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615 Interobserver Agreement and Reliability In Oncocytic Adrenocortical Tumors. A Comparison of Multiple Scores

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Background: The oncocytic variant is a rare subtype of adrenocortical tumors; its intrinsic histological features make the diagnosis of malignancy easily overestimated even using different classification systems.

Design: We collected 29 consecutive adult patients with primary oncocytic adrenocortical tumors who underwent surgery in our institution from 2007 to 2017. We reviewed 22 of 27 cases assessing Weiss score (WS), Weiss revisited score by Aubert (WR), Linn-Weiss-Bisceglia score (LWB), Helsinki score (HS) and the "reticulin" algorithm (RA).

The aim of the study was to measure the interobserver agreement and reliability among five pathologists.

Results: Concordance among pathologists (two residents and two general vs. one dedicated endocrine pathologists) was fair (κ=0.37, p<0.0001) regarding WS, moderate (κ=0.57, p<0.0001) regarding WR, almost perfect (κ=0.84, p<0.0001) regarding LWB and substantial regarding HS (κ=0.77, p<0.0001). Particularly, WS overestimated three cases, which were downgraded as "borderline lesions" with LWB, and revealed poor interobserver reliability for two parameters: high nuclear grade (r_i=0.36) and invasion of sinusoidal structures (r_i=0.47). According to WS, malignant cases were 45.5% (10/22) versus 31.8% (7/22) malignant neoplasms according to LWB, also confirmed by other scores (WR and HS). Interestingly, LWB-WR-HS malignant cases showed an average of Ki67 index of 10.2 and 28.6% (2/7) developed distant metastasis. However, LWB upgraded 26.6% (4/15) lesions as "uncertain malignant potential" as a result of poor reproducible parameters, in particular the invasion of sinusoidal structures. Evaluation of RA resulted helpful and reproducible in case of extensive loss (κ=0.96, p<0.0001); but it showed poor interobserver reliability (r_i=0.32), due to the ambiguous difference between normal and irregularly thickened fiber distribution.

Conclusions: LWB resulted accurate and reproducible to define malignant oncocytic adrenocortical tumors, followed by HS and WR. Nevertheless, "uncertain malignant potential" diagnosis still remains poorly reproducible and suggest a revision of minor criteria of LWB score.

616 Utility of Overnight STAT Processing of Thyroid Lobectomy in Triaging Indeterminate Fine Needle Aspiration Diagnoses: An Institutional Experience

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Background: In our institution, many thyroid resection specimens with indeterminate preoperative fine needle aspiration (FNA) diagnoses are triaged by overnight "STAT" processing with the final diagnosis provided the next morning by 10:00 am. The patients (pts) are kept in the hospital NPO overnight until the pathologist communicates the results to the surgeon. Completion thyroidectomy can be performed the day after surgery if needed or the pts are discharged home between one to two days after surgery if no completion thyroidectomy is indicated. In this study, we evaluated the utility of this approach in treating patients with indeterminate thyroid nodules.

Design: Institutional databases were queried for all thyroid surgeries for which the pathology diagnosis was requested "STAT" (January 2012-July 2017) and the pt had prior FNA sampling performed.

Results: Thirty-nine pts (29 females and 10 males) were included in this study. FNA results were classified according to the Bethesda System for Reporting Thyroid Cytopathology. The initial procedures performed were: lobectomy (n= 20), lobectomy and isthmusectomy (n= 18), and total thyroidectomy (n=1). Surgical pathology (SP) revealed malignancy in 25 cases; follicular carcinoma (n=2) and papillary carcinoma (n=23, with 8 pts only showing incidental papillary microcarcinoma). Eleven cases showed either non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) or well differentiated tumor of undetermined malignant potential. Correlation between the FNA and SP diagnoses is presented in Table 1.

Clinically significant malignant diagnoses resulted in completion thyroidectomy with or without neck lymph node dissection in 9 cases. The specimen demonstrated malignancy (papillary microcarcinoma) in 4 out of 9 patients with one case showing lymph node metastasis. The total time of hospital admission ranged from 9 to 96 hours.

Table 1. Correlation between FNA and surgical pathology diagnoses

FNA- Bethesda category	Cases (n=39)	Surgical Pathology Diagnosis		
		Benign	Intermediate *	Malignant
III	16	5	3	8
IV	21	2	6	13
V	2	0	0	2

* Intermediate (NIFTP, well differentiated tumor of uncertain malignant potential)

Conclusions: STAT review of thyroid resection specimens in patients with indeterminate FNA are useful for multiple reasons. They are cost effective due to a reduction of readmission rates for completion thyroidectomy. They also allow for rapid turn around time with actionable results without the common pitfalls due to artifact associated with frozen section evaluation.

617 Immunohistochemical expression of BRAF V600E is correlated with both PD-L1 and PD-1 expression in papillary thyroid carcinoma without a background of chronic lymphocytic thyroiditis

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Background: Immune checkpoint inhibitor therapies targeting PD-L1/PD-1 has shown efficacy in several types of human cancers. In papillary thyroid carcinoma (PTC), the tumor microenvironment concerning PD-L1/PD-1 is little known, and its correlation with BRAF V600E mutation is by far unknown.

Design: We examined the immunohistochemical status of PD-L1, PD-1, and BRAF V600E in PTC and detected their clinical significance together with the tumor microenvironment. Immunohistochemical analysis of PD-L1, PD-1, and BRAF V600E was performed on 110 cases of PTC with the diameter > 1cm and without harboring a background of chronic lymphocytic thyroiditis.

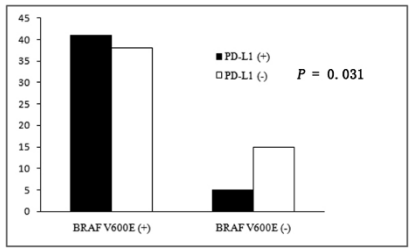
Results: Expression of PD-L1 was significantly correlated with an absence of psammoma bodies, and expression of PD-1 was significantly correlated with smaller tumor size and an absence of stromal calcification. There was a significant correlation between BRAF V600E and either of PD-L1 or of PD-1 expression. Tumor microenvironments were classified based on the PD-L1 and PD-1 expression, as type 1, PD-L1+/PD-1+, 40.9%; type 2, PD-L1-/PD-1-, 17.3%; type 3, PD-L1+/PD-1-,4.5%; and type 4, PD-L1-/PD-1+, 37.3%. BRAF V600E expression, the presence of psammoma body and the stromal calcification were statistically different among the four groups.

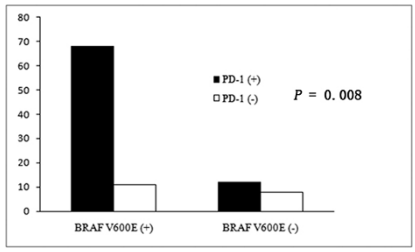
Table 1 The correlation between the PD-L1 expression and other clinicopathologic parameters

	PD-L1		P-value
	+ (46.4%)	- (53.6%)	
Age			
< 45 years	25	33	0.469
≥ 45 years	26	26	
Gender			
Female	41	38	0.063
Male	10	21	
Tumor size			
≤ 2 cm	36	36	0.199
> 2 and ≤ 4 cm	11	21	
> 4 cm	4	2	
Extrathyroid invasion			
-	6	14	0.105
+	45	45	
pT			
1b	5	12	0.345
2	2	2	
3	44	44	
4a	0	1	
pN			
0	18	21	0.536
1a	20	18	
1b	13	20	
Stage grouping			
I	3	10	0.271
II	1	1	
III	35	32	
IVA	12	16	
Psamomma body			
-	33	23	0.007
+	18	36	
Stromal calcification			
-	26	27	0.585
+	25	32	
Bone formation			
-	50	57	0.646
+	1	2	
Multifocality			
Unifocal	35	40	0.926
Multifocal	16	19	

able 2 The correlation between the PD-1 expression and other clinicopathological parameters

	PD-1		P-value
	+ (78.2%)	- (21.8%)	
Age			
< 45 years	44	14	0.534
≥ 45 years	42	10	
Gender			
Female	61	18	0.695
Male	25	6	
Tumor size			
≤ 2 cm	59	13	0.022
> 2 and ≤ 4 cm	25	7	
> 4 cm	2	4	
Extrathyroid invasion			
-	16	4	0.828
+	70	20	
pT			
1b	13	4	0.193
2	4	0	
3	69	19	
4a	0	1	
pN			
0	31	8	0.647
1a	31	7	
1b	24	9	
Stage grouping			
I	9	4	0.668
II	2	0	
III	54	13	
IVA	21	7	
Psamomma body			
-	43	13	0.718
+	43	11	
Stromal calcification			
-	47	6	0.010
+	39	18	
Bone formation			
-	84	23	0.624
+	2	1	
Multifocality			
Unifocal	59	16	0.857
Multifocal	27	8	





Conclusions: Since BRAF V600E mutation was reported to be associated with the loss of radioiodine avidity and with radioiodine treatment failure in PTC, the positive correlation between BRAF V600E and PD-L1/PD-1 expression indicates an opportunity of immunotherapy targeting PD-L1/PD-1 for a subset of PTC patients refractory to radioiodine therapy.

618 Papillary Thyroid Carcinoma (PTC) Emerging from Hashimoto Thyroiditis Demonstrates Increased PDL1 Expression, Which Persists with Metastasis

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Background: The PD1-PDL1 axis is critical for extinguishing auto-reactive T cells, but can be manipulated by neoplastic cells to evade immune destruction. Blockade of this pathway enhances anti-tumor immunity and has emerged as a key advance in treatment of several cancers, including melanoma and lung cancer. Preliminary evidence suggests that PDL1 expression is associated with a more aggressive course in PTC. Studies have also found that thyroiditis is associated with increased PDL1 expression by benign follicular epithelial cells. At the same time, therapeutic blockade of the PD1-PDL1 pathway has been associated with endocrine dysfunction, including hypothyroidism. With this in mind, we sought to determine whether PTC arising in a background of thyroiditis might express increased PDL1 compared to PTC arising within unremarkable thyroid.

Design: We performed IHC for PDL1 (E1J2J, Cell Signaling) on 10 cases of PTC arising in normal thyroid as well as 10 cases of PTC arising in Hashimoto thyroiditis. We also evaluated corresponding synchronous lymph node metastases for PDL1 expression. IHC was scored from 0-4+ based on the percentage of epithelial cells demonstrating membranous staining (<1%, 1-10%, 10-25%, 25-50%, >50%) in background thyroid, primary tumor, or metastatic PTC.

Results: PTC arising in normal thyroid nearly uniformly lacked PDL1 expression (average score 0.1 ± 0.1), which was also observed of corresponding lymph node metastases (average score 0.1 ± 0.1). Background normal thyroid did not express PDL1 (average score 0.0). In contrast, PTC arising in a background of Hashimoto thyroiditis demonstrated significant PDL1 expression (average score 1.5 ± 0.4), which persisted in metastases (average score 1.6 ± 0.5). Background benign thyroiditic follicular epithelium also demonstrated PDL1 expression (average score 1.0 ± 0.3).

Case	Background Thyroid	Diagnosis	PDL1 Primary Tumor	PDL1 Background Thyroid	PDL1 Metastatic PTC
1	HT	PTC classic	0	0	0
2	HT	PTC tall cell and Warthin-like	1	0	4
3	HT	PTC tall cell and Warthin-like	4	2	3
4	HT	PTC classic and Warthrin-like	1	1	1
5	HT	PTC classic	1	1	1
6	HT	PTC classic, Warthrin-like, tall cell	2	1	3
7	HT	PTC tell cell	1	1	1
8	HT	PTC classic	1	0	0
9	HT	PTC classic	1	0	1
10	HT	PTC classic and Warthin-like	3	3	NA
11	Normal	PTC classic and tall cell (10-20%)	0	0	0
12	Normal	PTC classic and tall cell (<5%)	0	0	0
13	Normal	PTC classic	0	0	0
14	Normal	PTC classic	0	0	0
15	Normal	PTC classic and tall cell (40%)	0	0	0
16	Normal	PTC classic and tall cell (20%)	1	0	1
17	Normal	PTC classic	0	0	0
18	Normal	PTC classic and tall cell (5-10%)	0	0	0
19	Normal	PTC classic	0	0	0
20	Normal	PTC classic	0	0	NA

HT = Hashimoto Thyroiditis, NA = Not Available

Conclusions: Hashimoto thyroiditis is the most common cause of hypothyroidism and has been associated with increased risk of PTC. By examining PDL1 expression in PTC arising in normal thyroid compared to Hashimoto thyroiditis, as well as in primary versus metastatic PTC, we demonstrate increased PDL1 expression in PTC arising in a background of Hashimoto thyroiditis. We speculate that the underlying pathology of the background thyroid influences the expression of PDL1 in PTC. We believe this to be a unique demonstration of an epigenetic event influenced by tumor-stromal interactions that may impact biological behavior and/or responsiveness to therapy in PTC.

