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ABSTRACTS

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537 The Role of PD-1 (PDCD1) Promoter Methylation (mPDCD1) in Merkel Cell Carcinoma

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Background: Merkel cell carcinoma (MCC) is an aggressive tumor with a 5-year relative specific survival rates of 41%, depending on the stage. Because of poor prognosis, especially for advanced MCC (stage III-IV sec. AJCC 2018), many efforts have been made to identify prognostic factors, such as advanced age, tumor thickness, tumor-infiltrating lymphocytes (TILs) and MCPyV positivity. Nevertheless, the only prognostic factor independently validated by multiple cohorts was clinical and pathological staging (TNM sec. AJCC 8th/2018).

Design: We collected 69 MCC from 1990 to 2015. DNA methylation level of *PDCD1* promoter was evaluated by quantitative Bisulfite-NGS with MiSEQ platform (Illumina). Bioinformatic analysis was performed in a GalaxyProject environment and using BSPAT-index. The study population was described and compared across subgroups using chi-square test or Fisher's exact, Mann-Whitney and Kruskal-Wallis tests. In the multivariate survival model, methylation was included as the main risk predictor, along with age, sex, clinical stage and all the other variables that in the univariate survival analyses obtained p-values ≤0.25.

Results: Low methylation level of *mPDC1* (*mPDC1*$_{low}$) was found in 42 (60.9%) patients. It was associated with younger age (76 vs 81 years, p=0.042), presence of TILs (78.6%, p<0.001), PD-L1 expression by TILs (54.8%, p=0.041) and PD-L1 expression by both TILs and tumour cells (69.0%, p=0.001). Comparison of clinicopathological features between *mPDC1*$_{low}$ and *mPDC1*$_{high}$ groups are summarized in *Table 1.* At the univariate survival analysis, the only two parameters significantly associated with a higher overall mortality risk were *mPDC1*$_{high}$ (p=0.023) and tumour size >2 cm (p=0.019). The Kaplan-Meier survival curves of these variables are showed in *Figure 1*. In the multivariate survival model (*Table 2*), four variables remained significantly associated to a higher risk of mortality: *mPDC1*$_{high}$ (HR=2.500, p=0.013), clinical stage III-IV (HR=2.660, p=0.009), size >2cm (HR=2.412, p=0.027) and angioinvasion (HR=2.296, p=0.036).

Conclusions: mPDC1 is a valid prognostic parameter in patients affected by MCC. In addition, it identifies two distinct families of MCCs, with several clinicopathological differences.

538 Evaluation of TROP-2, 5-HMC and IDH-1 Immunoreactivity in Anaplastic Thyroid Carcinoma: a Potential Prognostic Marker and Therapeutic Target?

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Disclosures: Kristine Astvatsaturyan: None; Mariza De Peralta-Venturina: None; Jinping Lai: None; Xuemo (Sean) Fan: None

Background: Anaplastic thyroid carcinoma (ATC) is a rare but highly aggressive malignancy responsible for up to 30-40% of thyroid cancer deaths, with a mortality rate that is over 90%, being one of the most lethal human tumors. To date, there are no specific targeted therapies for this subset of patients. Thus, there is an urgent need to identify therapeutic targets for ATC. TROP-2 is a type transmembrane glycoprotein which is over-expressed in some solid tumors and suggested to be a prognostic marker. Because of high expression in various human carcinomas, TROP-2 is a promising novel target for sacituzumab govitecan, antibody-drug conjugate (ADC). Another novel biomarker is 5HMC. Its definitive role in tumor suppressing or promoting modification also opens up new therapeutic targets. Additionally, IDH-1 mutations were significantly associated with increased overall survival in some malignancies. The current study attempts to evaluate immunoexpression of listed tumor biomarkers (TROP-2, 5-HMC, and IDH-1) in ATC to determine their potential utility as diagnostic and prognostic tools, as well as their possible impact on the selection of patients for targeted therapy.

Design: 24 consecutive cases of ATC diagnosed from 2012 to 2018 were retrieved from our database. 9 ATCs (37.5%) occurred de novo and 15 (62.5%) arose from malignant transformation of well differentiated carcinomas: classical variant of papillary thyroid carcinoma (PTC), follicular variant of PTC (FVPTC), and follicular thyroid carcinoma (FTC). Representative sections of formalin fixed paraffin embedded carcinoma samples were stained with TROP-2, 5-HMC, and IDH-1 antibodies. Immunoexpression was evaluated by three pathologists as stain intensity (1+ - 3+) and percentage of positively-stained cells.

Results: When compared with normal thyroid tissue, 5-HMC expression (nuclear stain) was moderately reduced in PTC (both classical and follicular variants) and FTC, and markedly reduced in ATC.

Strong, diffuse TROP-2 expression (>70%, 2-3+) was detected in 10 of 24 ATC cases (42%) and in 6 of 15 (40%) classical PTC and FVPTC. All FTC cases showed lack of TROP-2 expression.

The whole cohort including ATC, classical PTC, FVPTC, FTC and adjacent normal thyroid tissue showed absence of IDH-1 immunoexpression.

