant of papillary thyroid carcinoma (FVPTC) from cPTC in a cohort of 56 consecutive FNAs diagnosed as "Malignant" or "Suspicious for Malignancy". Residual FNA samples collected in CytoLyt using the ThinPrep method were available for 25 of the 56 cases for molecular analysis. Samples were evaluated for *BRAF*, *NRAS*, *HRAS*, and *KRAS* point mutations as well as *RET/PTC* and *PAX8/PPARG* fusions.

Results: In our cohort of 25 cases, the cytologist favored cPTC in 15 (60%) cases. Resection revealed cPTC in all 15 (100%), and molecular testing revealed a *BRAF* V600E mutation in 9 (60%) of these cases. The cytologist favored NIFTP/FVPTC in 7 cases. Six (86%) of these cases were follicular neoplasms (4 were NIFTPs) on surgical resection (no molecular alterations were detected in this subset of cases), and one case was a cPTC that demonstrated a *BRAF* V600E mutation. Three cases (12%) in our cohort were interpreted as indeterminate for cPTC vs NIFTP/FVPTC by cytomorphology. Two of these cases were cPTCs (both found to have a *BRAF* V600E mutation), and one was a *NRAS*-mutant poorly differentiated thyroid carcinoma.

Conclusions: Molecular analysis confirmed the cytologist's impression in 9 (41%) cases in our cohort (i.e. cPTC was favored and a *BRAF* V600E mutation was detected). Molecular testing could potentially have aided in the distinction between cPTC and NIFTP/FVPTC in 3 (12%) cases: one case that was favored to be a NIFTP/FVPTC on cytology but was a cPTC with a *BRAF* V600E mutation, and two cases that were characterized as indeterminate on cytology that were cPTC on resection and harbored a *BRAF* V600E mutation.

608 Creating Personalized Mathematical Models of Gene Expression in Thyroid Carcinoma

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Background: In the molecular era, a key challenge for precision medicine is translating big data into drug targets and improved survival for individual cancer patients. Many papillary thyroid carcinomas (PTCs) have an indolent course; however, a subset metastasize or invade nearby tissues. We aim to identify mechanisms of epithelial-to-mesenchymal transition and metastasis through mathematical models. Well-validated models may predict therapeutic response and suggest drug targets for future study. We present an analysis of a personalized mathematical model of thyroid carcinoma utilizing publicly-available gene expression data.

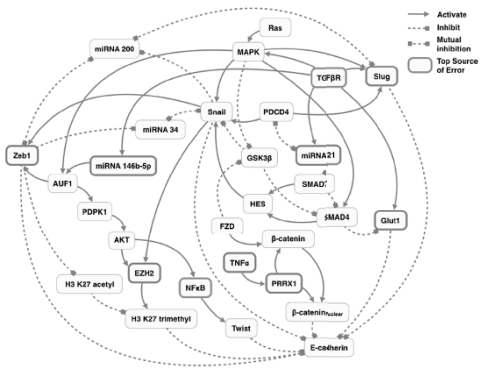

Figure 1: Model diagram of our personalized mathematical model of thyroid carcinoma gene expression. Thick outlined boxes indicate the top contributors to the error in a model fitted to a stage 1 papillary thyroid carcinoma patient and applied to other patients' gene expression data (Stages 1, 3 and 4).

Design: Our mathematical model of PTC, based on published molecular interactions, utilizes 30 ordinary differential equations (Fig. 1). Gene expression data from patients with PTC (classical type), including both tumor and normal tissue, are obtained from Genomic Data Commons. Simulations are performed in Python with the SciPy stack. Normal tissue gene expression values (RNA-Seq) are used as the model baseline, and the rates of the molecular interactions are optimized to predict 27 tumor gene expression values. The percent error for each gene expression value is calculated to compare simulated and patient tumor data.

Results: A model fitted to a patient with stage 1 PTC is applied to gene expression data for other patients with stage 1, 3 and 4 PTC. The errors of 18 of the genes range from 3% to 200% across all patients. The errors of the 9 remaining genes are above 200% in at least one patient, but in other patients are as low as 2%. The highest error is 40,000%. For one patient, one micro RNA level is predicted at a high level but is not detectable in the data. Both the lowest and highest mean errors occur in stage 1 patients. The model components with the largest errors are indicated in Fig. 1.

Conclusions: This work suggests that our model can be personalized to describe an individual patient's gene expression data. The large variability in errors in the same gene across multiple patients suggests the presence of individual variability that is not accounted for in a universal model. Comparison of individualized models may be useful to identify targets for future experimental study.

609 Thyroid Rests or PTC: Can Mutational or NGS Fusion Analysis Help Differentiation?

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Background: Thyroid rests in cervical lymph nodes have proven difficult to distinguish from metastatic thyroid carcinoma (PTC). BRAF V600E, BRAF 464-469, KRAS point mutations as also fusions involving PPARG, RET and Alk may be seen in thyroid carcinoma but would not be expected in benign rests. We investigated if using a next generation sequencing panel would differentiate benign rests from metastatic deposits.