619 Expression of Long Non-coding RNAs MALAT1 and HOTAIR in Gastroenteropancreatic NeuroendocrineNeoplasms

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Background: Long non-coding RNAs (lncRNAs) are well-recognized post-transcriptional regulators of gene expression. Recent studies have found multiple aberrantly expressed lncRNAs in adenocarcinomas of the digestive system. MALAT1 and HOTAIR are two lncRNAs that are overexpressed and are associated with adverse outcome in colorectal and pancreatic adenocarcinomas; however, their expression remains unexplored in neuroendocrine neoplasm development in these locations. In view of this, we examined the expression of MALAT1 and HOTAIR in gastroenteropancreatic neuroendocrine neoplasms.

Design: A tissue microarray was constructed with formalin-fixed paraffin-embedded specimens of 78 normal tissue (2 esophageal, 4 gastric, 28 small intestinal, 2 appendiceal, 1 rectal mucosa and 41 pancreatic parenchyma), 88 primary neuroendocrine neoplasms (1 esophageal, 3 gastric, 45 pancreatic, 27 small intestinal, 1 ileocecal, 9 appendiceal, 2 rectal) of various grades (63 grade 1, 18 grade 2, 7 grade 3) and 19 metastatic tumors from a total of 87 patients. In situ hybridization with RNAScope (Advanced Cell Diagnostics, Newark CA) probes for MALAT1 and HOTAIR was performed and graded by intensity of staining (0 to 3+) and percentage of cells staining positively.

Results: Strong (3+) expression of HOTAIR was seen in 38 (84%) pancreatic and 16 (37%) of gastrointestinal (1 esophageal, 3 gastric, 6 small intestinal, 4 appendiceal and 2 rectal) primary tumors, as well as >90% of normal tissue from each site. Strong (3+) expression of MALAT1 was seen in 19 (42%) pancreatic and 16 (37%) of gastrointestinal (1 esophageal, 2 gastric, 5 small intestinal, 6 appendiceal and 2 rectal) primary tumors, as well as in all normal tissue from all sites. Neither HOTAIR nor MALAT1 expression was significantly associated with tumor grade, size or metastasis.

Conclusions: This is the first report of HOTAIR and MALAT1 expression in neuroendocrine neoplasms in the digestive system. HOTAIR, but not MALAT1, is more strongly expressed in pancreatic tumors compared to gastrointestinal tumors. This may be of diagnostic utility in spite of the lack of prognostic significance of either marker in this cohort.

620 Clinicopathologic Features of Metastatic Follicular Thyroid Carcinoma Presenting with Thyroid Nodule vs Distant Metastasis

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Background: Follicular thyroid carcinomas (FTCs) metastasize hematogeneously in 10-15% of cases. Some patients present with distant metastasis (DM); others with a primary thyroid mass (PT). Features of FTCs presenting with DM have not been comprehensively described. We compare clinical & pathologic features of FTCs in patients who present with DM versus PT.

Design: 35 patients with FTC & visceral metastases were identified. H&E slides from 17 thyroidectomies were available. Clinical & histologic features were recorded from clinic notes, pathology reports, or H&E review when available. Next Generation Sequencing for 147 cancer-associated genes was performed on available carcinomas.

Results: 14/34 (41%) presented with DM; thyroidectomies from 11 were reviewed. Tumor size ranged from 0.4-6 cm (mean 2.5 cm). 6 had solid growth; 4 had ≥3 mitoses/10 hpf. 2 had necrosis. 2 had neither capsular (CI) nor vascular (VI) invasion; both had extensive intralesional fibrosis. 5 had CI but no VI; 3 had intralesional fibrosis. 4 had CI & VI. Presenting metastatic locations were bone in 11 (79%), lung in 2 (14%), adrenal/lung in 1. 4 paired primary & metastatic tumors were sequenced: *NRAS* mutation was found in 3 (1 p.Q61K, 2 p.Q61R, 1 also with *TERT* c.-124C>T). 1 had no pathogenic changes. 3 metastatic tumors were sequenced: 1 *HRAS* p.Q61R, 1 *HRAS* p.Q61K + *TERT* c.-124C>T, 1 *NRAS* p.Q61K + *TERT* c.-124C>T).

20/34 (59%) presented with PT; thyroidectomies from 2 were reviewed; histologic features were gathered from pathology reports in 3. Tumor size ranged from 2-10 cm (mean 4.4 cm). Solid growth was present in 2. Mitoses ranged from 3-7/10 hpf. Necrosis was present in 1. All had invasion & lacked intralesional fibrosis: 2 had CI but no VI; 3 had CI & VI. Initial metastatic locations were lung in 11 (55%), bone in 8 (40%), lung/liver/bone in 1. 1 paired primary & metastatic, 1 primary, & 1 metastatic tumor were sequenced showing, respectively: *TERT* c.-124C>T + *PTEN* p.R130Q, *NRAS* p.Q61K, *PTEN* p.E299*.

Conclusions: Clinical & pathologic features of patients with metastatic FTC who present with DM versus PT are different: mean tumor size was larger in PT (p=.05); initial bony metastases predominated in DM (p=.02) versus lung in PT (p=.02). Primary tumors in 7/11 DM patients had no invasion or CI only; 5 showed extensive obliterative fibrosis. We hypothesize that noninvasive or minimally-invasive tumors with such features may represent histologic regression. High rates of *TERT* promoter mutation were found (40% of tested tumors).

621 Spectrum of Non-BRAF Non-RAS Mutations in Papillary Thyroid Carcinoma in 418 Consecutive Thyroidectomy Cases

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Background: BRAF and RAS mutations are the main driver mutations in papillary thyroid carcinoma (PTC). However, both mutations are known to occur in benign neoplasms, suggesting these mutations might be insufficient for full malignant transformation, and a "second hit" may be needed. This "second hit" may be epigenetic in nature or, in a subset of cases, be provided by a second mutation. The purpose of this study was to evaluate the frequency and spectrum of non-BRAF/non-RAS (NBNR) mutations in a large cohort of resected PTC.

Design: 418 consecutive cases of resected PTC were subjected to Next Generation Sequencing using Ion Ampliseq Cancer Panel Hotspot v2, analyzing 207 amplicons covering mutations in 50 genes. Cases with NBNR mutations were identified and correlated to other clinicopathological parameters, including BRAF/RAS mutation status, age, sex, histology, multifocality, and TNM stages.

Results: The 418 PTC cases included 292 classical type (CPTC), 102 follicular variant (FVPTC), 5 tall cell variants and 19 other variants. 261 cases--239 (82%) of CPTC, 13 (13%) of FVPTC and 9 (38%) of other variants--had BRAF mutations. 54 cases-45 (44%) of FVPTC and 9 (3%) of CPTC and other variants--had RAS mutations. 103 cases had no BRAF or RAS mutations. 56 of 418 (13%) cases harbored 66 NBNR mutations. Among these, 27 cases had coexisting BRAF mutations, 10 had RAS mutations, and 19 had no BRAF/RAS mutations. The mutated genes included APC (12 cases), ATM (12), MET (9), JAK3 (7). FGFR3 (5), PIK3CA (3), PTEN (3), TP53 (5), MLH1 (2), EGFR (2), CDKN2A (3), KIT (1), AKT1

(1), and ERBB2 (1). None of the APC mutations were associated with familial adenomatous polyposis or cribriform-morular histology. KIT, and ERBB2 were only seen in tumors without BRAF/RAS mutations, suggesting them as potential driver mutations. AKT1, KIT, and MLH1 mutations were seen only in CPTC, while PTEN mutations, as previously shown, were found only in FVPTC. No significant correlations were seen between the presence of NBNR mutations and age, sex, histology, multifocality or T stage, but a marginally significant correlation was seen with higher N stage (p=0.049).

Conclusions: Universal mutational analysis of 418 PTC cases identified 14 NBNR mutations in 13% of PTC, including several not previously associated with PTC. Further analysis of these cases at the "tail" end of the PTC mutational frequency curve could identify potential driver mutations--e.g. KIT and ERBB2--and help shed light on the carcinogenesis of PTC.

622 Analysis of Histologic and Cytological Features of the Newly Classified Noninvasive Follicular Thyroid Neoplasm with Papillary-like Features (NIFTP), an Institutional Experience

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Background: Noninvasive follicular thyroid neoplasm with papillary-like features (NIFTP) is a newly proposed diagnostic entity of thyroid tumor, which has good prognosis and indolent clinical course. We reviewed the cases of thyroid tumor treated in our institution from 2004 to 2017, and compared the histologic and cytological features of NIFTP with other entities.

Design: The criteria proposed by the Endocrine Pathology Society (EPS) working group in 2016 are used to reclassify NIFTP from thyroid tumor previously diagnosed in our institution. The nuclear features of tumor cells from each group of NIFTP, FVPTC and classical PTC are analyzed by using the 3-point scoring scheme proposed by EPS with modification (see Table). The corresponding thyroid fine needle aspirates (FNA) results are also analyzed.

Results: A total 345 cases of papillary thyroid carcinoma (PTC) from 2004 to 2017 in our institution are reviewed, including 157 cases originally diagnosed as classical PTC and 182 cases as follicular variant PTC (FVPTC). 42 cases are reclassified as NIFTP, representing 22.3% of the previously diagnosed FVPTC, or 12.2% of all PTC. NIFTP occurs predominately in female patients with F:M~5:1. The average age is 52.3 years old and the average tumor size is 2.1 cm. The average nuclear score of NIFTP is 2.1, compared with 2.55 in FVPTC and 2.95 in classical PTC. As an indication for the difficulty of diagnosis, about 36% of NIFTP cases were sent for expert consultation when they were originally diagnosed as FVPTC, while only 8% other FVPTC and 4% classical PTC were sent for consultation. 84 cases of corresponding thyroid FNA were also reviewed. None of the NIFTP was diagnosed as "malignant/suspicious" by FNA, while 21% FVPTC and 38% classical

PTC were diagnosed as "malignant/suspicious".

Total cases = 345		NIFTP	FVPTC	Classic PTC
Total case numbers		42	146	157
Sex: F/M		35/7	117/29	114/43
Average Age (years)		52.3	50.2	47.3
Nuclear feature score*		2.1	2.55	2.95
Tumor size		2.1 cm	1.75 cm	1.8 cm
Expert consult cases#		15 (36%)	26 (8%)	6 (4%)
FNA	Case numbers	9	33	42
	Undiagnostic	1 (11%)	0 (0%)	8 (19%)
	Benign	5 (56%)	13 (39%)	4 (10%)
	Atypical	1 (11%)	7 (21%)	2 (5%)
	Follicular neoplasm	2 (22%)	6 (18%)	12 (29%)
	Malignant/suspicious	0 (0%)	7 (21%)	16 (38%)

*The nuclear score is using the 3-point scoring scheme proposed by the Endocrine Pathology Society working group in 2016, based on 3 categories: size and shape, nuclear membrane irregularities and chromtin characteristics; each category has 1 point, but only 0.5 point if features are very weak or focal.

Conclusions: Classical PTC has the most typical nuclear features of papillary carcinoma, but these features are less obvious in NIFTP, as shown by the lower nuclear score in NIFTP, and the higher percentage of NIFTP cases sent for expert consultation. The newly proposed NIFTP entity may not only avoid overdiagnosis of thyroid cancer, but also may potentially make it less challenging for pathologists in the diagnosis of thyroid tumor. Thyroid FNA appears not to be a sensitive method in the diagnosis of NIFTP.

623 Extra-adrenal plexiform infiltration in mature ganglioneuromas are predictive of gonadal type seroidogenesis and interstitial Leydig cells

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Background: Mature adrenal ganglioneuromas (MAGNs) are benign neoplasms of the combined neural crest, schwannian, and connective tissue origin, rarely occurring in the adrenal glands. This study presents the phenotypic and hormonal spectrum of these pre-operatively challenging neoplasms.

Design: Demographic, diagnostic, surgical, and pathologic findings of patients who were adrenalectomized as a result of MAGN were retrospectively reviewed from the database of a tertiary referral hospital. Clinical data, as well as follow-up data, were collected retrospectively. All the patients received operative resection.

Results: A total of 36 MAGN (24 males, 12 females) were retrieved. Mean age was 39.6 years (range 25–72). Thirty (83.3%) were asymptomatic, four (11.1%) complained of abdominal discomfort, and two (5.6%) had abdominal distension. Mean size of the tumors was 7.23 cm (range, 2.5-15 cm, twenty-four were larger than 5 cm). There was no recurrence, during a mean follow-up of 6.5 years (range, 1-10 years). A whorled appearance corresponding to interlacing bundles of Schwann cells and collagen fibers on histologic specimens was visualized in twelve tumors on T1- and T2-weighted images. Tumors with markedly high signal intensity on T2-weighted images consisted histologically of a significant amount of myxoid stroma and relatively few cellular and fibrous components. Tumors with intermediate to high signal intensity consisted of numerous cellular and fibrous components and little myxoid stroma.

The extra-adrenal extension was seen in 9 (6 males, three females) with a multifocal perivascular plexiform appearance and dystrophic calcification. These neoplasms were associated with gonadal type urinary steroid profile in women and interstitial Leydig cells.