Figure 1 - 538

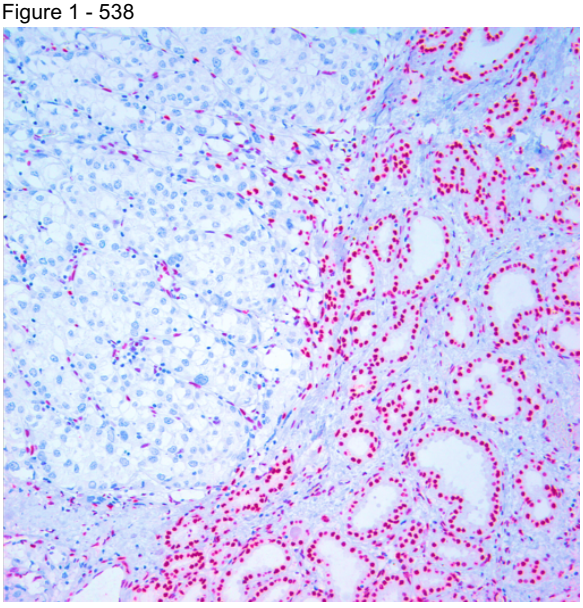
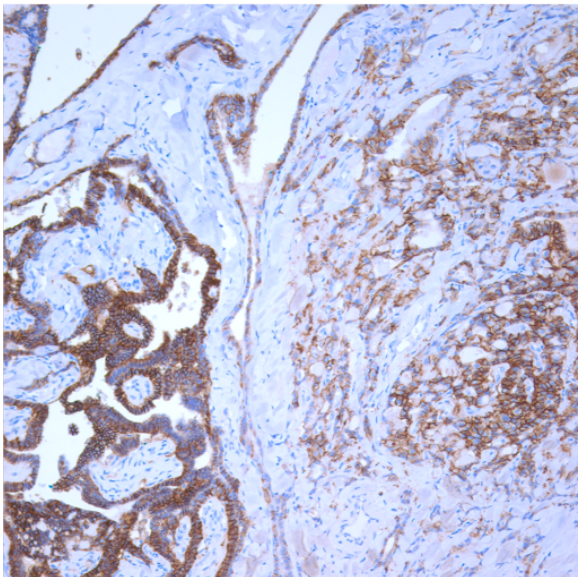


Figure 2 - 538



Conclusions: Significant reduction in 5-HMC immunoexpression and total lack of IDH-1 expression in ATC was observed.

High expression of TROP-2 in some ATCs suggests that these patients may benefit from ADC therapy targeting TROP-2.

539 PAX8 is Expressed in Less Than Half of Anaplastic Thyroid Carcinomas - Multi-Institutional Study Using Monoclonal Antibody MRQ-50

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Disclosures: Yanhua Bai: None; Zhiyan Liu: None; Haiyan Gu: None; Chan Kwon Jung: None; Jen-Fan Hang: None; Wei-An Lai: None; Andrey Bychkov: None

Background: PAX8 is the only thyroid transcription factor consistently maintained expression in anaplastic thyroid carcinoma (ATC) and therefore considered as the accurate specific marker of this rare tumor. Such utility was reported in several small series (PAX8 positivity in 70-80% cases), and those studies were mainly done with polyclonal anti-PAX8, which may show cross-reactivity with PAX5 and other PAX family members. MRQ-50 is the most widely used anti-PAX8 antibody in the routine pathology practice.

Design: To validate the utility of PAX8 as a marker of ATC in a large series, 127 cases of ATC were collected from 5 institutes. Immunostaining of MRQ-50 was performed to detect the expression pattern of PAX8. Hematoxylin and eosin stained sections of all cases were reviewed and were confirmed of the tumor components (epithelioid/squamoid, pleomorphic/giant cell, spindle). Co-existence of differentiated thyroid carcinoma (DTC) was recorded.

Results: PAX8 was expressed in 46.5% of ATC cases. Expression of PAX8 was positively correlated with epithelioid/squamoid components and co-existence of DTC, and adversely correlated with spindle components, but not correlated with other clinicopathological parameters, including age, gender, sampling method, and pleomorphic/giant cell components (Table 1). In the multi-variate logistic analysis, spindle components and co-existence of DTC were the significant factors affecting the PAX8 expression ($P < 0.05$).

Table 1 *The correlation between the PAX8 expression and other clinicopathological parameters in 127 cases of anaplastic thyroid carcinoma*

	PAX8 expression		*P*-value
	negative (53.5%)	positive (46.5%)	
Age			
≤55 years	10	5	0.278
＞55 years	58	54	
Gender			
Female	43	37	0.951
Male	25	22	
Sampling			
Biopsy	41	40	0.380
Surgery	27	19	
Epithelioid/squamoid components			
-	33	17	0.023
+	35	42	
Pleomorphic/giant cell components			
-	42	36	0.931
+	26	23	
Spindle components			
-	19	25	0.001
+	49	34	
Co-existence of DTC			
No	55	38	0.036
Yes	13	21	

DTC, differentiated thyroid carcinoma.

Conclusions: PAX8 reactivity detected by MRQ-50 is much lower than expected. This pitfall should be considered during diagnosis of ATC, especially when there were spindle components and no co-existing DTC.

540 p53 and Rb Immunohistochemistry as Molecular Surrogates Show Distinctive Patterns in Visceral and Cutaneous Poorly Differentiated Neuroendocrine Carcinomas

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Disclosures: Andrew Bellizzi: None

Background: Biallelic *TP53* and *RB1* inactivation is the genetic hallmark of small cell lung cancer. Extrapulmonary visceral (EPV) small cell carcinomas are less well studied, but many are expected to show the same. Merkel cell carcinoma (MCC) includes subsets driven by 1. Merkel cell polyomavirus (MCPyV), clonal integration of which drives tumorigenesis through sequestration of Rb and 2. UV-radiation, leading to *TP53* inactivation. The goal of this study is to describe patterns of p53 and Rb immunohistochemistry (IHC) as protein correlates of these molecular genetic events in poorly differentiated neuroendocrine carcinomas (PDNEC) of the lung (L) and EPV and in MCC.