Design: 61 cases in formalin-fixed paraffin-embedded[FFPE], from 2000 to 2016, were pulled from a tissue bank with IRB consent and reviewed by microscopy for areas of interest. Foci from FFPE blocks were selected, the tumors were enriched by microdissection or manually macrodissected, RNA was extracted and subjected to the Archer DX CTL fusion panel and analyzed on the Ion Torrent instrument. Mutations for BRAF and KRAS were further analyzed using pyrosequencing.

Results: 49 of 61 patients had known PTC. 24 cases with benign-appearing rests were BRAF, Kras and fusion negative in both the primary as also the rest. 4 cases had PTC with metastases and all had BRAF mutations. The remaining 4 cases had rests with no known PTC and were wild type (WT) for BRAF V600E, KRAS and fusions. The 14 indeterminate cases were all known PTC with 9 having metastases to other nodes. 3 had BRAF mutations in the primary and metastases. The sensitivity of BRAF V600E corresponding to PTC in primary, metastasis or rests was 56%, the specificity was 100%, the positive predictive value was 100% and negative predictive value was 48%. All cases were WT for KRAS with the exception of one rest with a mutation in Q61 codon which was seen in one of the two benign cases with benign goiter. All cases were WT for BRAF codons 464-469. A weak ALK fusion with an unknown partner identified in a BRAF negative PTC primary.

Conclusions: Versus other fusions, BRAF mutation in nodes has a high positive predictive value. BRAF status in PTC primary did not correlate with status in metastases, suggesting a mutational event possibly explaining the negative predictive value of 48%. Thus sequencing may be helpful in select cases but the low negative predictive value limits use in evaluation of indeterminate rests.

610 Pediatric Follicular Thyroid Carcinoma – Indolent Behaviour and Low Prevalence of RAS Mutations

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Background: The clinicopathological features and molecular profiles of follicular thyroid carcinoma (FTC) in pediatric patients are still unknown, while pediatric papillary thyroid carcinomas (PTC) have been published by many investigators.

Design: We clinicopathologically studied 41 consecutive FTCs from pediatric patients under 21 years of age and analysed the point mutations in codon 12, 13 and 61 of *NRAS*, *HRAS* and *KRAS* genes by direct sequencing.

Results: The pediatric FTCs were 1:6 in male to female ratio and 52.7mm in mean size. Multifocality was identified in two cases and only one case showed distant metastasis at time of operation. During a median follow-up time of 69 months, all patients were alive and tumor recurrence was detected in two patients (4.9%). There were no differences in clinicopathological features between the groups of patients under 16 and 16 – 20 years of age. Histologically, all pediatric FTCs were classified as minimally invasive subtype and varied in growth patterns such as small follicular (39%), follicular (14.6%), solid/trabecular (6%), oncocytic (4.9%) and mixed subtypes (26.8%). The mean Ki67 index was 5.7% and not statistically different among growth patterns. Direct sequencing revealed *NRAS* mutations in five cases (12.2%) and *RAS* mutations were associated with small tumor size ($p = 0.014$). *HRAS* or *KRAS* mutations were negative in all cases.

Conclusions: Our study is the largest series of pediatric FTCs so far. Pediatric FTCs behave an indolent clinical course and excellent prognostic outcome despite of their large tumor size. *RAS* mutations are uncommon in pediatric FTCs and show a potential association with low-risk tumors.

611 Cytologic Stratification of FLUS Improves Performance of Afirma

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Background: Afirma, an RNA-based assay, was developed to help categorize cytologically indeterminate nodules as benign with high sensitivity and negative predictive value (NPV), but NPVs from 75-98% continue to contribute to costly further testing and/or unnecessary resections of nodules classified as FLUS and assigned a 5-15% risk of malignancy by the Bethesda System. This study was designed to determine if stratification of FLUS using cytologic features improves the performance of Afirma in FLUS, the largest group of abnormal thyroid FNA diagnoses.

Design: Thyroid FNAs diagnosed as FLUS (Am J Clin Pathol 2009;132:658) from 1/1/2012-7/1/2016 with Afirma results and surgical follow-up were reviewed and categorized into 3 subsets: 1) atypical based on the presence of nuclear grooves/membrane irregularities, pseudoinclusions and/or papillary clusters (ATYP n=69); 2)

prominent Hurthle change (HC n=54); 3) usual when these changes were absent (U n=93). Of the 6628 thyroid FNAs evaluated, 836 (12.6%) were reported as FLUS for which 174 diagnostic Afirma results [83 (47.7%) benign and 91 (52.3%) suspicious] were available. Surgical follow-up was available for 10 of the Afirma benign and 51 of the Afirma suspicious cases.

Results: Afirma results and surgical follow-up are correlated before and after stratification of FLUS in Table 1. The 23 malignant nodules (0.5 - 4.8 cm; median 1.5 cm) include 22 PTC and 1 minimally invasive FTC. 88.9% of the HC cases are benign.