Conclusions: Pre-operative diagnosis of MAGNs remains difficult, in particular, those neoplasms with extra-adrenal extension. The presence in extra-adrenal neoplasms of dystrophic calcification, lobulated plexiform appearances, and gonadal type steroid in young females suggest the presence of Leydig cells, which is usually overlooked in males. A complete resection should be recommended once malignancy cannot be entirely excluded by pre-operative analyses.

624 NKX2-1 Amplification is Associated with Aggressive Features in a Subset of Differentiated Thyroid Carcinomas of Follicular Cell Origi

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Background: *NKX2-1* is located at the 14q13.3 region in the human genome and encodes thyroid transcription factor TTF-1, a master regulator of thyroid and lung epithelial development**.** Whereas *NKX2-1* amplification is found in about 10% of lung adenocarcinomas with evidence for lineage-specific oncogenic role, copy number changes in *NKX2-1* have not been studied in a broad histologic spectrum of thyroid carcinomas.

Design: Between January 2014 and September 2017, 349 thyroid carcinomas underwent clinical hybridization exon-capture next-generation sequencing mutational profiling by MSK-IMPACT™ to interrogate somatic variants in 341, 410 or 468 cancer-related genes. Cases harboring *NKX2-1* copy number gain of at least 2-fold detected by MSK-IMPACT™ were analyzed by FACETS analysis to confirm the *NKX2-1* amplification. Molecular profiles, histological and clinical features were collected and analyzed relative to the *NKX2-1* amplification status.

Results: *NKX2-1* amplification was detected in 9 of 349 (3%) thyroid carcinomas, and was found to be limited to 5 of 86 (6%) poorly differentiated thyroid carcinomas (PDTC), and 4 of 141 (3%) papillary thyroid carcinomas (PTC) including 3 tall cell variants (PTC-TCV) and one classical type (PTC-CT). No *NKX2-1* amplification was identified in any of 54 anaplastic thyroid carcinomas (ATC), 28 Hurthle cell carcinomas (HCC), 9 follicular thyroid carcinomas (FTC), or in any of 31 medullary thyroid carcinomas (MTC). Four (44%) *NKX2-1* amplified tumors harbored *BRAF* V600E, and 3 (33%) *NRAS* Q61R variants. Interestingly, *TERT* promoter hotspot mutations occurred in 8 (89%) cases and showed a trend towards higher occurrence in *NKX2-1* amplified cases in comparison to 57% (193/340) frequency in *NKX2-1* neutral thyroid carcinomas (p=0.08, Fisher's exact test). Among 7 patients with clinical follow up, 6 (86%) presented at stage T3, and all 7 (100%) had recurrence including distant metastasis in 5 (71%) cases. One patient initially diagnosed with PTC-TCV presented with the local recurrence as ATC after 13 months.

Conclusions: High predominance of both, aggressive histological subtypes including PTC-TCV, and *TERT* promoter mutations among *NKX2-1* amplified thyroid carcinomas suggests *NKX2-1* amplification can be associated with relatively more aggressive tumor biology. Further studies are needed to explore the presence of *NKX2-1* amplification as an adverse prognostic marker in a subset of differentiated thyroid carcinomas of follicular cell origin.

625 Ovarian steroid cell tumor, not otherwise specified: Insights into steroidogenesis by immunohistochemical analysis

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Background: Ovarian steroid cell tumors, not otherwise specified (SCT-NOS) are rare tumors of uncertain cell lineage. Individuals often demonstrate virilization at clinical presentation due androgen production by the tumor cells. Herewith, we present data from immunohistochemical characterization of steroidogenic pathways in ovarian SCT-NOS by utilizing immunohistochemical stains for various enzymes involved in steroidogenesis.

Design: Three recently diagnosed SCT-NOS at our institution were analyzed with a panel of immunohistochemical stains for enzymes associated with adrenal and ovarian steroidogenesis. This panel included CYP11A1 (cholesterol side-chain cleavage enzyme, P450scc), CYP17A (17α hydroxylase), CYP19A (Aromatase), 17-βHSD 1/2/3/5 (17β –hydroxysteroid dehydrogenase), SRD5A 1/2- (5α-reductase), STS (Steroid sulfotransferase), EST (Estrogen sulfotransferase), 3βHSD (3β hydroxysteroid dehydrogenase), DHEAS (Dehydroepiandrosterone sulfate), and CYP21 (21α hydroxylase).

Results: All tumors (3/3) demonstrated diffuse moderate to strong cytoplasmic expression of CYP11A1, CYP17A, CYP19A, 3βHSD, STS, EST, 17-βHSD1/2/5 and SRD5A2 and were negative for CYP21, 17-βHSD3, SRD5A1 and DHEAS. The pattern of steroidogenic enzyme expression indicates ovarian steroidogenesis leading to synthesis of various estrogens and androgens rather than ectopic adrenocortical steroidogenesis.

Conclusions: Our analysis of steroidogenic enzyme expression in a limited number of SCT-NOS indicates that ovarian steroidogenesis pathway enzymes play a major role in the production of various estrogens and androgens leading to virilization. One of the enzymes demonstrated in our study, 17-βHSD5 (AKR1C3), is critical in the conversion of androstenedione to testosterone whose expression has been previously demonstrated in normal ovarian theca cells. Also, increased activity of 17-βHSD5 has recently been demonstrated in hormone-dependent cancers. Although the role of 17-βHSD5 in SCT-NOS tumorigenesis is not well characterized at this time, these preliminary results suggest that 17-βHSD5 may play a pivotal role in androgen production and testosterone-dependent tumor survival.

626 Molecular Diagnosis of Medullary Thyroid Carcinoma

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Background: The diagnosis of medullary thyroid carcinoma (MTC) can be challenging in thyroid fine needle aspiration (FNA) cytology specimens. Its cytologic appearance and molecular features can overlap with other thyroid neoplasms and thereby prevent a definitive diagnosis. The current study was designed to identify distinguishing molecular characteristics for MTC versus other thyroid neoplasms for use in limited specimens such as FNA biopsies.

Design: Unstained FFPE slides from twelve specimens (primary and metastases), obtained from eleven MTC cases were micro-dissected and analyzed for: (i) oncogene point mutation analysis (including *BRAF, RAS, PIK3CA, PAX8/PPAR, RET/PTC* translocations) using next generation sequencing; (ii) microRNA (miR) classifier analysis utilizing a 10 miR panel trained on 257 reactive, benign, malignant specimens; and (iii) quantitative evaluation of PAX8 and NKX2.1 messenger RNA (mRNA) levels. The results were compared to papillary thyroid carcinomas (PTC).

Results: Oncogene point mutations (*HRAS*) were detected in 3 of 11 MTCs with remaining being negative for target panel genes. While the mRNA level of PAX8 was consistently greater relative to NKX2.1 in PTC, the relationship was reversed in all MTCs. The miR profile of MTC differed strikingly from that of PTC with increased relative expression of four markers (miRs 375, 551, 146 and 31). All MTC could be distinguished from PTC using this combination molecular approach.

Conclusions: We show that MTC can be differentiated from PTC based on mutational genotype, relative mRNA expression levels of NKX2.1 vs PAX8 and differential miR expression profile. Molecular tests based on these findings can be applied to FNA of thyroid nodules when cytology evaluation is indeterminate or when a medullary carcinoma is considered in the differential diagnosis. The molecular abnormalities could also provide guidance in this era of targeted therapy.

627 TERT Copy Number Alterations, Promoter Mutations and Rearrangements in Adrenocortical Carcinomas: Clinico-pathologic and Molecular Analysis of 62 Cases

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Background: Recent molecular characterization of adrenocortical carcinomas (ACC) by The Cancer Genome Atlas has highlighted a high prevalence of *TERT* alterations in ACC. In addition, the association of *TERT* expression with whole-genome doubling, commonly seen in disease progression, has emphasized its role as a potential driver alteration. Herein, we have characterized *TERT* alterations in a large cohort of ACC, to better understand its role in disease progression.

Design: 62 cases of ACC were profiled for copy number alterations, and 54 were profiled for promoter mutations and structural variants by a hybridization-capture based next generation sequencing assay which targeted the promoter and all exons of *TERT*. FISH for *TERT* amplification was performed on 10 samples.

Results: *TERT* alterations were identified in 24 cases of ACC. The mean age at diagnosis was 52 years (10 males, 14 females). 8 patients had metastatic disease at diagnosis and an additional 5 developed metastases over an average duration of follow up of 70 months (13 of 24, 54%). The mean reported size and weight were 13.3cm and 1534g, respectively. Histopathologic review of 16/24 (67%) available cases revealed a diffuse pattern of growth, <25% areas with clear cytoplasm, necrosis, vascular and capsular invasion in at least 11/16 (69%) cases, with a mean mitotic count of 18 per 50 high power fields.

A C>T promoter mutation at position -124, relative to the transcription start site, was identified in 3 (of 54, 6%) cases. 21 (of 62, 34%) cases had *TERT* amplification (mean fold change: 2.2). This was confirmed by FISH for 10 cases which showed either amplification or high level polysomy. A single case with *TERT* amplification showed a rearrangement of the *TERT* promoter region with *CLPTM1L*. Importantly, amplifications in ACC were mutually exclusive events suggesting that either event could potentially serve as a driver alteration.

Associated pathogenic mutations involved *APC, NF1, CTNNB1* and *TP53* genes in 2 cases, each. Associated copy number alterations included losses of *CDKN2A* and *CDKN2B* (4 cases), *SMARCB1* (1 case), as well as gains of *TSC2* (4 cases), *CDH1* and *STK11* (3 cases, each).

Conclusions: 1.*TERT* alterations in ACC predominantly involve gene amplifications in a third of all cases of ACC, with a smaller subset harboring promoter mutations at position -124.

2. Over half of these tumors are associated with metastases.

3. Prospective large studies are needed to validate the prognostic impact of increased *TERT* expression in ACC.

628 Utility of digital image analysis in the identification of tall call variant of papillary thyroid carcinoma (TCV-PTC): Are we ready for the next step?

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Background: The criteria in the 2017 WHO Classification of Endocrine Organs for TCV-PTC include the identification of cells that are 2-3 times as tall as they are wide in >30% of a given tumor. At present, the designation of a cell as "tall" and the percent of the tumor that is composed of tall cells is a semiquantitative estimate achieved by visual assessment. This method is subjective and subject to inter-observer variability. Our goal is to utilize digital image analysis to develop a computer-assisted objective approach to more precisely diagnose TCV-PTC.

Design: 17 cases containing the diagnostic term "tall cell" in their pathology reports and 21 cases of classical PTC were selected. H&E slides were scanned using a Pannoramic 250 Flash III scanner and the

whole-slide images were analyzed using the Definiens TissueStudio v4.3 software (Munich, Germany). The regions of interest for analysis were manually selected and the magnification for cellular analysis was 10x. Individual cells were segmented and length, width, and length-to-width ratio were calculated from each tumor cells. Other geometric cellular features (shape index, number of pixels, elliptic fit, circularity, ellipticity) were collected.

Results: On average, a total of 544997 cells were detected and analyzed per case. Cells with a ≥2:1 and ≥3:1 length to width ratio were identified in each case (40003 and 2046 mean number of cells per case, respectively). The percent of the tumor composed of cells with a ≥2:1 ratio ranged from 3.9-9.63%; while it varied from 0.22-0.59% for cells with a ≥3:1 ratio. The other geometric cellular features were significantly different in the cells with ≥2:1 ratio as compared to non-tall cells (<2:1).

Conclusions: Our findings allow for the identification of tall cells with length-to-width ratios of ≥2:1 and ≥3:1. However, none of our cases met the percentage threshold proposed by the 2017 WHO Classification for the diagnosis of TCV-PTC. The low tumor percentages of tall cells reported in our study might correlate to the higher total number of tumor cells evaluated per case, potentially causing a dilution effect. In any event, our findings appear to challenge the current diagnostic criteria for TCV-PTC and subsequent studies to validate our findings are needed. Digital image analysis has advantages over traditional visual assessment in the identification and quantification of specific cell features, such as tall cells, potentially providing a more objective method for diagnosing TCV-PTC.

629 Impact of the Modified Morphologic Criteria for Tall Cell Variant of Papillary Thyroid Carcinoma

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Background: Tall cell variant (TCV) is considered an aggressive subtype of papillary thyroid carcinoma (PTC). The morphologic criteria for TCV were recently modified in the 2017 WHO Classification of Tumors of Endocrine Organs, with a decrease in both the required height of cells (3X as tall as wide modified to 2-3X as tall as wide) and in the percentage of tumor demonstrating a tall cell morphology (a "predominance of tall cells" suggesting a cutoff of ≥50% modified to ≥30%). The aim of this study was to determine if the change in criteria would result in a significant increase in the percentage of tumors that meet criteria for TCV.

Design: We evaluated a cohort of 97 consecutive PTCs diagnosed within a 12-month period at our institution that were classical type, PTC with a tall cell component, or TCV**.** For each case, slides were reviewed to determine the percentage of the tall cell component (0%, 1-9%, 10-29%, 30-49%, and ≥50%) and the height of the cells in this component (2-3X as tall as wide versus 3X as tall as wide).