Design: p53 and Rb IHC was performed on tissue microarrays of 30 L-PDNECs, 21 EPV-PDNECs, and 41 MCCs. p53 IHC was assessed as follows: missense-mutation pattern (diffuse, strong staining obscuring nuclear detail), null pattern (complete absence of protein expression), wild-type pattern (weak staining sometimes with occasional stronger staining cells), indeterminate pattern (staining greater than typical of wild-type and less than typical of missense-mutation pattern). The first two patterns are considered indicative of *TP53* mutation. Rb IHC was scored as intact (any nuclear staining) or lost (complete absence of staining). MCPyV large T antigen (CM2B4) IHC had previously been performed on the MCCs. Fisher's exact test was used with $p<0.05$ considered significant.

Results: p53 mutant-pattern IHC was seen in 76% of L-PDNECs and EPV-PDNECs, which was more frequent than in MCC (39%; p=0.0007). Rb IHC loss was more frequent in L-PDNEC (87%) than in either EPV-PDNEC (55%; p=0.021) or MCC (44%; 0.0004). MCPyV-positive MCCs were more frequently Rb intact and p53 wild type (each 92%; 11/12) than were MCPyV-negative MCCs (Rb intact 36%; 8/22; p=0.0031 and p53 wild type 26%; 6/23; p=0.0003). p53-mutant IHC was more likely to be missense in L-PDNECs and null in EPV-PDNECs (p=0.0026). Detailed data are presented in the Table.

IHC Pattern	L-PDNEC	EPV-PDNEC	MCC
p53 missense	59%	19%	25%
p53 null	17%	57%	14%
p53 mutant (missense + null)	76%	76%	39%
p53 wild type	10%	19%	47%
p53 indeterminate	14%	5%	14%
Rb lost	87%	55%	44%
Rb intact	13%	45%	56%

Conclusions: Our results largely bear out the dogma described in the introduction. The EPV-PDNEC group is the most interesting, with qualitatively different p53 IHC-mutant patterns and less frequent Rb inactivation than in L-PDNEC suggesting that it represents a heterogenous group, including tumors driven by non-small cell carcinoma genetics.

541 Molecular Features of Thyroid Hurthle Cell Lesions: Can pre-surgical Molecular Analysis by ThyroSeq and Afirma differentiate Benign vs. Malignant Hurthle cell nodules?

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Disclosures: Brendan Belovarac: None; Cheng Liu: None; Tamar Brandler: None

Background: Fine needle aspiration (FNA) biopsies are often the first step in the evaluation of thyroid nodules. Hurthle cells are readily identified on cytology specimens, but their significance is challenging to establish. Cytology preparations demonstrating a predominance of Hurthle cells often fall into indeterminate Bethesda categories, as they may represent lesions ranging from hyperplasia to carcinoma. Molecular tests, including ThyroSeq and Afirma, have been developed to aid in the pretest assessment of risk of malignancy. The literature elucidating the molecular profile of Hurthle cell lesions, particularly malignant lesions, is limited. While research into the molecular alterations in Hurthle lesions has been increasing recently, samples sizes have remained small. Our study comes to add to the limited but growing literature on the molecular profiles of Hurthle cell lesions.

Design: We examined the pathology reports for all cases of Hurthle lesions present within our system between 01/2013 and 09/2018, identifying 82 cases. Demographic data and lesion characteristics were collected. Slides were retrieved and reviewed. Molecular testing results performed on patients' preceding FNA specimens were recorded.

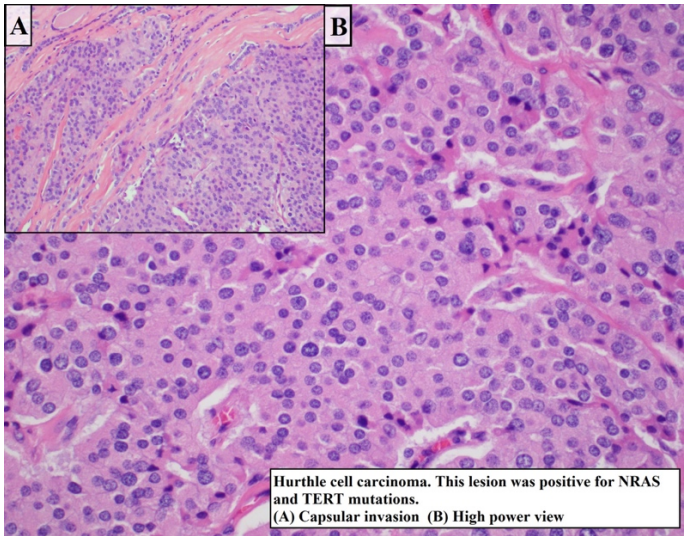
Results: Of the 82 cases, 22 were Hurthle cell carcinomas (26.8%), 47 were Hurthle cell adenomas (57.3%), and 13 consisted of Hurthle cell adenoma with coexistent papillary thyroid carcinomas (HCA+PTC), (15.8%). 55 (67%) of the cases had molecular testing performed on Hurthle cell lesions prior to surgical resection: 31 had Afirma testing results and 26 had ThyroSeq results; two had both tests. Of the 31 Afirma tests sent, 30 were "suspicious" results: 5 (17%) carcinoma, 20 (66%) adenoma and 5 (17%) HCA+PTC. Of the 26 ThyroSeq tests sent, 22 had genetic alterations identified: 8 (36%) carcinoma, 9 (41%) adenoma, and 5 (22%) HCA+PTC. Specific results identified by ThyroSeq are included in the results table.