	Excision Results					
	Benign	Malignant	Sensitivity	Specificity	PPV	NPV
ALL FLUS						
Afirma Benign excised (10)	8	2	91%	21%	41%	80%
Afirma Suspicious excised (51)	30	21				
STRATIFIED FLUS						
ATYP FLUS						
Afirma Benign excised (3)	3	0	100%	21%	42%	100%
Afirma Suspicious excised (19)	11	8				
HC FLUS						
Afirma Benign excised (1)	1	0	100%	6%	12%	100%
Afirma Suspicious excised (17)	15	2				
U FLUS						
Afirma Benign excised (6)	4	2	85%	50%	73%	67%
Afirma Suspicious excised (15)	4	11				

Conclusions: - Cytologic stratification of FLUS improves performance of Afirma in the ATYP and U subsets.

- Afirma has the lowest specificity and PPV in the HC subset of FLUS, suggesting that Afirma testing may not be useful in FLUS nodules exhibiting prominent Hurthle changes.

612 Malpractice Climate Is Predictive of Thyroid Cancer Incidence

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Background: The incidence of thyroid cancer in the United States has increased markedly over the past several decades, while thyroid cancer mortality has remained static. Thyroid cancer overdiagnosis may be a partial cause. Possible mechanisms of overdiagnosis include unnecessarily low thresholds for imaging and biopsy, as well as low diagnostic thresholds in pathology. Malpractice concerns may drive these low thresholds. Given malpractice law is regulated at the state level, we set out to investigate the effects of state-level malpractice climate on state-level thyroid cancer incidence.

Design: State-level data on thyroid cancer incidence were collected from the Centers for Disease Control database (https://nccd.cdc.gov/uscs/). Epidemiologic data associated with thyroid cancer incidence, including race, income, and obesity were likewise collected from the United States Census Bureau database (https://www.census.gov/data.html). Malpractice climate was quantified as the number of malpractice payouts per year per 100,000 people, with data taken from the National Practitioner Data Bank (https://www.npdb.hrsa.gov/resources/aboutStatData.jsp). A repeated measures multivariate model was created with thyroid cancer incidence as the outcome and malpractice climate as a predictor variable, controlling for known risk factors (1999 to 2010).

Results: Evaluating all years individually from 1999 to 2010, univariate logistic regression models showed states with higher thyroid cancer incidence tended to have higher median income, higher percentage of Caucasians, and increased malpractice payouts ($p<0.001$, all associations except race in 1999 in which $p=0.062$). In a multivariate logistic regression repeated measures model, state-level thyroid cancer incidence was significantly positively correlated with number of malpractice payouts ($p<0.001$), when controlling for year, race, and income (all of which statistically significant in model, $p<0.01$). Obesity was not significant when added to the model.

Conclusions: The results suggest state-level malpractice environment is predictive of thyroid cancer incidence, when controlling for known risk factors for thyroid cancer. Though the mechanism for this association is unclear, it remains possible that malpractice concerns drive defensive overdiagonsis of thyroid cancer. Further work is required to better understand this association.

613 Differential Gene Expression Analysis of Invasive and Non-Invasive Follicular Variant of Papillary Thyroid Carcinoma

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Background: The "follicular variant" (FV) of papillary thyroid carcinoma (PTC) is controversial. While invasive FV-PTC is capable of metastasis like classic PTC, there is low risk of metastasis in FV-PTC lacking invasion. The latter has thus been renamed "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) by The Endocrine Pathology Society. As invasive and noninvasive FV-PTC appear to be distinct entities, we set out to identify molecular differences between them.

Design: The authors identified 65 cases of FV-PTC with available lymph node staging data in The Cancer Genome Atlas (TCGA) database (https://gdc-portal.nci.nih.gov/). Scanned digital slides were reviewed and each was designated as invasive, noninvasive, or cannot determine. Differential expression between invasive and noninvasive cancers was determined using t-tests with false discover rate (FDR) multiple test correction (from TCGA RNA seq data). Hierarchical clustering was performed based on differentially expressed genes. The resulting expression clusters were compared to sequencing and chromosomal rearrangement data.

Results: Of the 65 reviewed cases, 18 were invasive, 29 were noninvasive, and 18 were undetermined. Invasive tumors were strongly associated with lymph node metastasis (odds ratio 22, $p<0.001$; Fisher test) and were enriched in *BRAF* V600E mutations ($p=0.024$, Fisher test). Expression analysis identified 699 genes differentially expressed between invasive and noninvasive tumors ($q<0.05$, FDR). Hierarchical clustering based on identified genes divided tumors into two clusters: one contained all *RET*, *BRAF*, and *NTRK3* rearrangements and 82% of *BRAF* V600E mutants; the other contained all *RAS* mutants. Node metastases were more common in the *BRAF* mutant cluster than the *RAS* mutant cluster (40% cluster members vs 9% cluster members, $p=0.021$, Fisher).

Conclusions: Genes differentially expressed between invasive and noninvasive FV-PTCs divided tumors into *RAS* and *BRAF* mutant groups. This is consistent with the well-described finding that *RAS* and *BRAF* mutant thyroid tumors differ in gene expression. That FV-PTCs in this study showed the entire range of molecular alterations identified in classic PTC, and behavior of invasive FV-PTC was similar to that of classic PTC, the utility of the designation "follicular variant" is questioned from a molecular standpoint, particularly in the era of NIFTP.