Results: Of the 97 cases, 54 (55.6%) entirely lacked a tall cell component. With tall cells defined as at least 3X as tall as wide, none had 1-9% tall cells, 1 (1.0%) had 10-29% tall cells, 1 (1.0%) had 30-49% tall cells, and 8 (8.3%) had ≥50% tall cells. With tall cells defined as being at least 2-3X as tall as wide, 7 (7.2%) had 1-9% tall cells, 12 (12.4%) had 10-29% tall cells, 9 (9.3%) had 30-49% tall cells, and 15 (15.5%) had ≥50% tall cells. The number of cases classified as TCV increased significantly with the modification in criteria put forth in the new WHO: 8 (8.3%) cases met the old criteria for TCV (cells 3X as tall as wide in ≥50% of the tumor), whereas 24 (25%) cases met the new criteria for TCV (cells 2-3X as tall as wide in ≥30% of the tumor) (p=0.0032).

Conclusions: We found that the modified morphologic criteria for TCV put forth in the new WHO tripled the number of cases that would be classified as TCV. This change in classification would have significant sequelae for the risk stratification of patients with PTC.

630 Left Laterality of Adrenal Cortical Carcinomas is More Common and Associated with Improved Overall Survival: Results in 2,376 Patients

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Background: Adrenal cortical carcinoma (ACC) has been reported to have a predilection for the left adrenal gland, but the resulting impact on patients' outcomes remains unknown.

Design: The National Cancer Database comprises ~70% of newly-diagnosed cancers in the US and was queried for all ACCs with laterality data from 2004-2014. χ^2 and t-test were used as appropriate. Overall survival (OS) was estimated by Kaplan-Meier methods, compared by log-rank test; and risk-adjusted with proportional hazards.

Results: Of 2,376 included patients, ACCs more commonly presented on the left (54% vs 46% right), with similar proportions of AJCC stages: 1 (7%), 2 (41%), 3 (12%), and 4 (40%). Laterality was not associated with distant metastasis (M0).

In M0 ACC patients, there was no difference between left vs right lateralities in age at diagnosis (53 yrs vs 52), sex, comorbidity index, race, nodal status, venous and sinusoidal invasion, mean tumor weight (0.47 kg vs 0.56) or size (13.3 cm vs 15.0), or radiotherapy rates (15% vs 17%). Left ACCs more often underwent resection (97% vs 93% right), and were less likely pT4 (5% vs 10% right) or to receive chemotherapy (29% vs 35%, all p<0.05).

Pathologic assessment of large vein involvement (i.e. IVC, adrenal/suprarenal, or renal vein) was available in 25% of patients. Although there was no difference in the overall rate of vascular involvement, left ACC was significantly associated with more renal (23% vs 3%) and suprarenal (55% vs 40%), but less IVC (23% vs 57%), involvement. Cases where only the IVC was involved were overwhelmingly linked with right laterality (77%).

In proportional hazards analyses adjusted for patient, tumor, and treatment characteristics; left laterality of M0 ACCs was associated with significantly improved OS (HR 0.80, 95%CI: 0.67-0.96, p=0.02). Unadjusted 5yr OS rates for M0 ACCs were: left 53% (95%CI: 49-57) vs right 48% (95%CI: 43-52).

Conclusions: Using a national cohort, we demonstrate ACC's predilection for the left adrenal gland and identify a link between left laterality and renal vein involvement and right laterality and IVC involvement. Notably, after adjusting for patient, tumor, and treatment characteristics, left laterality of ACCs was significantly associated with improved OS compared to right laterality, suggesting that laterality may play a role in the outcomes of ACCs.

631 Making Inroads into the Molecular Characterization of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP): Previously Unreported Mutations

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Background: NIFTP is a recently described entity, a proposed subset of follicular variant of papillary thyroid carcinoma (FVPTC) defined by strict histopathological criteria with an indolent biologic behavior. Few studies have addressed the mutational profile of NIFTP, reporting RAS mutations or no detectable mutations as the most common finding. Less frequently identified were BRAFV600E or BRAFK601E mutations. The objective of the current study is to further expand the knowledge of the molecular profile of NIFTP.

Design: A retrospective review of a total 73 FVPTC cases diagnosed at our institution from 2006 to 2016 identified 12 cases eligible for NIFTP reclassification by the proposed criteria. Material from five of those cases was available for further study; formalin-fixed paraffin-embedded sections were submitted for the Ion AmpliSeq™ Cancer Hotspot Panel v2 (CHP2) assay. Sequence variants were identified with Variant Caller plug-in 4.0 using validated custom parameters. Variant annotation was performed by querying COSMIC, dbSNP and ClinVar databases. Clinical follow-up data was obtained from the electronic medical records.

Results: Please see Table 1.

Table 1. Molecular findings from five NIFTP cases using the Ion AmpliSeq™Cancer Hotspot Panel v2 (CHP2) assay and clinical follow-up (FUP) data.

Case Number	Variant(s) Identified	Follow-up Duration (years)	Clinical Status
1	BRAF-K601E (Pathogenic), ATM-S1691R (Variant of uncertain significance)	Lost to FUP	Unknown
2	HRAS-Q61K (Likely pathogenic)	2	Free of disease
3	SMAD4-R189C (Variant of uncertain significance)	6	Free of disease
4	No clinically significant variants	8	Free of disease
5	No clinically significant variants	6	Free of disease

Conclusions: Although based on a limited number of cases, the present study expands the knowledge regarding the molecular profile of NIFTP by the detection of SMAD4-R189C and ATM-S1691R mutations. Further molecular evaluation of additional cases will be important to elucidate the significance of these findings.

632 Targeted Next-Generation Sequencing Reveals High Mutational Burden in Aggressive Thyroid Cancers

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Background: Widely invasive follicular thyroid carcinoma (wFTC), poorly differentiated thyroid carcinoma (PDTC), and anaplastic

thyroid carcinoma (ATC) are aggressive thyroid tumors, often with a fatal outcome. However, a subgroup of patients (pts)within each group shows a better overall survival rate. Little is known about the genetic background of these less aggressive tumors. To determine the prevalence of genetic alterations in a panel of selected genes in patients with varying survival in wFTC, PDTC, and ATC.

Design: Ninety-one cases of aggressive thyroid cancers were reviewed and morphologically and immunohistochemically categorized. Next generation sequencing (NGS) was performed in microdissected FFPE samples from 30 wFTC, 30 PDTC, and 31 ATC using MiSeq (Illumina) for genetic analysis of the entire genes in: HECTD1, PIK3CA, CTNNB1, RET, RASAL1, AKT1, EIF1AX, ALK, PTEN, TP53, HRAS; KRAS, NRAS, and BRAF. The genes were covered by 996 amplicons. Within CLC Genomic workbench (Quiagen), NGS sequencing data were mapped to human genome (version hg19). Data from different databases were annotated (e.g. Cosmic, Ensembl, ClinVar, dbSNP, JBrowse, ExAC, HGMD, EVS). Clinical data and follow-up were available in 70 pts.

Results: In wFTC, PDTC and ATC, a total of 89, 46, and 52 genetic alteration respectively, were found. The incidence of alterations in wFTC, PDTC, and ATC for the investigated genes was as follows: HECTD1: 18%/9%/3%, PIK3CA: 9%/0%/9%, CTNNB1: 9%/3%/3%, RET: 21%/15%/19%, RASAL1: 27%/12%/9%, AKT1: 0%/3%/3%, EIF1AX: 6%/0%/6%, ALK: 28%/9%/12%, PTEN: 24%/12%/16%, TP53: 24%/15%/19%, HRAS:3%/12%/9%, KRAS: 4%/0%/0%, NRAS: 15%/3%/22%, and BRAF: 27%/9%/16%. Whereas the number of genetic alterations was correlated with poor survival rates for ATC, survival rates in PDTC and wFTC were independent of the incidence of alterations in the investigated genes.

Conclusions: Targeted whole gene analysis of aggressive thyroid cancers reveals a high incidence of genetic alterations. Mapping the mutational landscape of these tumors identifies genes potentially associated with tumorgenesis, some of which may be targets for therapeutic intervention.

633 Angiosarcomas of the Thyroid are a Distinct Entity from Anaplastic Thyroid Carcinomas: An Immunohistochemical and Molecular Study

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Background: Thyroid angiosarcomas (ASs) are rare malignant tumors characterized by vessel formation and immunophenotype common to endothelial cells. Due to their rarity, only a limited number of studies are available. Therefore, we undertook this study in order to better characterize the immunophenotype of thyroid AS and to explore if AS is a separate entity or represents the endothelial extreme in the differentiation spectrum of anaplastic thyroid carcinoma (ATC).

Design: A total of 10 surgically resected ASs were collected and immunohistochemistry for BAP1, CD31, c-myc, D2-40, ERG, ID1, p16, p53, p63, pankeratin, PAX8, smooth muscle actin (SMA) and, TTF1 was performed and scored as percentage of positive cells. The results were compared to immunoprofile of 22 ATCs. Moreover, we applied NGS to analyze *TP53* mutations.

Results: The immunohistochemical results are summarized in table 1. Among the vascular markers, CD31, ERG and, ID1 showed a consistent positivity in all analyzed ASs, while D2-40 was negative in 9 of 10 (90%) ASs. On the other hand, CD31 and ERG were positive in 1 (5%) and 2 (9%) of 22 ATCs in a low percentage of cells, whereas both D2-40 and ID1 were positive in the 55% of analyzed ATCs (12 of 22 and 11 of 20, respectively). The markers of thyroid lineage differentiation, PAX8 and TTF1, were completely negative in ASs, but focally positive in 11(50%) and 1(5%) of 22 ATCs, respectively. Moreover, p63 and SMA tend to be negative in ASs and variably positive in ATCs. Finally, c-myc, p16 and, pankeratin showed a variable positivity in both ASs and ATCs. p53 showed a wild-type pattern in all ASs and a mutated pattern in 71% of ATCs (15 of 21). Coherently, we found *TP53* mutation in 9 of 11 (82%) ATCs, but not in 4 ASs. BAP1 resulted positive in all cases evaluated, 5 ASs and 15 ATCs.

Table 1: Comparison of immunohistochemical results between 10 angiosarcomas and 22 anaplastic carcinomas of the thyroid.

Immunostainings	n (%)	ANGIOSARCOMAS	ANAPLASTIC CARCINOMAS	p-value
c-myc , total Negative (<1%) Positive (≥1%)	32 17 (53) 15 (47)	10 5 (50) 5 (50)	22 12 (55) 10 (45)	n.s.^
c-myc mean (range)	15% (0%-90%)	17% (0%-90%)	14% (0%-80%)	n.s.*
CD31, total Negative (<1%) Positive (≥1%)	32 20 (63) 12 (37)	10 0 (0) 10 (100)	22 20 (91) 2 (9)	<0.0001^
CD31 mean (range)	30% (0%-100%)	93% (60%-100%)	1% (0%-20%)	<0.0001*
D2-40, total Negative (<1%) Positive (≥1%)	32 19 (59) 13 (41)	10 9 (90) 1 (10)	22 10 (45) 12 (55)	0.0237^
D2-40 mean (range)	16% (0%-100%)	9% (0%-90%)	19% (0%-100%)	0.0419*
ERG, total Negative (<1%) Positive (≥1%)	31 21 (68) 10 (32)	9 0 (0) 9 (100)	22 21 (95) 1 (5)	<0.0001^
ERG mean (range)	26% (0%-100%)	92% (70%-100%)	0% (0-5%)	<0.0001*
ID1, total Negative (<1%) Positive (≥1%)	26 9 (35) 17 (65)	6 0 (0) 6 (100)	20 9 (45) 11 (55)	n.s.^
ID1 mean (range)	37% (0%-100%)	86% (60-100%)	23%(0-100%)	0.005*
p16, total Negative (<1%) Positive (≥1%)	31 15 (48) 16 (52)	9 2 (22) 7 (78)	22 13 (59) 9 (41)	n.s.^
p16 mean (range)	21% (0%-100%)	30% (0%-50%)	17% (0%-100%)	n.s.
p53+, total Wild-type pattern Mutated pattern	31 16 (52) 15 (48)	10 10 (100) 0 (0)	21 6 (29) 15 (71)	0.0002^
p53 mean (range)	34% (0%-100%)	21% (1%-40%)	40% (0%-100%)	n.s.
p63, total Negative (<1%) Positive (≥1%)	32 19 (59) 13 (41)	10 9 (90) 1 (10)	22 10 (45) 12 (55)	0.0237^
p63 mean (range)	18% (0-100%)	0% (0-1%)	27% (0-100%)	0.0153*
Pankeratin, total Negative (<1%) Positive (≥1%)	32 7 (22) 25 (78)	10 3 (30) 7 (70)	22 4 (18) 18 (82)	n.s.^
Pankeratin mean (range)	36% (0-100%)	36% (0-90%)	35% (0-100%)	n.s.
PAX8, total Negative (<1%) Positive (≥1%)	32 21 (66) 11 (34)	10 10 (100) 0 (0)	22 11 (50) 11 (50)	0.006^
PAX8 mean (range)	14% (0-100%)	0%	21% (0-100%)	0.022*
SMA, total Negative (<1%) Positive (≥1%)	31 21 (68) 10 (32)	9 9 (100) 0 (0)	22 12 (55) 10 (45)	0.0297^
SMA mean (range)	14% (0%-100%)	0%	19% (0%-100%)	n.s.*
TTF1, total Negative (<1%) Positive (≥1%)	32 31 (97) 1 (3)	10 10 (100) 0 (0)	22 21 (95) 1 (5)	n.s.^
TTF1 mean (range)	0% (0-1%)	0%	0% (0-1%)	n.s.*

Total, number of cases analyzed;

^Fisher's test; *Mann-Whitney test; + p53 Wild-type pattern, 1%-59% of positive cells and, p53 mutated pattern, either 0% or 60%-100% of positive cells.