Figure 1 - 541

ThyroSeq Molecular Testing Results

	Molecular Alteration	n
Hurthle Cell Adenoma	MET Overexpression	2
	EIF1AX	2
	KRAS	1
	Copy Number Variant	3
	TP53	1
Hurthle Cell Carcinoma	NRAS	4
	TERT	2
	PIK3CA	1
	TP53	2
Hurthle Cell Adenoma with Coexistent Papillary Carcinoma	KRAS (within adenoma)	1
	DICER1 (within adenoma)	1
	TERT (within PTC)	1

Figure 2 - 541



Hurthle cell carcinoma. This lesion was positive for NRAS and TERT mutations.
(A) Capsular invasion (B) High power view

Conclusions: Hurthle cell malignancies are uncommon tumors with unique molecular profiles. The literature on molecular alterations of Hurthle lesions is limited, and our study has shown that Hurthle cell adenomas and carcinomas may have different genetic alterations on molecular testing; though there may be molecular overlap between the two (i.e. TP53 mutation). Unlike papillary thyroid carcinoma, no BRAF mutations were found. More comprehensive molecular studies may help in distinguishing benign vs. malignant Hurthle cell lesions and improve the predictive value of molecular testing.

542 An integrated immunohistochemical and molecular approach identifies biologically distinct Gastro EnteroPancreatic - Neuroendocrine Neoplasms (GEP-NENs) with prognostic and predictive relevance

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Background: Clinical outcome of Gastro EnteroPancreatic- Neuroendocrine Neoplasm (GEP-NENs) can be predicted by the integrated evaluation of Ki-67 and morphology. The World Health Organization (WHO) distinguishes GEP-NENs as follows: Well Differentiated (WD) and Ki67 <20% (NET G1-G2), WD and Ki67 >20% (NET G3), Poorly Differentiated and Ki67 >20% (NEC).

Design: In 73 consecutive GEP-NEN patients (***pts***) we applied a new Ki-67 threshold (? and >55%) for further dissecting NEC, and evaluated the prevalence and clinical relevance of gene mutations and PD-L1 immuoreactivity by Next Generation Sequencing (NGS) with Cancer Hot Spot Panel (Thermofisher) and immunohistochemistry (IHC), respectively.

Results: 19 NET G1-G2, 15 NET G3 and 39 NEC were identified. Ki-67 was ?55% (NEC?55) in 9 NEC and >55% in 30 NEC (NEC>55). Overall,34/73 (46%) GEP-NENs showed gene mutations by NGS, mainly represented by TP53 (33%), KRAS (5%) and BRAF (4%) mutations. Gene mutations were significantly enriched in NEC>55 (67,6%) than NEC?55% (14,7%) or in NET (8,8% G1-2, 8,8% G3). PD-L1 expression occurred exclusively in intra-tumoral lymphocytes of NEC>55% (14/73, 19%). Median overall survival (OS) was not reached in NET G1-G2, 4.3 years (yrs) in NET G3, 1.8 yrs in NEC?55 and 0.7 yrs in NEC>55 (p<0.0001). OS was 2.3 yrs in NGS Wild-Type (WT) ***pts*** , 0.7 yrs in ***pts*** with at least one mutation (p<0.0001), 0.8 yrs in PD-L1 positive ***pts*** and 1.7 yrs in PD-L1 negative ***pts*** (p=0.0004). At univariable analysis, NEC vs. NET G3, NEC>55 vs. NEC?55, *TP53* and/or *BRAF* mutated *vs.* WT and PDL1 positive *vs.* negative ***pts*** were statistically associated with poorer cancer specific survival. At multivariable analysis, only our newly proposed classification reached significance (NEC?55 vs NET G3, HR=14.1, 95% CI=2.23-89.8, p=0.005; NEC>55 vs NET G3, HR=25.8; 95% CI=3.93-169.0, p=0.0007).

Conclusions: The modified GEP-NEN classification identifies NEC>55 as a biologically and prognostically distinct subtype, as confirmed by its higher mutational burden, specific TP53/BRAF mutated signature, PDL-1 immunoreactivity and poorer survival. Our data also pave the way for a personalized approach in GEP-NEN patients' treatment.

543 Further Characterization of Classical Papillary Thyroid Carcinoma with "Hobnail-like" Features

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Disclosures: Tiffany Chen: None; Kristine Wong: None; Sara Higgins: None; Brooke Howitt: None; Justine Barletta: None

Background: Hobnail cytomorphology can be seen in true hobnail variant of papillary thyroid carcinoma (PTC) and in classical PTC, which can develop "hobnail-like" features as a form of degenerative or ischemic atypia. We previously reported that classical PTC with hobnail-like features lack findings frequently associated with true hobnail variant (such as increased mitotic activity and high rates of gross extrathyroidal extension, dedifferentiation, and secondary oncogenic mutations). In this study we further characterized classical PTC with hobnail-like features, evaluating their clinical outcome and immunohistochemical profile.