614 The Flip Side of NIFTP: An Increase in Rates of Unfavorable Histologic Parameters in the Remainder of Papillary Thyroid Carcinomas

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Background: The term noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was recently proposed to replace noninvasive follicular variant of papillary thyroid carcinoma (FVPTC) both to promote more conservative management of these tumors and spare patients the psychological burden of a cancer diagnosis. This reclassification will lower the incidence of papillary thyroid carcinoma (PTC). In addition, it could result in an increase in the rates of unfavorable histologic parameters for PTC overall because NIFTPs had previously accounted for many of the tumors without these features. Our aim was to evaluate the potential impact of the reclassification of NIFTP on the rates of extrathyroidal extension (ETE), lymphovascular invasion (LVI), and lymph node metastases in PTC.

Design: Our database consisted of all PTCs clinically over 1 cm diagnosed on surgical resection between August 2010 and August 2012. The histopathologic characteristics, including PTC subtype, tumor size, presence of ETE and LVI, and surgical margin and lymph node status were all recorded. Tumor slides for cases initially diagnosed as FVPTC were reviewed to identify tumors that would now be classified as NIFTPs.

Results: Our cohort included 348 cases of PTC, of which 94 (27%) would now be classified as NIFTPs. After excluding NIFTPs from the PTC category, there were increased rates of ETE (26% up from 19%, $p = 0.046$), LVI (37% up from 27%, $p = 0.010$), and lymph node metastases (26% up from 19%, $p = 0.045$) among the remaining PTCs.

Conclusions: Our results indicate that the downgrading of a subset of PTCs to NIFTP will increase the rates of ETE, LVI, and lymph node metastases observed in the remainder of PTCs by statistically significant margins. Additional studies are warranted to investigate whether this increase in unfavorable histologic parameters will in turn result in a change in the prognosis for PTC overall as a result of the NIFTP shift.

615 Outcome of Large Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP)

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Background: In 2016, encapsulated papillary thyroid carcinoma, follicular variant without invasion was renamed NIFTP in order to
reduce overtreatment of this indolent tumor. However, many endocrinologists remain uneasy about managing large (≥ 4 cm) NIFTP conservatively without radioactive iodine (RAI) therapy. The objectives of this study are to characterize the clinicopathologic characteristics and outcome of large NIFTP in order to assist therapeutic decision making.

Design: The pathology database of three tertiary hospitals were searched for large (≥ 4 cm) NIFTP. Cases with separate foci of carcinoma were excluded. Seventy four cases fulfilled the inclusion criteria. Among them, 56 (76%) had at least 2 years of clinical follow up (FU), and 49 (66%) had ≥ 4 years of FU. The clinicopathologic characteristics were reviewed and documented by three endocrine pathologists.

Results: The median size of the NIFTP was 4.5 cm (range 4.0 – 8.0). The entire capsule was sampled in 45 (61%) tumors while in the remaining 29 (39%)cases it was submitted representatively with a median of 2.1 blocks per cm of tumor examined. Large NIFTP had a female preponderance with a male:female ratio of 1: 1.8 and presented at a median age of 48 years. There were no lymph node metastases at diagnosis in all patients including all cases (n=23) with nodal tissue available for microscopic examination .Twenty-four (32%) underwent thyroid lobectomy alone, and 32 (43%) did not receive radioactive iodine (RAI) ablation. No recurrence was observed in the entire cohort including all 28 patients with ≥ 2 years of FU who did not receive RAI therapy (median FU: 7.5 years). Among patients with ≥ 4 years of FU, all 25 individuals without RAI therapy did not recur with a median FU of 11.2 years. Patients with larger tumor size tended to receive postoperative RAI ablation ($p =0.001$).

Conclusions: Similar to their small counterparts, large NIFTP appear to have an extremely low risk of recurrence, even when treated conservatively without RAI therapy. Surgical treatment alone appears to be adequate for large NIFTP.

616 Primary Thyroid Carcinoma with Low-Risk Histology and Distant Metastases: Clinico-Pathologic and Molecular Characteristics

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Background: Distant metastases (DM) are a rare occurrence in well differentiated thyroid carcinoma and are the main cause of death. The aim of our study was to analyze the clinical, pathologic, and molecular features of primary thyroid carcinoma with low risk histology that develop DM.

Design: Detailed clinico-pathologic review and targeted next generation sequencing were performed on a cohort of well-differentiated thyroid carcinoma lacking gross extrathyroidal extension, extensive vascular invasion or significant lymph node metastases but exhibiting distant metastases.