Conclusions: To the best of our knowledge, this is the largest series of ASs of the thyroid. Based on our findings, the vascular markers CD31 and ERG are the most reliable immunomarkers to differentiate ASs from ATCs, whereas D2-40 and ID1 are equivocal. Interestingly, the complete lack of PAX8 and TTF1 in all ASs argues against an origin from the follicular thyroid cell, as opposed to ATCs.

634 A Lower Ki 67 Labelling Index (LI) Cut-Point Improves the Prognostic Assessment and Might Aid in the Diagnosis of Adult Adrenocortical Tumors

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Background: Treatment and prognostic evaluation of adrenocortical carcinomas (ACC) mainly relies on an image-based staging system (ENSAT), and in the proliferative index assessed by Ki67 IHC. However, the Ki67 LI cut point of 10% might be hindering more effective interventions in aggressive tumors with indexes <10%.

Design: We identified 146 adult patients with adrenocortical tumors (ACT) that underwent surgery with curative intent in a single institution, from 1985 to 2011 – allowing for a minimum 5-year follow up. ACT was classified as adenoma (ADA, n=72) or carcinoma (ACC, n=66) according to the Weiss criteria (≥ 3). The Ki-67 LI was assessed in hot spot areas by automatized counting (Image Pro Plus 4.5 software) and individual visual estimation by two pathologists. Cut-point and intervals for the Ki67 LI were transposed from other studies or defined by ROC curves according to our results.

Results: The Ki67 LI of all ACT showed good accuracy for defining the diagnosis of malignancy (ROC AUC = 0.821, p <0.001): a cut-point of 3% depicted a specificity (Sp) of 98.7%. Amongst the ACC, the Ki67 LI demonstrated good accuracy (AUC =0.856, p<0.001) on determining negative events: the 3% cut-point showed a sensitivity (Sn) of 84% and a Sp of 73% for unfavorable outcome (10% cut-point: Sn = 65%; Sp = 85%). Both cut-points were significantly correlated with poor OS and DFS (p<0.001). Stratifying patients according to their Ki67 LI in <3%; 3

– 20%; ≥20% improved the correlation with outcome when compared to the traditional fashion (<10%; 10 – 20%; ≥20%). This was exemplified by the number of deceased patients in the former: 4/30 (13%), 12/24 (50%), 13/16 (81%), and latter 9/40 (23%); 7/14 (50%); 13/16 (81%) subcategorizations. Eyeball estimation showed similar correlation rates in both situations (3%: r=0.728, p<0.001; 10%: r=0.735, p<0.001). In the multivariate, the Ki67 LI ≥ 3% remained as a significant predictor of reduced OS (HR 5.1, CI 1.5-16.8, p= 0.008) and DFS (HR 5.1, CI 1.7-14.7, p= 0.003).

Conclusions: The Ki67 LI is a useful prognostic and a potential diagnostic tool in adult ACT: a 3% cut-point, for instance, could be useful in underrepresented specimens. Also, applying this cut-point instead of 10% in ACC enhances risk stratification with no penalty to eyeball estimation, and might improve the clinical management of patients with 3 – 10% indexes.

635 A Simple Yet Powerful Algorithm Including Ki67 Labeling Index (LI) Helps Predict Outcome in Pediatric Adrenocortical Tumors (ACT)

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Background: Currently, there are no pathological classifications or biomarkers consolidated for prognostic assessment of pediatric ACT. While clinical follow-up remains as the most reliable predictor of biological behavior in this population, we aimed at investigating and possibly adopting stablished criteria from the adult tumors.

Design: We identified 44 pediatric ACT (<15 years) with long-term follow-up (115 ± 85 months) that underwent surgery with curative intent in a single institution. Tumors were classified as clinically benign (CB, n=35) or malignant (CM, n=9) bestowing negative evens (i.e. local or distant recurrence, or cancer-related death). The Ki-67 LI was assessed in hot spot areas by automatized counting (Image Pro Plus 4.5 software).

Results: The mean Ki67 LI of CB and CM tumors were 10.5% ± 11.3% and 29.3% ± 18.0%: higher than reported in the literature for their corresponding adult tumors. The Ki67 LI showed good accuracy on determining negative events (ROC AUC=0.816, p=0.004): the 20% index showed sensitivity (Sn) of ~80% and specificity (Sp) of ~87%. Wieneke (AUC=0.897, p=0.001) and Weiss (AUC=0.830, p=0.002) scores also showed promising results. In the latter, the cut-point should be shifted from ≥3 (diagnostic in adults) to ≥6 positive criteria for a more accurate distinction of the biological behavior. Multiple clinicopathological features were associated with outcome including Wieneke ≥3 (OS: p=0.001; DFS: p<0.001), Weiss ≥6 (OS: p=0.008; DFS: p=0.025), Ki67 LI ≥20% (OS: p=0.013; DFS: p<0.001) and ENSAT III+IV (OS: p<0.001; DFS: p<0.001). In the multivariate analysis, Ki67 LI ≥20% (HR 50.48, CI 3.89-654.59, p= 0.003) and ENSAT III+IV (HR 51.56, CI 3.26-814.48, p= 0.005) remained as predictors of DFS; only Ki67 LI ≥20% (HR 12.82, CI 1.01-162.89, p= 0.049) remained as a predictor of OS. By combining a Weiss ≥6 (+1) and Ki67 LI ≥20% (+1), we also generated a simple algorithm that helps predict outcome in pediatric ACT, illustrated by differences in recurrence between the 3 groups: sum=0 (0/15), sum=1 (2/20, 10%), sum = 2 (7/9, 78%). Similar results were obtained when combining Weineke ≥3 with Ki67 LI ≥20% (0, 33%, 71%).

Conclusions: Clinicopathological criteria adopted in adult ACT could also improve prognostic assessment in the pediatric population, provided their cut-points get amended to higher values. This was further explored in our proposed algorithm, that could standardize – and possibly simplify – the pathological evaluation of ACT in both adult and pediatric population.

636 The Spectrum and Clinical Features of Paragangliomas

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Background: Paragangliomas (PGLs) are relatively rare endocrine neoplasms that derive from components of the autonomic nervous system. We report clinicopathological features of a large series of PGLs.

Design: A retrospective review of the institutional pathology records from 2001 to 2016 identified 210 patients with PGLs. Clinical and pathological features of the patients were reviewed.

Results: The most common sites were in the head and neck (120), including carotid body (74), jugulotympanic (28), vagal (4), parapharyngeal (2), laryngeal (1), thyroid (1), sella turcica (1), and neck, NOS (9). Abdominal sites included peri-adrenal, para-aortic, interaortocaval, and paracaval retroperitoneal (44), bladder (14), pancreas (2), liver and porta hepatis (3), mesentery (2), duodenum and para-duodenal (3), and renal/perirenal (2). Mediastinal disease included lung (5), cardiac (3) and mediastinal, NOS (8). In addition to 8 conventional spinal PGLs, 4 cauda equina-type PGLs were also identified. Two of three duodenal/para-duodenal tumors and one of six pulmonary tumors were gangliocytic PGLs. Histologically confirmed multiple primary PGLs were identified in 16 (7.6%) patients. Evidence of histologically confirmed metastatic disease was present in 13 (6.19%) patients. Among those, 12 had solitary primaries at the time of the detection of their metastatic disease. Metastatic PGLs originated most frequently from abdominal (8) sites followed by the head and neck (4) and mediastinal (2) primaries. The metastatic sites were lymph nodes and bone, and bilateral lung with lymph node metastasis in one patient with no germline predisposition. The status of SDHB immunohistochemistry (IHC) was available from 161 tumors. Among the tested tumors, 65 (40.37%) had SDHB deficiency, and 11 (6.8%) had indeterminate IHC status due to either technical challenges or focal loss of staining. SDHB deficiency was seen in 77.7% of 9 patients with metastatic PGLs with available SDHB data. In addition, SDHB deficiency was noted in 53.8% of 13 patients with multifocal disease for whom SDHB data were available. Among the multifocal presentations, two of six with intact SDHB expression had proven VHL disease.

Conclusions: Our study highlights the wide variety of locations of PGLs and emphasizes the importance of thorough pathology evaluation including accurate diagnosis and application of routine SDHB IHC, distinction of metastatic disease from multifocal primary lesions for prognostication and prediction of genetic susceptibility.

637 Synchronous Multiple Pituitary Neuroendocrine Tumors of Different Cell Lineages

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Background: We report clinicopathological features of a large series of synchronous multiple pituitary neuroendocrine tumors (PitNETs) of different cell lineages.

Design: Retrospective review of pathology records from 2001-2016 identified 13 synchronous multiple pitNETs from 1055 pitNETs classified using transcription factors, hormones and other biomarkers. Clinical, radiological and histopathological features of these tumors were reviewed.

Results: The series included 7 females and 6 males. Mean age at diagnosis was 55.23 years (range: 36-73). Imaging was unavailable for 4 patients; among the other 9, mean tumor size was 2.23 cm (range: 0.9-3.9). Five patients had acromegaly, four had Cushing disease and 4 had clinically non-functional tumors. Twelve had double pitNETs; one had a triple pitNET. The most common tumor type was corticotroph (n=8; 6 densely and 1 sparsely granulated and 1 Crooke cell; 3 densely and 1 sparsely granulated were clinically silent). Gonadotroph tumors (n=8), and somatotroph tumors (n=5; 4 sparsely granulated and 1 densely granulated somatotroph) were followed by lactotroph tumors (n=4; all sparsely granulated), poorly differentiated Pit-1 lineage tumor (n=1), and plurihormonal tumor (n=1). A 54-year-old man with Cushing disease had MEN1-driven Crooke cell and gonadotroph tumors. The triple pitNET consisted of a multilineage plurihormonal tumor associated with a gonadotroph and a sparsely granulated lactotroph tumor. The Ki67 (available from 10 specimens) ranged from 1% to 5% in individual tumors. Radiological and biochemical follow-up was available for 10 and 11 patients respectively. Radiological tumor persistence/recurrence was identified in 3 patients with double pitNETs consisting of sparsely granulated lactotroph and gonadotroph tumors (n=1), sparsely granulated somatotroph and silent corticotroph tumors (n=1), and gonadotroph and silent corticotroph tumors (n=1) with cavernous sinus invasion. Biochemical persistence was noted in four patients with double pitNETs consisting of sparsely granulated somatotroph and silent corticotroph tumors (n=2), gonadotroph and Crooke cell tumors (n=1), and densely granulated somatotroph and silent corticotroph tumors (n=1).

Conclusions: Multiple PitNETs had hormone excess due to one tumor component; invasive growth and aggressive histological subtypes predicted disease persistence/recurrence. The use of transcription factors along with hormones is crucial to distinguish and subtype multiple pitNETs.

638 Ki-67 in Neuroendocrine Component Drives Prognosis in GEP MANECs: Study on Retrospective Centralized Analysis of 160 Patients

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Background: Gastroenteropancreatic (GEP) mixed adeno-neuroendocrine carcinomas (MANECs) are composed by a neuroendocrine carcinoma (NEC) and a non-NEC component, each representing at least 30% of the tumor burden. At present, prognostic factors for MANECs are largely unexplored. We investigated the clinical-pathological features of a multicenter large series of MANECs.

Design: Surgical specimens of 200 GEP-MANECs patients were centrally reviewed in terms of morphology, immunohistochemical (IHC) features (p53, SSTR2a, Beta-Catenin, Bcl-2, p16, Rb1, ALDH and CD117), and genomic (TP53, KRAS and BRAF, in 80 cases) features. Mitotic Index (MI), and Ki-67 index (Ki-67) were evaluated separately in the NEC and non-NEC components. These data were correlated with Overall Survival (OS).

Results: Diagnosis of MANEC was confirmed in 160 GEP cases distributed as follows: 92 colonic, 44 gastro-esophageal and 24 biliary-pancreatic. Median OS was 13.2 months. After adjustment for primary tumor site, Ki-67 of the NEC component (but not in the non-NEC component) was the most powerful prognostic marker. In particular, compared to patients with Ki67<55% (median OS=40.4 months) those with Ki-67≥55% had a 9-fold risk of death (HR 9.0 [95% CI 5.1-15.9] p<0.0001) and a median OS of 12.2 months. MI (HR 1.7 [1.2-2.4], p=0.003) was a weaker prognostic index. Colon site (HR 1.71 [1.23-2.39], p=0.002) and the occurrence of *KRAS*, *BRAF* or *TP53* mutations (HR 2.8 [1.6-4.8], p=0.0002) were significantly associated with an unfavorable survival. No single IHC marker in either component resulted statistically significant. Similarly, the prevalence of each tumor component was not significantly associated with OS.