Design: Our cohort includes 16 consecutively resected classical PTC with hobnail-like features comprising at least 10% of the tumor that were resected between 2016 and 2017 and 7 true hobnail variant of PTC (cases from prior abstract). We performed immunohistochemistry for p53 and MIB on these cases. To evaluate the clinical behavior of classical PTC with hobnail-like features, we identified an additional 20 cases that were resected between 2005 and 2007.

Results: All 16 cases of classical PTC with hobnail-like features evaluated by immunohistochemistry had a Ki67 proliferative index less than 5% and showed a wild-type p53 staining pattern. In contrast, 6 (86%) cases of true hobnail variant had a Ki67 proliferative index over 5% (mean 15%), and one case showed diffuse p53 staining. For the 20 classical PTC with hobnail-like features with clinical follow-up data, the mean follow-up time was 11 years (range 7-13 years). Nineteen cases had no evidence of disease (NED) at last follow up, and one case had a lymph node recurrence 2 years after initial resection. In contrast, among the true hobnail variants, 3 patients died of disease (mean survival of 16 months), one developed a local recurrence, and 3 patients had NED at last follow-up (mean follow-up of 22 months).

Conclusions: Classical PTC with hobnail-like features can be a morphologic mimicker of true hobnail variant. We found that classical PTC with hobnail-like features has an indolent clinical course compared to true hobnail variant. Additionally, we showed that evaluation of Ki67 proliferative index can aid in distinguishing these two entities.

544 Follicular Thyroid Neoplasms: Clinicopathologic Features of Atypical Adenomas versus Follicular Carcinomas

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Disclosures: Vincent Cracolici: None; Nicole Cipriani: None

Background: Follicular thyroid neoplasms require thorough histologic evaluation in order to distinguish benign adenomas from follicular thyroid carcinomas (FTC). Capsular (CI) &/or vascular invasion (VI) are necessary to diagnose FTC, which can be further qualified as minimally invasive (CI only), encapsulated angioinvasive (with both CI & VI), and widely invasive. Adenomas may be diagnosed as atypical when there is 1) capsular irregularity but no CI, 2) undermining of endothelium by tumor cells but no VI, 3) solid growth, 4) increased mitoses, or 5) tumor necrosis, without CI or VI. We compare the features of atypical adenomas (AA), indolent (non-metastasizing) FTCs (iFTC), & metastatic FTCs (mFTC).

Design: Our internal pathology archive was surveyed for patients with AA (n=26), iFTC (n=25), or mFTC (n=37). Glass slides &/or pathology reports were used to assess tumor size, encapsulation, oncocytic change, necrosis, CI, VI, solid growth, and mitotic activity. Clinical data were gathered from the electronic medical record.

Results: Mean age at presentation for patients with AA, iFTC, and mFTC was 53.1, 47, and 62.2 years, respectively (p=.0002). Oncocytic change was seen in 13% of iFTC, 40% of AA, and 44% of mFTC (p=.04). As is definitional, CI and/or VI were not identified in any AA (p< .0001). CI was identified in 63% of iFTC and 80% of mFTC (p>0.2). VI was identified in 44% of iFTC and 60% of mFTC (p>0.2). See Table 1 for comprehensive data reporting.

Statistical analysis (ANOVA, Chi-squared testing) performed with Vassar Stats software.

Table 1: Clinicopathologic Features of AA, iFTC, and mFTC

	AA (n=26)	iFTC (n=25)	mFTC (n=37)
Mean age (years, range) *	53.1 (27-81)	47 (16-66)	62.2 (30-87)
Mean follow-up (months, range)	12.9 (0-64)	19.3 (1-67)	55 (0-276)
Mean tumor size (cm, range)	3.3 (0.5-12)	3.7 (1.4-8.2)	3.5 (0.7-11)
Encapsulated (n)	68% (17/25)	76% (19/25)	95% (18/19)
Oncocytic (n)**	40% (10/25)	13% (3/24)	44% (8/18)
Tumor Necrosis (n)	8% (2/25)	17% (4/24)	22% (4/18)
Solid Growth (n)	36% (9/25)	58% (14/24)	65% (11/17)
Mitoses ≥3/10 hpf in solid areas (n)	77% (7/9)	42% (6/14)	72% (8/11)
CI Present (n)***	0/26	63% (15/24)	80% (16/20)
≥4 foci of CI (n)	0	33% (5/15)	31% (5/16)
VI Present (n)***	0/25	44% (11/25)	60% (12/20)
≥4 foci of VI (n)	0	18% (2/11)	33% (4/12)
Capsule entirely evaluated (n)	82% (19/23)	90% (18/20)	55% (11/20)

*p=0.0002

**p=.04

***p=<.0001 overall, iFTC vs mFTC p>0.2

Conclusions: Patients with iFTCs are significantly younger than those with AA or mFTC (p=.0002). Oncocytic change is more common in AA & mFTC than in iFTC (p=.04). As expected by definition, CI and VI are only present in FTCs and not identified in any cases of AA. With regard to mFTC & iFTC, there is no significant difference between the frequency of CI & VI. Similarly, there is no significant difference in the relative percentage of cases of mFTC & iFTC with four or more foci of CI or VI.