Results: Primary well-differentiated thyroid carcinoma with low risk histologic features and DM was a rare occurrence, accounting for only 3% of metastatic non-anaplastic thyroid carcinoma. All 15 cases meeting the inclusion criteria harbored DM at presentation. The majority (11/15, 73%) of these tumors were follicular variant of papillary thyroid carcinoma (FVPTC), especially the encapsulated form (n = 8). The remaining patients harbored encapsulated Hurthle cell carcinoma (n = 2), encapsulated follicular carcinoma (n = 1), and papillary carcinoma classical variant (n = 1). Of the 12 encapsulated carcinomas, 10 (83%) had capsular invasion only and no vascular invasion. Ninety-two percent of the tumors exhibited extensive intra-tumoral fibrosis. Among the 8 tumors that were subjected to next generation sequencing analysis, *RAS* mutation was the main driver (5/8, 62.5%), and *TERT* promoter mutation was highly prevalent (6/8, 75%). In 4 cases, *TERT* promoter mutations were associated with *RAS* or *BRAF* mutations. *BRAF*-mutated classical variant of papillary carcinoma also presented with DM but was less common (12.5%). In 11 (73%) of 15 cases, the clinician was able to diagnose distant disease based on the clinical presentation. In 3 of 4 incidental cases that were genotyped, *TERT* promoter mutations were found.

Conclusions: When distant metastases occur in primary thyroid carcinoma with low risk histology, they are almost always found at presentation. The majority are encapsulated FVPTC with capsular invasion only. *TERT* promoter mutations occur at a higher rate than that seen in PTC in general and may help explain the aggressive behavior of these histologically deceptive primary carcinomas.

617 Both Anterior Pituitary Hormone-Negative and Transcription Factor-Negative Pituitary Adenomas ("True" Null Cell Adenomas)

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Background: Recent reports have showed that immunoreactivity for transcription factors such as pituitary transcription factor 1 (Pit-1), T box factor (Tpit/TBX19), estrogen receptor (ER), and steroidogenic factor 1 (SF-1) are very useful to classify clinically non-functioning pituitary adenomas. Null cell adenomas (NCAs) of the pituitary gland have been defined as having no clinical symptoms associated with altered hormone production, and showing no detectable pituitary hormones and transcription factors on immunohistochemical examination. However, the clinicopathological and histopathological features of NCAs have not yet been clarified enough so far.

Design: We reviewed case series of pituitary adenomas operated on at Toranomon hospital between 2008 and 2011. In all cases, clinical symptoms and laboratory data were evaluated, as well as histology in H&E sections, and immunoreactivity for anterior pituitary hormones. As for the cases showing no excessive secretion in blood nor immunostaining for anterior pituitary hormones, additional examinations were performed using tissue microarray for detecting expressions of transcriptional factors mentioned avobe. Once the diagnosis of NCA was confirmed, the cases were further observed by electron microscopy (EM).

Results: In all 1071 pituitary adenoma cases, only six (0.6%) were found to be immunonegative for all anterior pituitary hormones and transcription factors. Five patients were female. All cases were macroadenomas (> 1 cm in size) and two were giant adenomas (> 4 cm). Histologically, perivascular pattern and pseudorossettes were seen in three cases, and the other three cases showed a diffuse pattern with oncocytic changes. EM examination demonstrated poorly differentiated tumor cells with sparsely scattered intracellular organelles in these six NCAs. Honeycomb Golgi pattern was found on EM in two cases and accumulation of mitochondria was accompanied in four cases.

Conclusions: In our study, NCAs were found to be very rare than previously thought, accounting for only 0.6% of all pituitary adenomas if we are taking into account the results of immunohistochemistry for various transcription factors of anterior pituitary hormones. NCAs could have similar histopathological and ultrastructural features to corticotroph or gonadotroph adenomas.

618 Oncogenic Roles of Multiple Long Non-Coding RNAs in Papillary Thyroid Carcinoma

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Background: Long non-coding RNAs (lncRNAs) participate in transcription and in epigenetic or post-transcriptional regulation of gene expression, and may contribute to carcinogenesis. lncRNAs have been associated with epithelial to mesenchymal transition (EMT), maintenance of stemness, and may play a role as prognostic factors in thyroid cancers. We analyzed the expression of three lncRNAs, HOX transcript antisense intergenic RNA (HOTAIR), PVT1 and Regulator of Reprogramming (ROR) in benign and malignant thyroid tissues to determine their role in thyroid tumor development and progression.

Design: Tissue microarrays (TMAs) were constructed using formalin-fixed paraffin-embedded (FFPE) tissues of normal thyroid (NT, n=10), nodular goiter (NG, n=10), follicular adenoma (FA, n=32), follicular carcinoma (FCA, n=28), papillary thyroid carcinoma (PTC n=28), follicular variant of papillary thyroid carcinoma (FVPTC, n=29), and anaplastic thyroid carcinoma (ATC, n=10). In situ hybridization (ISH) was performed on the TMA using RNAscope® probes for HOTAIR, PVT1 and ROR, and analyzed with Vectra imaging technology, Nuance® and inForm ® software. qRT-PCR was performed on a subset of the TMA cases (n=16).