Conclusions: Our study provides evidence that Ki-67 in the NEC component is the most powerful prognostic biomarker in GEP-MANECs patients. Colon primary site and *KRAS, BRAF* or *TP53* mutations are also associated with poorer prognosis.

639 Fascin-1 as a Putative Prognostic Biomarker in Adrenocortical Carcinoma

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Background: Adrenocortical carcinoma (ACC) is an uncommon tumour with incompletely elucidated pathogenesis and poor prognosis. The morphological approach may sometimes pose difficulties in distinguishing benign from malignant neoplasms and ultimately predicting tumour behaviour. For these reasons, a genetic approach is strongly advised to identify molecular changes and avail greater diagnostic and prognostic prowess. Novel molecular markers could then be introduced in routine pathological practice by means of immunohistochemical techniques.

Design: We assessed the diagnostic and prognostic value of Fascin-1, previously identified through proteomic analysis as a biomarker differentially expressed between ACC and normal adrenals. Fascin-1 expression was quantified by immunohistochemistry and Western blot analysis in samples from a consecutive series of n=36 ACCs and n=37 adrenocortical adenomas (ACAs). Invasion capacity of cultured H295R ACC cells with conditional overexpression of Steroidogenic Factor-1 (SF-1) and silenced Fascin-1 was evaluated in a culture (Matrigel) model.

Results: Fascin-1 expression occurred in 73% ACCs and 36% ACAs (c^2=15.6, p<0.001), with optimal correlation between the two detection techniques. Positive Predictive Value and Negative Predictive Value of Fascin-1 to discriminate between ACC and ACA were, however, low (57% and 78%, respectively). Notably, Fascin-1 expression significantly predicted recurrence and mortality in the ACC group as assessed by Kaplan-Meier analysis (Log rank 0.049 and 0.027, respectively). No significant correlation was found with the other clinico-pathological parameters considered (tumour size, Weiss score, Ki-67 index, secretion). Finally, Fascin-1 knockdown in H295R ACC cells impaired SF-1-induced cytoskeletal remodelling and invasion.

Conclusions: Our findings suggest that Fascin-1 has limited diagnostic value but may influence ACC cells invasiveness triggered by SF-1 overexpression, thus constituting a putative prognostic and targetable biomarker of ACC.

640 Expression of Pulmonary Biomarkers Surfactant Protein A (SP-A) and Napsin A in Papillary Thyroid Carcinomas

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Background: Surfactant protein A (SP-A) is normally secreted by alveolar type II penumocytes and Clara cells. It is also expressed in portion of lung adenocarcinomas and is used as a specific marker for detection of these types of tumors. It has been shown that SP-A expression is not limited to the lung and might be found in small amount in various tissues, but its expression in the thyroid tissue has not been reported yet. Napsin A also is a highly expressed molecule in normal pulmonary tissue and is a sensitive marker for pulmonary adenocarcinoma; however, it has been shown that about 5% of papillary thyroid carcinomas also express napsin A. In the current study, we aimed to evaluate the expression of these pulmonary biomarkers in papillary thyroid carcinomas and some other thyroid lesions.

Design: 123 thyroid resection cases were selected and categorized based on their pathologic diagnosis into 4 groups including papillary thyroid carcinoma (93 cases), follicular neoplasm (10 cases), multinodular goiter (10 cases) and chronic lymphocytic thyroiditis (10 cases). All of the cases were stained for SP-A and napsin A and the staining extent was scored semiquantitatively from 0 to 3+.

Results: Among 93 cases of papillary thyroid carcinoma, 17 (18%) cases were positive for SP-A and 23 (24%) cases were positive for napsin A, with staining extent ranging from 1+ to 3+. Also 12 (13%) cases were positive for both SP-A and napsin A and interestingly, each of these cases showed the same staining extent for both markers. None of the cases of follicular neoplasm, multinodular goiter or chronic lymphocytic thyroiditis showed positive staining for SP-A or napsin A.

Conclusions: The results of the current study showed that significant number of papillary thyroid carcinomas can express one or both pulmonary biomarkers SP-A and napsin A. In addition, thyroid transcription factor 1 (TTF-1), a molecule of thyroid, is routinely detected in pulmonary adenocarcinomas. It seems that these two tissues, as well as carcinomas arising from them, can share some of the gene expressions which can create diagnostic confusion for the pathologists. The knowledge about these expressions is crucial and necessitates the conjunction of other thyroid markers such as thyroglobulin and PAX8 to distinguish thyroid carcinomas from lung adenocarcinomas in the context of metastatic tumors.

641 Validation of the Oncomine Comprehensive Cancer Panel Assay for the Detection of Genetic Alterations in BRAF/RAS Mutation-Negative Papillary Thyroid Carcinomas

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Background: The use of targeted next-generation sequencing (NGS) panels for the detection of mutations has aided in the diagnosis, prognosis and the selection of targeted therapy in thyroid cancer. Recurrent somatic mutations in BRAF and RAS occur in 60-70% and ~13% of papillary thyroid carcinomas (PTC), respectively. The Oncomine Comprehensive Cancer Panel (OCP) interrogates single nucleotide variants (SNVs), insertion/deletion (indel), and copy number alterations (CNAs) in DNA and gene fusions in RNA from tumor-enriched FFPE tissue. In this study, we investigated the utility of OCP in identifying genetic alterations in BRAF/RAS-mutation negative PTCs.

Design: DNA and RNA extracted from 43 BRAF/RAS-mutation negative PTC samples were subjected to NGS using the OCP v2 assay, interrogating 143 unique cancer genes including an RNA panel consisting of 23 fusion driver genes. Sequencing data was analyzed by the Ion Reporter™ Software 5.0 (Thermo Fisher Scientific).

Results: Among the 43 BRAF/RAS-negative PTCs, 17 cases (40%) were found to have gene fusions: 7 CCDC6-RET, 4 ETV6-NTRK3, 2 TPR-NTRK1, 1 PAX8-PPARG, 1 SPECC1L-RET, 1 NCOA4-RET, and 1 EML4-ALK. CCDC6-RET, ETV6-NTRK3, and TPR-NTRK1 fusions were seen in both classical and follicular variants. PAX8-PPARG and NCOA4-RET fusions were identified in the follicular and solid variants, respectively. No genetic alterations were detected in 60% of the BRAF/RAS-negative PTCs, suggesting molecular alterations other than those targeted by this assay.

Conclusions: Here we report the analytical performance of the OCP assay to detect genetic alterations in BRAF/RAS-negative PTC samples. 40% of the BRAF/RAS-negative PTCs showed recurrent somatic gene fusions, demonstrating that OCP is robust and specific in detecting genetic alterations in tumor RNA from FFPE tissues.

642 Prostrate specific membrane antigen (PSMA) in various thyroid tumors and its potential role in the management of thyroid tumors

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Background: Prostate specific membrane antigen (PSMA) is a type II, transmembrane glycoprotein expressed by prostatic epithelium. Recently, PSMA expression has been reported in the endothelium of different tumors including lung, breast, glial tumors, colorectal carcinomas, etc. The aim of this study is to evaluate PSMA expression in various thyroid tumors.

Design: A total of 117 thyroid tumors, including 26 classic papillary thyroid carcinoma (PTC), 37 follicular variants of PTC, 13 follicular carcinomas (FTC), 8 Hürthle cell carcinoma, 16 tall cell variants of PTC, and 17 follicular adenomas were identified from Archives of Surgical Pathology Department. Immunohistochemical stain for PSMA was performed on the representative sections of tumor with sufficient adjacent peritumoral normal thyroid tissue. PSMA+ vessels were counted inon 4 areas: cold (low expression), moderately hot (moderate expression), and hot (high expression), and the largest representative areas, each on one 20x HPF. The overall PSMA+ vessels is sum of all 4 counts for each tumor. D2-40 immunostain was also performed on the same sections to identify lymphatic vessels.

Results: Results: PSMA is only expressed in vessels within the tumors or at the tumor capsules. No PSMA reactivity is seen in vasulature of the peritumoral normal thyroid and any lymphatic vesssels. Only two of 117 tumors showed complete lack of PSMA+ vasculature. The overall scores of the intratumoral PSMA+ vessels are shown in Table

Type Tumor	No. of case	Overall PSMA+Vessel	Median
FC	13	65.23	77.5
FVPC	37	42.12	33.9
PC	26	33.54	24
HCFC	8	41.11	40
TCPC	16	127.05	143.12
Adenoma	17	81.64	26.14
Total	177		

Conclusions: PSMA is commonly expressed in the angiovasculature within the tumors but not outside the tumor. PSMA is not expressed in lymphatics. PSMA might play a role in tumor angiogenesis in thyroid cancer. Intratumoral PSMA+ vasculature is seen in malignant and benign tumors. Interestingly, tall cell variant of PTC showed the highest PSMA expression, and follicular carcinoma showed higher expression of PSMA than papillary carcinoma.

Due to the restricted intratumoral vascular expression, PSMA might be considered as a potential therapeutic target for thyroid carcinoma.

643 Orthopedia Homeobox (OTP) Expression in a Well-Differentiated Neuroendocrine Tumor Supports a Bronchopulmonary Origin

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Background: Well-differentiated neuroendocrine tumors (NETs) often (10-20%) present as metastases of occult origin. In this setting, TTF-1 expression, though specific for a bronchopulmonary origin, is only 30% sensitive. Orthopedia homeobox (OTP), a transcription factor with expression normally confined to the central nervous system, was recently identified by gene expression profiling as a lung NET marker. In a few studies, OTP expression has been described in 80% of typical (n=348) and 50% of atypical (n=84) lung carcinoids, with no expression in non-lung NETs, though only a small number have been tested (n=53). Expression has also been shown to connote a favorable prognosis.

Design: OTP immunohistochemistry was performed on the following 716 neoplasms: NETs of the lung (77 typical, 12 atypical carcinoid), jejunoileum (178 primary, 258 metastatic), pancreas (80 primary, 66 metastatic), and other (12 duodenum, 4 Meckel, 3 appendix, 1 ampulla, 1 colon) and poorly differentiated neuroendocrine carcinomas (NEC) of the lung (9 small cell, 15 large cell). All cases were in tissue microarray (triplicate 1 mm cores) except 43 of the lung NETs and the 24 NECs (whole sections). Expression was evaluated for intensity (0-3+) and extent (0-100%) with an H-score calculated (intensity*extent). Vital status was available for 47 lung NETs. Fisher's exact and Mann-Whitney tests were used with $p<0.05$ considered significant.

Results: OTP was expressed by 82% of typical and 50% of atypical lung carcinoids ($p=0.024$) with mean (median) H-scores of 197 (225) and 145 (135), respectively ($p=0.19$). Otherwise, OTP expression was only seen in 1 pancreatic NET (0.7% of pancreatic and 0.2% of all non-lung NETs) and was not seen in NECs (0%). This 1 pancreatic NET was shown to express the pancreatic NET markers Islet 1 and PAX6. The proportion of patients surviving was identical among OTP+ (64%) and OTP- (64%) lung NETs ($p=1$).

Conclusions: OTP is expressed by 80% of typical and 50% of atypical carcinoid tumors of bronchopulmonary origin, with expression in non-lung NETs considered exceptional. Given 2-3x increased sensitivity relative to TTF-1, we have adopted OTP IHC as part of a panel approach to identify NET site of origin.

644 CXCR4 is Highly Expressed by Poorly Differentiated Neuroendocrine Carcinoma: A Novel Diagnostic, Prognostic, and Potential Therapeutic Target

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Background: The chemokine receptor CXCR4 has numerous roles in health and disease: its natural ligand CXCL12 causes stem cells to home to the bone marrow, anti-CXCR4 therapy mobilizes stem cells, germline mutations cause primary immunodeficiency (WHIM syndrome), sporadic mutations are found in 30-40% of lymphoplasmacytic lymphomas, and it serves as a co-receptor for T-cell-tropic HIV strains. CXCR4 is widely expressed by cancer. CXCR4-based nuclear medicine imaging and peptide receptor radionuclide therapy are in development, and our group has a clinical and research interest in managing neuroendocrine cancer patients with these modalities. One of our goals is to use CXCR4 immunohistochemistry (IHC) to aid in patient selection.

Design: CXCR4 IHC (clone UMB-2; 1:250) was performed on tissue microarrays of 95 poorly differentiated neuroendocrine carcinomas (NEC) and 66 gastroenteropancreatic well-differentiated neuroendocrine tumors (NET). Expression was scored for intensity (0-3+) and extent (0-100%) with an H-score calculated (intensity*extent). Age, gender, stage at diagnosis (localized, regional, distant), primary site (lung, extrapulmonary visceral, skin), SSTR2A IHC results, and vital status were available for most patients. Cox regression models were used to assess the impact of these variables on survival. Fisher's exact test was used to analyze contingency data ($p<0.05$ significant). We deployed CXCR4 IHC clinically in January 2017, and we also relate our prospective experience.