Tumor size, encapsulation, necrosis, solid growth, & mitotic activity do not differ between the groups. Features of atypia (necrosis, solid growth, mitoses) in the absence (AA) or presence (iFTC) of invasion does not correlate to metastatic behavior. In the absence of invasion, necrosis, solid growth, or increased mitoses may not be diagnostic of carcinoma. Additionally, the number of foci of CI or VI idenfitied in FTC may not predict metastatic behavior.

545 Are Abortive Papillae in Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) Predictor of BRAFV600E mutation?: Reclassification and Outcome Study

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Background: NIFTP is considered an indolent tumor when rigid morphological criteria are applied. Possible association between the presence of abortive papillae and $BRAF^{V600E}$ mutation has not been studied. $BRAF^{V600E}$ immunostain with the VE1 antibody has been reported to have a sensitivity and specificity close to 100% when compared with molecular assays. The aim of this study is to identify NIFTP by a retrospective review of cases of FVPTC, and to assess the outcome and $BRAF^{V600E}$ expression in NIFTP with and without abortive papillae.

Design: Thyroid tumors diagnosed as FVPTC or NIFTP over a period of 18 years (2000 – 2017) were identified using the laboratory information system. The final pathology reports were reviewed and potential NIFTP were retrieved. The archived slides for these cases were independently reviewed by 2 pathologists. $BRAF^{V600E}$ (clone: VE1) immunostain was performed on representative tumor blocks. The modified current diagnostic criteria (Nikiforov, 2018) were used to define NIFTP. Clinical information including follow up data was obtained from the electronic medical records. Statistical analysis was performed.

Results: Among the 1918 cases with the diagnosis of papillary thyroid carcinoma (PTC), 589 (30.7%) were FVPTC. After the review of final pathology reports, 136 cases of potential NIFTP were identified. After the review of the archived pathology slides, 29 lesions were morphologically reclassified as NIFTP. Four (13.7 %) of these were positive for $BRAF^{V600E}$; thus 25 lesions were finally categorized as NIFTP, representing 4.2 % of the FVPTC and 1.3 % of the PTC. The mean age of the NIFTP patients was 50 years, 87.5 % were females. The mean size of the lesions was 1.4 cm (0.1-4.0 cm). Intranuclear pseudoinclusions were not identified, and abortive papillae were identified in 60 % of NIFTP. No association was found between the presence of abortive papillae and $BRAF^{V600E}$ expression (p=0.3). The average follow up was 70 (28-166) months. No adverse events (recurrence or metastasis) were reported.

Conclusions: NIFTP was an uncommon lesion representing 4.2 % of FVPTC and 1.3 % of PTC. Intranuclear pseudoinclusions were not observed. No correlation was found between the presence of abortive papillae and the $BRAF^{V600E}$ expression in morphological NIFTP. Modification of current morphological criteria to include $BRAF^{V600E}$ immunohistochemistry test may stratify NIFTP with benign outcome. As strictly defined, NIFTP behaved as a benign neoplasm.

546 IGF2 Immunohistochemistry in Neuroendocrine Neoplasms Reveals Frequent Strong Expression in Pheochromocytoma and Paraganglioma: Pitfall and Potentially Useful Diagnostic Adjunct

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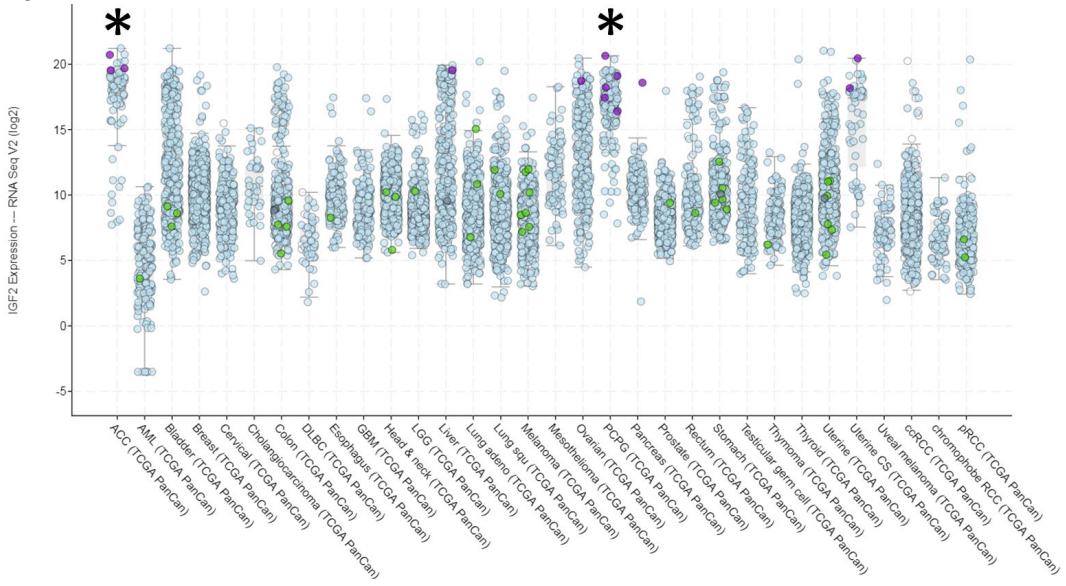
Background: Overexpression of the imprinted gene insulin-like growth factor 2 (IGF2) is a nearly ubiquitous finding in adrenal cortical carcinoma (ACC). Its role was suggested by the clinical association between ACC and Beckwith-Weidemann syndrome and was confirmed 15-years ago through gene expression profiling. Recently, some endocrine pathologists have begun using IGF2 immunohistochemistry (IHC) as a diagnostic marker for ACC in the differential with adrenal cortical adenoma, with strong dot-like/perinuclear staining favoring the former. One of us recently clinically onboarded IGF2 IHC, and there are scant data on IGF2 expression outside of this specific diagnostic context. In reviewing publicly available TCGA gene expression data, along with ACC, we were surprised to see pheochromocytoma/paraganglioma (PHEO/PARA) among the most strongly expressing tumors (Figure 1). We sought to compare IGF2 IHC expression in a cohort of PHEO/PARAs and well- and poorly differentiated neuroendocrine tumors (NETs) and carcinomas (NECs).