Results: By ISH, most of the positive signals for all three lncRNAs were localized to the cell nucleus. There was increased expression of all three lncRNAs in well differentiated carcinomas with the highest level of expression in PTCs comparing to NT ($p< 0.05$). ROR and HOTAIR expression is higher in PTCs comparing to NG and FA ($p< 0.05$). PTCs expressed higher levels of PVT1 and ROR compared to FCs ($p <0.05$). In ATCs, expression of HOTAIR and ROR was much lower than in the well differentiated thyroid carcinomas ($p<0.05$). Expression of HOTAIR in ATC was lower than NT ($p<0.05$), while expression of ROR and PVT1 was not different in ATC, NT, FA or NG. qRT-PCR analysis supported the ISH data. Furthermore, qRT-PCR analysis of a PTC cell line induced to undergo EMT by TGFbeta treatment showed a 4- to 5- fold increase in expression of PVT1 and ROR, indicating a role of these lncRNAs in EMT.

Conclusions: HOTAIR, PVT1 and ROR, are up-regulated in well differentiated thyroid carcinomas compared to normal and benign thyroid tumors with the highest levels of expression in PTCs. Surprisingly, the lncRNAs levels in ATCs were lower or not significantly different from NTs or benign thyroid tumors, suggesting that the oncogenic role of lncRNAs in thyroid tumor progression is manifested mainly in the development of well differentiated thyroid cancers.

619 Actionable Genetic Mutations Are Rare in Pituitary Carcinomas and Atypical Pituitary Adenomas

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Background: Pituitary carcinomas are very rare neoplasms defined by the presence of cerebrospinal and/or systemic metastasis. It is sometimes difficult to distinguish carcinomas from atypical adenomas and adenomas by histological features. Many patients die of pituitary carcinomas within two years of diagnosis regardless of treatment modalities. Identification of genetic mutations in pituitary carcinomas and atypical adenomas may help in the diagnosis of these neoplasms and lead to alternative therapeutic approaches.

Design: Two primary pituitary carcinomas, adrenocorticotropin hormone- producing (ACTH) and prolactin- producing (PRL),along with their local recurrences and metastatic foci (liver and vertebrae), two atypical adenomas (ACTH and nonfunctional with local invasion) and three pituitary adenomas(ACTH, PRL and nonfunctional) were analyzed for gene mutations by next generation sequencing (NGS). After DNA extraction, multiplex PCR and clonal amplification of 207 amplicons targeting regions of 50 common actionable genes associated with cancer were performed. NGS of enriched amplification products was performed on the Ion Torrent Personal Genome Machine. Sequences were aligned and analyzed using the Torrent Suite Software relative to reference DNA sequences. Immunohistochemical staining (IHC) for p53 and for Ki-67 was also performed.

Results: One of the two pituitary carcinomas (ACTH) along with its recurrence and the liver metastasis were positive for TP53 mutation (E349 c.1045G.T). The PRL carcinoma, the atypical adenomas and the three adenomas did not have any clinically significant mutations. IHC for p53 was positive in the case with TP53 mutation while all of the other cases were negative. Ki-67 proliferative index was increased for both carcinomas (5% to 30%) compared to the atypical adenomas and adenomas (<5%).

Conclusions: Pituitary carcinomas with proven metastatic disease and atypical pituitary adenomas have relatively few actionable mutations, aside from TP53 mutation which has been previously reported in a subset of pituitary carcinomas/atypical adenomas. Despite low frequency, the presence of actionable mutations in some pituitary carcinomas may lead to targeted therapies for these tumors and assist in the diagnosis.

620 Significance of Ki67 Proliferative Index in Carcinoid Tumors Involving Ovary

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Background: Primary ovarian carcinoid tumors are rare neoplasms that constitute less than 0.1% of all ovarian carcinomas. A majority of primary ovarian carcinoids occur in association with mature cystic teratoma. However, metastatic carcinoid tumors involving ovary are relatively common. Although cell proliferative rate is an important factor in the determination of neuroendocrine tumor prognosis, limited data is available regards Ki67 proliferation index in predicting the physiological features of carcinoid tumors involving ovary.

Design: Pathology files of Mayo Clinic Rochester (1995-2014) were searched for ovarian carcinoid /well-differentiated neuroendocrine tumor (NET). The diagnoses were confirmed by reviewing Hematoxylin-and-eosin slides and appropriate IHC stains if available. Clinical characteristics were collected from medical records. All cases were stained with antibody against Ki67 (Mouse anti-human Clone MIB-1, DAKO) and the slides were scanned using the Aperio ScanScope AT Turbo Instrument (Leica Biosystems). Digital analysis was performed with Aperio® ePathology Solutions software (Leica Biosystems) by a cytotechnologist trained in digital image analysis.