Results: In the retrospective cohort, CXCR4 was expressed by 84% of NECs with a mean (median) H-score of 120 (104) and only 4.5% of NETs (mean/median H-score 3) ($p<0.0001$).

On multivariable analysis, only distant metastasis ($p<0.01$) and CXCR4 expression ($p=0.04$) were significantly associated with survival. Patients with an H-score >30 were 2.5x more likely to die than those with no staining.

Prospectively, 76% of 21 NECs (mean; median H-score 181; 255) and 0% of 25 non-lung NETs (including 5 well-differentiated G3 tumors) have been positive. 47% of 15 lung NETs have been positive, including 9 of 10 atypical carcinoid tumors (mean; median H-score 113; 140).

Conclusions: NECs are usually CXCR4-positive, with expression typically moderate to strong; in these tumors expression is prognostically adverse. Expression in NETs appears largely restricted to atypical carcinoid tumor of lung origin. High expressors are ideal candidates for CXCR4-based imaging and peptide receptor radionuclide therapy.

645 Core needle biopsy as primary diagnostic method of thyroid nodules

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Background: Core needle biopsy (CNB) is a useful procedure in thyroid nodule diagnosis, often used after an inconclusive (indeterminate or nondiagnostic) fine needle aspiration (FNA). Observer experience and practice setting impact on CNB diagnoses are unknown. CNB performance and influence of pathologist experience and type of sign-out(general vs subspecialty) in a center where US-guided CNB is the primary diagnostic method of thyroid nodules are presented.

Design: Consecutive thyroid CNBs performed between 2002-2017 were included and pathology reports reviewed. Bethesda system diagnostic categories (BDC 1-6) were used to code the CNB and excision diagnoses. The noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP) and encapsulated follicular variants of papillary thyroid carcinoma (EFVPTC) diagnosed in excision specimens as well as BDC 5 and 6 diagnoses were collapsed and considered malignant for analysis. CNB diagnoses were rendered

by a cytopathologist or surgical pathologist on general sign-out (2002-2012) and on Head and Neck/Endocrine service (2013-2017). Pathologist experience was rated by number of CNB reads. The CNB performance relative to excision results and indeterminate rate (BDC-3) was compared by observer and time periods.

Results: Of 680 patients with 745 nodules, 517 underwent excision. There were overall 28 (4%)non-diagnostic CNBs and 104 (14%) were indeterminate. CNB sensitivity, specificity and accuracy for malignancy detection was 88%,94%, and 91%, respectively. The rate of BDC-3 diagnoses was lower in subspecialty than general signout setting (11% vs 25%, p=0.0001) and for more experienced compared with less experienced observers (12% vs 28%, p=0.0004). NIFTP/EFVPTC cases (n=27) were diagnosed in CNB as neoplastic in 14 (52%), malignant in 5 (18%), benign in 5 (18%) and indeterminate in 2 (7%) of the conclusive cases, 1 being inadequate.

Conclusions: Thyroid CNB has excellent adequacy rate and good accuracy for malignant disease. Pathologist experience with thyroid CNB and subspecialty signout setting decreased the indeterminate diagnoses. Most NIFTP were correctly classified as neoplastic/malignant in 70% of cases by CNB and terminology of follicular-patterned neoplasm with cytologic atypia is proposed for such cases.

646 Clinicopathological Classification of Pituitary Adenomas: A Monocentric Retrospective Analysis Of 567 Patients

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Background: In 2013 a French group has proposed a new five-grade clinicopathological classification of pituitary adenomas based on invasion and proliferation.

Design: The aim of our study is to evaluate the reproducibility of this classification in a large series of consecutive cases of pituitary adenomas collected in a single center.

Results: Five hundred sixty-seven PAs with an available follow-up (mean 5.7 years, range 0.3-17.7 years) were found. Based on immunohistochemical data, these cases included 253 FSH/LH, 148 GH, 85 PRL, 72 ACTH and 9 TSH tumours. Applying the French classification criteria, 387 tumours were grade 1a; 51 were grade 1b; 89 were grade 2a and 40 were grade 2b. During the follow-up, 60 patients developed recurrence or progression of the primary pituitary adenoma. The mean recurrence/progression time was 5.6 years. At the last follow-up, 130 of 567 patients showed evidence of disease and the remaining 437 patients recovered. Univariate Cox regression models on the determinants of disease showed a significantly higher risk of disease and higher risk of progression or tumor recurrence in patients with PRL, ACTH and FSH-LH tumor type compared with patients with somatotroph tumor, in macroadenoma (only for higher risk of disease), and in patients with tumor grades 1b and 2b. Conversely no statistically significant difference was found by sex groups and age.

Multivariable Cox regression analysis identified tumor grades 1b, 2a and 2b as the only independent predictive factors of disease (HR=2.689, p=0.001 for grade 1b; HR=1.787, p=0.025 for grade 2a; HR=5.224, p< 0.001 for grade 2b) and tumor grade 1b and 2b to be the only independent predictive factors of recurrence/tumor progression (HR=4.567, p< 0.001 for grade 1b; HR=6.487, p< 0.001 for grade 2b). In the overall sample, tumor grading is the main factor emerging in a decision tree analysis to stratify patients according to the risk of recurrence/progression.

Conclusions: Our study underlines the accuracy of tumor grade proposed by French classification to predict the clinical behavior of all type of pituitary adenomas, in particular in PRL, ACTH and FSH/LH tumor type, tumor grade is the most reliable prognostic pathologic parameters for detecting patients with a high risk of recurrence/progression and of post-operative complete remission.

647 Comparison of Serotonin to the Midgut Marker CDX2 to Assign Site of Origin in a Well-Differentiated Neuroendocrine Tumor

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Background: Well-differentiated neuroendocrine tumors (NETs) frequently (10-20%) present as metastasis of occult origin, typically arising in the jejunoileum or pancreas. We use a primary panel of immunostains including CDX2/Islet 1/PAX6 in this setting, with CDX2 representing our "midgut marker." Manuscript reviewers frequently challenge our selection of CDX2 (despite extensive literature demonstrating 90% sensitivity), based in part on the fact that it is expressed by 15% of pancreatic NETs. Several have advocated strongly for serotonin in this setting (as jejunoileal NETs recapitulate EC cells), but there is little data on the frequency and extent of serotonin-positivity in midgut NETs. EC-cell tumors arise at other sites, but this is considered rare. The purpose of this study is to evaluate the usefulness of serotonin as a midgut NET marker.

Design: Serotonin and CDX2 immunohistochemistry was performed on tissue microarrays (TMAs) of 430 jejunoileal (174 primary, 256 metastatic) and 142 pancreatic (79 primary, 63 metastatic) NETs; TMAs of 44 lung NETs were also stained for serotonin (19 previously shown to be CDX2-negative). Expression was evaluated for intensity (0-3+) and extent (0-100%) with an H-score calculated (intensity*extent). McNemar's test was used to compare the sensitivity of serotonin and CDX2 for midgut NET with p<0.05 considered significant.

Results: CDX2 was expressed by 90% of midgut (mean H-score 181) and 16% of pancreatic (mean H-score 108) NETs, while serotonin-positivity was seen in 81% of midgut (mean H-score 108) and 3% of pancreatic NETs (mean H-score 102). Detailed expression data are presented below. No (0%) lung NET expressed serotonin. CDX2 demonstrates superior sensitivity for midgut NET (p=0.000014), but the addition of serotonin increases overall sensitivity from 90 to 96%. All 4 serotonin-positive pancreatic NETs expressed PAX6; 2 expressed Islet 1.

	CDX2		Serotonin	
	% positive	Mean H-score (if +)	% positive	Mean H-score (if +)
Jejunoileal 1°	94%	219	88%	98
Jejunoileal metastasis	88%	152	75%	115
Pancreas 1°	11%	115	3%	102
Pancreas metastasis	22%	104	3%	102

Conclusions: Serotonin is less sensitive but more specific than CDX2 for assigning midgut origin. Serotonin-positivity argues strongly against a pancreatic origin. Based on these results we have added serotonin as a "second-tier" NET site of origin marker.

648 Nicotinamide Phosphoribosyl Transferase Immunohistochemistry Differentiates Thyroid Follicular Carcinomas from Follicular Adenomas

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Background: Thyroid neoplasms constitute less than 1% of all human cancers, with common subtypes being follicular adenomas (FA), and follicular (FC), papillary (PC), medullary, and anaplastic carcinomas (AC). Histologically, FA and FC can be very similar and with both surrounded by a thin fibrous capsule. However, FCs show capsular or surrounding thyroid parenchymal or vascular invasion, the later can be within or beyond the capsule. Previously nicotinamide phosphoribosyl transferase (Nampt) was shown to be elevated in thyroid FC and PC, compared to benign thyroid tissue. Based on this we examined Nampt expression in thyroid FAs compared to FC, PC, and AC.

Design: We used tissue microarray technology to examine Nampt immunohistochemical intensity expression in 12 cases each of benign thyroid, FAs, FCs, PCs, and ACs. The expression levels were measured by two pathologists. Nampt immunohistochemical expression was determined as immunostain intensity scored on a 0-3 scale, with 3 being maximal. Immunostain intensity was scored with no staining being 0, light staining as 1, moderate staining as 2, and heavy staining as 3. The percentage of cells stained was measured with no detectable staining as 0, 1-33% as 1, 34-66% as 2, and 67-100% as 3. The final IHC score was the product of the percent of cells stained multiplied by the intensity score, allowing for a maximal score of 9 and a minimal score of 0.

Results: Nampt expression was low in benign thyroid tissue and FAs, and highly expressed in the FCs, PCs, and Acs (intensity x percentage score+/-standard error of the mean) ; benign thyroid 1.17 +/-0.13, FA 1.75+/-0.25, FC 7.75+/- 0.45, PC 8.00+/-0.58, and AC 7.83+/-0.71.

Conclusions: Our findings show that compared to malignant thyroid neoplasms, FAs show very low Nampt immunohistochemical expression. Additionally, for the first time Nampt immunohistochemical expression is shown to be increased in thyroid AC. Our findings suggest that Nampt immunohistochemical expression may prove useful in differentiating thyroid FA from FC.

649 PREVIOUSLY PUBLISHED

650 Neuroendocrine Site of Origin Immunohistochemistry in Primary and Metastatic Neuroendocrine tumors

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Background: Neuroendocrine tumors (NET) are known to present as metastasis of occult origin in 10-20% of cases, which causes a dilemma for pathologists and clinicians. Many immunohistochemical panels has been utilized to distinguish the site of origin in theses tumors. In this study, we aimed to use PAX8, TTF-1, CDX2 and Cadherin 17 (CAD17) to study the immunoprofile of primary and metastatic neuroendocrine tumors.

Design: Tissue microarray was constructed using 3 mm core tissue (3 cores per case), and consisted of 157 cases (150 patients). Immunohistochemical staining for PAX8, TTF-1, CDX2 and CAD17 were performed. Nuclear staining (first three stains) and membranous staining (CAD17) were scored as negative (-), weak/focal (w) and positive (+).

Results: PAX8 stain is positive in 60% of pancreatic and 26% of rectal NET. TTF-1 stained 75% of lung tumors and less than 20% staining was seen in pancreatic and gastric NET. Combination of CDX2 and CAD17 staining was seen in all appendiceal tumors, 92% of terminal ileum tumors and 50% of duodenal tumors. The immunoprofile of primary and metastatic NET are summarized in table 1.

Tumor site	PAX8	TTF-1	CDX2	CAD17
Stomach (n=12)	1	1	2	4
Duodenum (n=16)	1	0	8	11
Terminal ileum (n=17)	0	0	13	14
Appendix (n=12)	0	0	12	12
Colon (n=50)	13	1	8	48
Pancreas (n=16)	10	3	5 (weak)	12
Lung (n=23)	1	17	1	7
Liver mets from pancreas (n=4)	3	0	1	3
Liver mets from TI (n=2)	0	0	2	2
Lymph node mets from TI (n=5)	0	0	2	4

Conclusions: Four- antibody panel provides valuable information about the origin of NET and will be helpful to guide clinical work up for the origin of metastatic NET. In the absence of PAX8 and TTF-1 expression, combination of CAD17 and CDX2 is indicative of appendicial, terminal ileum or duodenal tumor site.

651 Unusual Anaplastic Thyroid Carcinomas

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Background: A small subset of patients with anaplastic thyroid carcinoma (ATC) have tumors in which the anaplastic component comprises a small percentage of the tumor or who have a relatively prolonged survival. To understand the prognostic significance of a minor anaplastic component as well as the morphologic and molecular characteristics of cases that pursue an atypical clinical course, we performed a clinicopathologic and molecular analysis of a small cohort of cases of ATC with unusual histopathologic and clinical features.

Design: We performed a search of ATC resected at our institution from January 2010 to August 2017 and identified 5 cases in which the anaplastic component comprised <10% of the tumor. Three cases of ATC with an atypical clinical course were also independently identified, one of which had also been selected in our initial cohort. Clinical records, tumor slides, and molecular data (when available) were reviewed for each case.