Design: We performed IGF2 IHC (clone S1F2; 1:1000) on tissue microarrays (tumors arrayed as triplicate 1 mm cores) of the following tumors: 128 PHEOs, 144 PARAs, 183 NETs (57 pancreas, 45 jejunoileum, 37 medullary thyroid, 32 lung, 7 duodenum, 5 appendix), 94 NECs, and 3 gangliocytic paragangliomas. Expression was assessed for intensity (0-3+) and extent (0-100%), and an H-score was calculated.

Results: PHEOs uniformly (100%) and PARAs nearly uniformly (87%) expressed IGF2, typically presenting as diffuse, strong (rather than dot-like, perinuclear) staining. The remaining tumors occasionally expressed IGF2 (12% of NETs, NECs, and GCPs in aggregate); staining was typically weak and patchy, though rare tumors (3%) demonstrated diffuse, strong staining indistinguishable from that seen in PHEO/PARA (5 pancreatic and 2 lung NETs and 1 lung NEC had H-scores >200). At an H-score threshold of >/=200, IGF2 was 75% sensitive and 97% specific for a diagnosis of PHEO/PARA vs. all other neuroendocrine neoplasms; at an H-score threshold of >/=100, it was 87% sensitive and, again, 97% specific. Detailed expression data are presented in the Table.

Tumor Type	% Positive	Mean (Median) H-score (if positive)
Pheochromocytoma	100%	270 (300)
Paraganglioma	87%	235 (270)
Pancreas NET	19%	129 (145)
Jejunoileum NET	0%	NA
Medullary thyroid carcinoma	14%	9 (7)
Lung NET	16%	124 (10)
Duodenal NET	14%	13 (13)
Appendiceal NET	80%	22 (20)
NEC	7%	45 (7)
Gangliocytic paraganglioma	0%	NA

Figure 1 - 546



Conclusions: In line with the publicly available gene expression profiling data, PHEO/PARAs demonstrate frequent, strong IGF2 expression, recognition of which is imperative to avoid an incorrect diagnosis of ACC. Given these results, we would consider using IGF2 IHC clinically to support a diagnosis of PHEO/PARA over NET/NEC.

547 Immunohistochemistry for Novel Site of Origin Markers in the Distinction of Midgut from Pancreatic Well-Differentiated Neuroendocrine Tumors Identified by Gene Expression Profiling

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Background: Well-differentiated neuroendocrine tumors (NETs) frequently present as metastases of occult origin. We routinely perform site of origin (SOO) immunohistochemistry (IHC) in this setting. Most tumors prove to be of jejunoileal (JI) or pancreatic (P) origin. We employ CDX2 as our first-line midgut marker; while 90% sensitive, it is expressed by 15% of PNETs. We have subsequently added serotonin as a second-line marker, which is more specific but only 80% sensitive. Our first-line PNET markers ISL1 and PAX6 have

a combined 95% sensitivity and are never expressed by JINETs. Our group recently completed gene expression profiling on a cohort of JI and PNETs. The goal of this study was to mine this data to identify new midgut NET markers to translate into clinical IHC tests.

Design: RNAseq data, expressed as FPKM, were available from primary JI and PNETs (20 each). We searched for transcripts strongly and most differentially expressed in JINETs relative to PNETs. We identified SLC18A1 (236 FPKM JINET; 1.6 FPKM PNET) and MEP1A (78 FPKM JINET; 0.014 FPKM PNET) as candidates. We optimized commercially available antibodies to SLC18A1 (polyclonal; ImmunoStar) and MEP1A (rabbit monoclonal; Sino Biological) and performed IHC on a large cohort of well-differentiated tumors from diverse anatomic sites, including 306 NETs (94 jejunoileum, 70 pancreas, 45 lung, 37 medullary thyroid, 24 appendix, 16 stomach, 14 duodenum, 6 rectosigmoid), 22 pheochromocytomas, and 20 paragangliomas. Fisher's exact and Mann-Whitney tests were used with $p<0.05$ considered significant.

Results: SLC18A1 was expressed by 100% of JINETs with mean/median H-scores of 240 (i.e, diffuse, strong staining) and 57% of PNETs with mean/median H-scores of 75/68 (i.e., weak to moderate staining) ($p<0.0001$ for JINET vs PNET frequency and H-score). At an H-score threshold of >/=150, SLC18A1 was 100% sensitive and 97% specific for JINET vs PNET. MEP1A was more frequently expressed in JINET (89%) than PNET (66%) ($p=0.0004$), but H-scores overlapped ($p=0.85$). Detailed expression data are presented in the Table.