Results: A total of 36 cases (median age 68, range 33-83), including 9 ovarian primary (median age 68, range33-73) and 27 metastatic carcinoid cases (median age 64, range 36-83), were investigated in the current study. Eight of 9 (89%) ovarian primary carcinoids are associated with mature teratoma. Twenty two metastatic carcinoid (81.5%) were from gastrointestinal origin, 4 (14.8%) from pancreatic origin and 1 (3.7%) from posterior thorax location. There was significant difference of Ki67 expression between primary

(mean 3.6%, range 0.6 – 8.4%) and metastatic carcinoid tumor (mean 11.5%, range 1.3 – 46.7%) (p=0.0019). The survival time was much shorter in patients with metastatic carcinoid tumor (median survival 5.8 years) comparing to those with primary ovarian carcinoid tumor (median 14.2 years) (p=0.0005). A strong association between Ki67 index and patient survival time was identified (Hazard ratio 1.11, p=0.001).
Conclusions: Comparing to primary ovarian carcinoid tumor, metastatic carcinoid tumor usually exhibits a higher Ki67 index and a worse outcome. Ki67 index is significantly associated with the survival time in patients with carcinoid tumor involving ovary.

Gastrointestinal Pathology

621 Tubulovillous Adenomas with Serrated Features Are Precursors to KRAS Mutant Colorectal Carcinoma

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Background: Conventional adenomas and serrated polyps represent precursor lesions to two separate pathways of colorectal carcinoma. Occasionally, tubulovillous adenomas (TVA) show focal features resembling traditional serrated adenomas, including ectopic crypt foci, luminal serration, and cytoplasmic eosinophilia. The biologic significance and molecular findings associated with this histologic variant of TVA are largely unknown. The goal of this study was to investigate the frequency of KRAS and BRAF mutations in TVA with serrated features (sTVA) in comparison to a control group of TVA.
Design: 27 consecutive sTVA and a control group of 27 TVA matched for highest degree of concurrent dysplasia/carcinoma were evaluated. Specimens were analyzed for mutations in KRAS codon 12/13 and BRAF codon V600E; other variants in KRAS and BRAF were not evaluated in this study. Somatic variants in KRAS and BRAF were identified by dideoxy sequencing (assay limit of detection 15%).
Results: The mean age of the sTVA group was 68.9 (M:F 1.5:1) and mean age for the TVA group was 63.0 (M:F 1:1.1). All 27 TVA were wild type for BRAF mutation. One sTVA (3.7%) was positive for the BRAF V600E mutation. KRAS analysis was completed on 22 TVA and 24 sTVA. sTVA were significantly more likely to harbor KRAS mutations (66.7% vs. 18.2%, p=0.001). A summary of the KRAS mutations is shown in Table 1. When cases in which KRAS testing was not completed were excluded, there was still no significant difference in the distribution for the highest grade of concurrent neoplasia in the sTVA and TVA groups (p=0.67).

Table 1: Summary of KRAS mutations in TVA and sTVA

KRAS 12/13 Genotype	TVA	sTVA
G12D	0 (0%)	4 (16.7%)
G12R	1 (4.5%)	0 (0%)
G12S	0 (0%)	1 (4%)
G12V	1 (4.5%)	5 (21%)
G13C	1 (4.5%)	1 (4%)
G13D	1 (4.5%)	5 (21%)
WT	18 (82%)	8 (33.3%)
Total:	22	24

Legend: TVA=tubulovillous adenoma; sTVA=TVA with serrated features; WT=wild type

Conclusions: We confirm results of few prior studies showing more frequent KRAS mutation in sTVA versus TVA. However, we addressed the shortcoming of prior studies by controlling for degree of associated dysplasia/carcinoma in our design. KRAS mutation is a molecular correlate of the mixed histology of sTVA and may explain the literature's tenuous data suggesting a higher risk of advanced outcomes in these polyps.

622 Age Less Than Forty Is Predictive of Mismatch Protein Loss in Colorectal Tubulovillous Adenomas

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Background: Lynch Syndrome (LS) is a genetic syndrome driven by germline mutations in mismatch repair (MMR) protein complexes which result in an increased risk of numerous neoplasms. Mutations are most frequently encountered in the *MLH1*, *MSH2*, *MSH6*, or *PMS2* genes. Immunohistochemical (IHC) testing using antibodies against the MMR proteins has been well documented for LS screening in CRC specimens; however, few studies have examined the use of MMR IHC screening in the general population before the development of frank malignancy. Here we aim to explore the possibility of LS screening in patients <50 years old who have adenomas with villous features.
Design: Our surgical pathology archives were searched for cases of colorectal adenomas with villous features from 1/1/1997-5/31/2016 in patients < 50 years old. Patients with a known history of CRC, LS, or familial adenomatous polyposis were excluded. Slides were reviewed and those that did not meet strict criteria for villous morphology were excluded. Sixty-nine cases were identified in patients < 45 years old and were compared to a cohort of 27 cases of patients 45-50 years old recieved between 1/1/2013 and 7/31/2015. All 96 cases underwent IHC testing with antibodies against MSH6 and PMS2. Cases with abnormal staining for either of these proteins underwent additional IHC testing with antibodies for MLH1 and MSH2. Abnormal staining was defined as less than 10% of adenomatous cells exhibiting positive nuclear staining.
Results: Abnormal MMR IHC staining was identified in four out of 31 cases (13%) in patients less than 40 years old and in one out of 38 cases (3%) in those 40-45 years old. None of the 27 cases from those 45-50 years demonstrated loss in MMR staining. Of the five cases that showed MMR abnormalities, two showed isolated loss of MSH6, one showed isolated loss of PMS2, one showed loss of MSH2 and MSH6, and one showed loss of MLH1 and PMS2. The difference in the MMR loss rate by IHC between the three groups approaches statistically significant (p= 0.065).
Conclusions: MMR IHC testing of CRCs has been well described; however, testing of adenomas has only been described previously in limited fashion and when done has been enriched for patients with LS. Here we identified a propensity for polyps with villous features from younger patients to display MMR IHC abnormalities. These results suggest that MMR IHC testing of adenomas with villous features in patients less than 40 years old may assist with the identification of LS.