Results: Of the cases with a minor anaplastic component, 2 were in a background of hobnail variant of papillary thyroid carcinoma (PTC), 1 in tall cell variant (TCV) of PTC, 1 in angioinvasive follicular thyroid carcinoma (FTC), and 1 in follicular variant of PTC (FVPTC). A *BRAF* V600E mutation was detected in the hobnail and TCV cases. The 2 patients with ATC arising in hobnail PTC developed distant metastases and died of disease with an average disease-specific survival (DSS) of 15 months. The patient with ATC in a background of angioinvasive FTC had a protracted course but eventually developed rapid progression of distant disease (DSS 28 months). The 2 patients with a minor component of ATC in a background of TCV and FVPTC currently have no evidence of disease (26 and 30 months follow-up time, respectively). The 2 patients identified on the basis of an atypical clinical course (no evidence of disease with follow-up times of 35 and 5 months) had tumors that were entirely comprised of ATC. Significantly, both of these tumors had *MSH2* mutations detected by sequencing and were confirmed to be mismatch repair (MMR) deficient by immunohistochemistry.

Conclusions: Thyroid carcinomas with a minor component of ATC can pursue a variable clinical course that may be driven in part by the histopathologic characteristics of the background tumor. Rare ATC with MMR deficiency may pursue a protracted clinical course, despite aggressive histology of the primary tumor. The MMR status may also have implications for checkpoint inhibitor therapy.

652 Molecular Alterations According to Characteristics of Tall Cell Component

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Background: Tall cell variant (TCV) is considered an aggressive subtype of papillary thyroid carcinoma (PTC). The morphologic criteria for TCV were recently modified in the 2017 WHO Classification of Tumours of Endocrine Organs, with a decrease in both the required height of cells and in the percentage of tumor demonstrating a tall cell morphology. To better understand the correlation between morphology, molecular alterations, and clinical behavior, we investigated the clinicopathologic features and molecular alterations of a cohort of PTCs according to the characteristics of the tall cell component.

Design: Our first cohort consisted of consecutively resected classical PTCs and PTCs with a tall cell component diagnosed between October 2016 and August 2017 that had molecular characterization through a targeted, next-generation sequencing assay. A second cohort of TCV that demonstrated aggressive clinical behavior (defined as those with T4 disease, disease recurrence, or tumor dedifferentiation) was also evaluated using the same sequencing assay. Slides were reviewed to determine the percentage of the tall cell component (0%, 1-9%, 10-29%, 30-49%, and ≥50%) and the height of the cells in this component. Molecular alterations were categorized as either putative oncogenic driver mutations or likely pathogenic secondary mutations.

Results: Our first cohort included 31 cases of PTC, of which 18 (58%) had <10% tall cells (with tall cells defined as at least 2-3X as tall as wide), 4 (13%) had 10-29% tall cells, 3 (10%) had 30-49% tall cells, and 6 (19%) had ≥50% tall cells. Sequencing revealed a putative driver mutation in all cases. A *BRAF* V600E mutation was identified in all cases with ≥10% tall cells and in 14 (78%) cases with <10% tall cells. A pathogenic secondary mutation was detected in only one (4%) of 25 cases with <50% tall cells, whereas they were detected in 2 (33%) of 6 cases with ≥50% tall cells (all *TERT* promoter mutations). Of the clinically aggressive cohort, all cases with slides available for review had ≥50% tall cells and 3 (43%) had secondary mutations (all *TERT* promoter mutations).

Conclusions: We found that secondary oncogenic mutations were more frequently identified in tumors with ≥50% tall cells and that clinically aggressive TCVs all had ≥50% tall cells with approaching half harboring secondary oncogenic mutations. Our findings suggest that additional studies are warranted to better define morphologic criteria for TCV.

653 A Potential Pitfall for Hobnail Variant of Papillary Thyroid Carcinoma

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Background: Hobnail variant of papillary thyroid carcinoma (PTC) is an aggressive subtype of PTC. This tumor is defined as having a hobnail cytomorphology with micropapillary or complex papillary architecture comprising >30% of the tumor. Hobnail variant typically harbors a *BRAF* V600E mutation; additionally, the majority have secondary oncogenic mutations that likely contribute to the aggressive biology of these tumors. We evaluated a cohort of PTCs to evaluate for potential mimics of hobnail variant of PTC.

Design: Our database included all consecutively resected PTCs with classical or tall cell morphology from August 2016 to August 2017. We evaluated cases for hobnail cytomorphology (apically located nuclei, prominent nucleoli, increased nuclear to cytoplasmic ratio) and quantitated the percentage of these features within the tumor. We also identified a second small cohort of "true" hobnail variant PTC (all of which pursued an aggressive clinical course or showed tumor dedifferentiation or high grade features). When available, molecular information from targeted next-generation sequencing was recorded.

Results: Of the 97 consecutively resected PTCs with classical or tall cell morphology, 9 (9%) cases showed hobnail cytomorphology in >30% of the tumor and 7 (7%) cases showed hobnail morphology in

10-30% of the tumor. The hobnail cells were predominantly associated with thick, hyalinized, variably edematous fibrovascular cores and appeared to be a form of degenerative atypia. Mitoses numbered at most 1 per 10 HPFs in all cases. Of the 16 cases with a "hobnail-like" morphology, 8 (50%) had molecular data available: 7 cases had a *BRAF* V600E mutation and one had a *BRAF* fusion. Significantly, no putative secondary pathogenic mutations were identified in any of the cases. In the second small cohort of "true" hobnail variant of PTC, the cores lacked the hyalinization and edema seen in cases with a "hobnail-like" morphology. In the areas with hobnail morphology, mitoses numbered up to 3-6 per 10 HPFs. The one case in this second cohort with sequencing data demonstrated a *TERT* promoter mutation in addition to a *BRAF* V600E mutation.

Conclusions: Classical PTC can show degenerative atypia that mimics the cytomorphology of hobnail variant. This pitfall should be taken into consideration before diagnosing hobnail variant of PTC.

654 Outcome of non-invasive encapsulated follicular variant of papillary thyroid carcinoma (NI-EFVPTC) with oncocytic features

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Background: In 2016, NI-EFVPTC was renamed as NIFTP in order to reduce overtreatment of this indolent tumor. However, as the study cohort did not explicitly include tumor with oncocytic features, such lesions are still labelled and staged by some pathologists as FVPTC. It is therefore crucial to evaluate the clinical outcome of oncocytic NI-EFVPTC in order to assist therapeutic decision making.

Design: A stringent clinico-pathologic review was conducted in three tertiary hospitals for patients having oncocytic NI-EFVPTC who did not receive post-operative radioactive iodine (RAI) treatment, did not harbor separate foci of carcinoma and met the histologic criteria of NIFTP. A total of 43 patients fulfilled the study entry criteria.

Results: The oncocytic NI-EFVPTC predominantly affected women (F: M ratio = 2.3:1) and patients in their 50s (median = 55, range: 8 – 82). The median tumor size was 2.5 cm (range: 1.0 – 5.0 cm). There were no distant or lymph node metastases at diagnosis in all patients including all cases (n=13, 30%) with nodal tissue available for microscopic examination. Twenty-one patients (49%) underwent lobectomy alone, while the remaining received total thyroidectomy. No recurrence was observed in the entire cohort (n=43) including all 38 patients with at least 0.5 year of FU (median FU: 5.2 years) and all 35 patients with at least 2 years of FU (median FU: 5.3 years). Among patients with ≥ 5 years of FU, all 20 individuals did not recur with a median FU of 7.5 years (range 5.1 – 20.5 years).

Conclusions: Oncocytic NI-EFVPTC, when stringently selected for, lacks metastasis at presentation and follows an extremely indolent clinical course, even when treated conservatively with lobectomy alone without RAI therapy. Consideration should be given to include oncocytic NI-EFVPTCs as NIFTP in order to avoid overtreatment of these highly indolent tumors.

655 Clinicopathological Study of 32 ACTH-negative Tpit-positive Corticotroph Adenomas

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Background: In the present classification of pituitary adenomas, it is recommended that expressions of transcriptional factors, such as Pit-1 and SF-1, should be investigated as well as pituitary hormones. However, there are some technical difficulties in practicing these immunohistochemical examinations in laboratories. To elucidate clinicopathological features of hormone-negative adenomas and to make sure whether silent ACTH adenomas can be predictable among hormone-negative adenomas without transcriptional factor staining, we identified and investigated Tpit-positive ACTH-negative corticotroph adenomas from our archival cases.

Design: We reviewed 1071 cases of pituitary adenomas operated at Toranomon hospital between 2008 and 2011, which were classified with immunohistochemical stainings of pituitary hormones and transcriptional factors. More than 1% of immunostained cells for pituitary hormones were regarded as positive. ACTH-negative Tpit-positive corticotroph adenomas were investigated by clinicopathological study, histopathological examination, and electron microscopic observation.

Results: We identified 119 cases that were negative for all pituitary hormones, and 32 cases of ACTH-negative Tpit-positive corticotroph adenomas that accounted for 26.9% of hormone-negative adenomas. Thirty-two ACTH-negative Tpit-positive adenomas were all macroadenomas (>1.0cm), including 7 giant adenomas (>4.0cm). All cases were female, except one male case. The mean age of the patient was 53.1years. In comparison with SF-1/ER-positive LH/FSH-negative gonadotroph adenomas, ACTH-negative Tpit-positive adenomas were more likely to have lobulated shape and showed invasion to cavernous sinus (Knosp grade IV).

In HE stains, perivascular pattern and pseudorosette structure without oncocytic change were often seen in Tpit-positive ACTH-negative corticotroph adenomas. The tumor cells showed diffuse nuclear positivity for Tpit, though, in some cases, the expression was fairly weak. In CAM5.2 stains, tumor cells showed characteristic positivity of perinuclear pattern. On electron microscopic examination, "Honeycomb-Golgi" structure was seen in 28 cases.

Conclusions: Tpit-positive ACTH-negative corticotroph adenomas had a characteristic clinical, histological and ultrastructural features compared with hormone-negative gonadotroph adenomas. Thus silent corticotroph adenomas seemed to be almost predictable in hormone-negative adenomas based on their distinct clinical and histopathological findings.

656 NKX6.1: Immunohistochemical (IHC) Analysis in Lung and Pancreatic Neuroendocrine Tumors (NET)

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Background: NKX6.1 is a homeobox transcription factor that is required for the development and regulation of endocrine cells in the pancreas. NKX6.1 expression has been demonstrated in pancreatic and duodenal NETs; however, it has not been studied in lung NETs. We investigated the expression of NKX6.1 in NETs of the lung and compared them with those arising in the pancreas utilizing fine needle aspiration (FNA) cell blocks (CB).

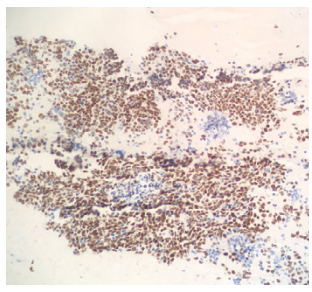
Design: Pulmonary and pancreatic NETs diagnosed by FNA were evaluated. A total of 50 cases were evaluated; 30 were from the lung [8 carcinoid tumors (CT), 6 atypical carcinoids (AC), 11 small cell neuroendocrine carcinomas (SCNEC), and 5 large cell neuroendocrine carcinomas (LCNEC)]. Additionally, 20 were from the pancreas [17 well-differentiated pancreatic neuroendocrine tumors (PanNET) and 3 poorly differentiated pancreatic neuroendocrine carcinomas (PanNEC)]. The FNA CBs were stained with NKX6.1 and Ki-67. Nuclear staining with NKX6.1 was considered positive. All cases in our cohort were positive for synaptophysin IHC staining as confirmation of neuroendocrine differentiation.

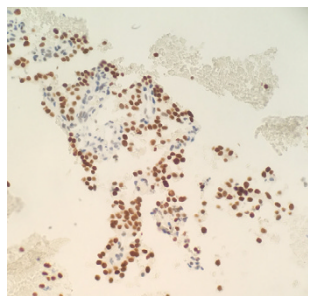
Results: Table 1: IHC staining results

Figure 1: Lung CT with diffuse strong staining (NKX6.1; 20x)

Figure 2: PanNET with crisp nuclear staining (NKX6.1; 40x)

Diagnosis	NKX6.1 (%)	Ki-67 (range %)
CT (n=8)	5/8 (63%)	1-5%
AC (n=6)	5/6 (83%)	2-5%
SCNEC (n=11)	9/11 (82%)	61-95%
LCNEC (n=5)	4/5 (80%)	81-92%
PanNET (n=17)	12/17 (71%)	1-17%
PanNEC (n=3)	3/3 (100%)	20-78%





Conclusions: NKX6.1 is a useful marker in diagnosing lung NETs, which has not been previously demonstrated. The staining is more pronounced in intermediate and high grade NETs and less so in low grade lung NETs such as CT. Pancreatic NETs also show a similar pattern with higher grade tumors demonstrating more pronounced and robust staining. Although NKX6.1 may have limited utility in determining the origin of a NET, it is a useful IHC marker of neuroendocrine differentiation, more notably expressed in higher grade NETs of the lung and pancreas.