623 Clincopathologic Studies of PD-L1 Expression on Esophageal Adenocarcinoma and Squamous Cells Carcinoma

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Background: Programmed death ligand 1 (PD-L1) is a ligand for the inhibitory programmed death receptor 1 (PD-1). Induction of PD-L1 expression on tumor cells leads to the inhibition of immune responses against cancer. Therefore, blockage of PD-1 or PD-L1 can activate the anti-tumor activity. Our study investigated the PD-L1 immunohistochemistry in both esophageal adenocarcinoma (EAC) and squamous cell carcinoma (ESCC).
Design: TMA of 101 EAC and 27 ESCC were immunohistochemically stained for PD-L1. Expression of PD-L1 was scored for positive, negative and percentage (0-100%) for positive cells. The data were analyzed byPearson Correlation.
Results: Of 101 AC cases, 12 (12%) were positive for PD-L1 immunostain. Of 27 SCC cases, 6 (22%) were positive for PD-L1 immunostain. The PD-L1 expression in EAC were significantly correlated with female, but not correlated with other clinicopathologic features including age, differentiation, lymph nodes, survival and staging. The mean and median of the percentage of PD-L1 positive tumor cells is 43% and 35% in EAC and is 21% and 15% in ESCC. The PD-L1 expression is not significantly associated with proliferation index Ki67, MCM4 and MCM7.
Conclusions: PDL-1 expression is relative low in EAC (12%) and ESCC (22%). PD-L1 expression is significantly associated with female.

624 Prevalence of Immunohistochemically Demonstrable Helicobacter Pylori in Biopsies without Histologic Evidence of Gastritis

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Background: Helicobacter pylori is a major cause of gastritis, with virtually all infected patients demonstrating moderate to severe acute and/or chronic inflammation. In fact, the presence of the bacteria in otherwise normal gastric biopsies is believed to be rare. Since we perform reflexive immunohistochemistry (IHC) on all gastric biopsies with a requisition request to rule out H. pylori, we decided to study the prevalence of immunohistochemically demonstrable H. pylori in the absence of inflammation (HPy+/Inf-).
Design: We reviewed gastric biopsies with reflexive H. pylori IHC performed in our institution between 2007 and 2015. HPy+/Inf- biopsies were selected on the basis of the presence of antral mucosa, undetectable or minimal nonspecific inflammation and a positive IHC result. All IHCs were performed in the same laboratory under the same protocol.
Results: A total of 15,460 gastric biopsies with IHC for H. pylori were evaluated and six HPy+/Inf- cases were initially identified. Of these, two were later demonstrated to represent H. heilmannii by IHC (2/6 = 33%), making the prevalence of true HPy+/Inf- cases 0.0003% (3/10,000 biopsies). All HPy+/Inf- cases were women, with a median age of 31 yrs (range 4-66 yrs). Of these, one had a history of previously treated H. pylori gastritis 4 years prior to the current biopsy. The youngest patient had type 2 Gm1 gangliosidosis with functional immunosuppression, and the remainder two patients did not have significant comorbidities.
Conclusions: The prevalence of H. pylori in the absence of inflammation is extremely low (0.0003%), making inflammation a good surrogate for the presence of the bacteria, and an effective trigger for IHC studies when the organism is not readily identifiable on H&E slides. Reflexive IHC upon a request to rule out H. pylori may be justified in some institutions for other reasons, such as improved turnaround time. Additionally, IHC might also be considered in biopsies without significant inflammation when there is a history of treated H. pylori gastritis or immunosuppression. Also, in our experience, 33% of HPy+/Inf- cases actually represented H. heilmannii infection, thus justifying the immunohistochemical confirmation of this organism in the context of a suggestive bacterial morphology. Our data suggest that neither H. pylori "colonization" nor Hpy+/Inf- purely as a result of the vagaries of random sampling ("sampling error") occur.

625 Molecular Lymph Node Staging in Rectal Carcinomas: Can It Be Performed?

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Background: Pathologic hematoxylin and eosin (H&E) lymph node (LN) staging in colorectal carcinomas (CRC) may not provide robust prognostic data, as up to 20% of stage II CRC patients recur from disease within 5 years of intended curative surgery. Recent studies have addressed that molecular staging in colon carcinomas using CK19 mRNA can correlate with classical high risk factors, and there is increasing evidence that it can be used on a daily basis. Nevertheless, there is lack of data regarding the use of this technique in rectal carcinomas.