Anatomic Site	SLC18A1 % Positive	SLC18A1 Mean (Median) H-score (if positive)	MEP1A % Positive	MEP1A Mean (Median) H-score (if positive)
Jejunoileum	100%	240 (240)	89%	125 (118)
Pancreas	57%	75 (68)	66%	131 (131)
Lung	78%	87 (87)	58%	64 (37)
Medullary Thyroid	86%	55 (50)	16%	20 (17)
Stomach	50%	44 (50)	75%	72 (19)
Duodenum	79%	121 (130)	36%	57 (27)
Appendix	86%	222 (215)	33%	56 (47)
Rectosigmoid	100%	53 (47)	0%	NA
Pheochromocytoma	100%	187 (174)	77%	29 (20)
Paraganglioma	90%	123 (128)	67%	67 (20)

Conclusions: Based on these results, we have added SLC18A1 as a NET SOO IHC marker, with diffuse, strong staining favoring a midgut origin. The protein is better known as VMAT1 and has an established role in enterochromaffin and chromaffin cell biology. We observed strong MEP1A IHC staining in the small intestinal brush border and suspect gene expression data for this marker to partly reflect non-neoplastic contamination.

548 Comparison of Pathological Scores for Predicting Metastasis in Pheocromocitoma and Paraganglioma: a Single-Center Experience

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Background: The Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP) has been proposed for predicting the metastatic potential of pheochromocytoma and paraganglioma (PPGLs) to overcome the limitations of the Pheochromocytoma of the Adrenal Scaled Score (PASS). Since PPGLs metastasize rarely and often late, it is difficult to predict their biological behavior. The aim of the study was to retrospectively compare PASS and GAPP scoring systems in a single-institution case series.

Design: 47 consecutive cases of PPGLs were collected and reviewed, assessing both PASS and GAPP scores. SDHB/SDHA immunohistochemical expression was evaluated. Complete follow-up data were obtained.

Results: The cohort included 17 male and 30 female patients, with a mean age of 53 years. The mean size of the primary tumor was 4 cm. Lymph node metastasis occurred in 8.5% (4/47) of patients, with an average follow-up of 40.7 months. PASS score >=4 was recorded in 29.8% of cases. According to GAPP score, 23.4% (11/47) of cases were classified as well-differentiated (WD), 63.8% (30/47) as moderately-differentiated (MD) and 12.8% (6/47) as poorly-differentiated (PD). WD PPGLs reached a PASS score between 1 and 7, MD PPGLs obtained a PASS score between 1 and 10, and PD PPGLs included tumors that achieved a PASS score between 5 and 14. Based on GAPP score, all WD PPGLs were non-metastatic, while 2 out of 28 (7%) MD and 2 out of 6 (33.3%) PD PPGLs were metastatic. In contrast, 1 out of 14 (7.1%) PPGLs with a PASS <4 and 3 out of 33 (9.1%) PPGLs with a PASS >=4 were metastatic. Statistical analysis revealed that the GAPP scoring system tended to predict metastases ($p = 0.05$), whereas the PASS score did not ($p = 0.82$). Furthermore, the metastatic disease didn't correlate with ki-67 index and mitotic activity. Loss of SDHB staining was found in 10.6% (5/47) of tumors: four

cases were classified as MD PPGLs and one as PD-PPGL with metastatic disease; however, none of these patients had a hereditary paraganglioma-pheochromocytoma syndrome.

Conclusions: In the present cohort, the GAPP scoring system was able to discriminate PPGLs with benign behavior and to predict the metastatic disease, and it certainly represents a valid tool for risk stratification. However, the results of our study highlighted that also other prognostic criteria are required in order to assess the metastatic potential in MD-PPGLs group, and that GAPP should be integrated in a multidisciplinary approach for a better management of patients.

549 Well-Differentiated Neuroendocrine Tumor Site of Origin Immunohistochemistry in Pituitary Adenoma Reveals Frequent Expression of "Pancreatic" Markers and the Biotheranostic Target SSTR2A

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Background: We recently encountered a pituitary carcinoma initially presenting as a liver metastasis, mimicking a well-differentiated neuroendocrine tumor (NET) of occult origin. NETs frequently (10-20%) present as metastases of occult origin, and we routinely employ a panel of site of origin (SOO) immunostains (IHC) in this setting. Although our case had an "uninformative" immunophenotype and strong ACTH expression led to the correct diagnosis, this "near miss" spurred us to study expression of NET SOO IHC in a cohort of pituitary tumors. We also studied two NET biotheranostic markers (SSTR2A, CXCR4) that we routinely employ.

Design: Tissue microarrays were constructed from 66 pituitary adenomas (those with sufficient tumor to array as triplicate 1 mm cores). The presence of any clinical hormone secretion/clinical syndrome was recorded (i.e., ACTH, GH, prolactin, TSH). IHC was performed for ACTH; GH; ISL1, PAX6, PR, ATRX (pancreas markers); CDX2 (midgut); SATB2 (rectum); PrAP (midgut, rectum); OTP (lung); clusterin (non-midgut); SSTR2A; and CXCR4. For each marker, intensity (0-3+) and extent (0-100%) of expression was evaluated, and an H-score was calculated (intensity*extent). Fisher's exact test was used with $p<0.05$ considered significant.

Results: Tumors frequently expressed the pancreatic NET markers ISL1 (47%), PAX6 (26%), and PR (27%); 1 tumor weakly expressed SATB2. No tumor expressed CDX2, PrAP, or OTP. ATRX was uniformly intact. Strong clusterin expression was seen in 88% of tumors. SSTR2A expression was frequent (41%) and was strong (H-score >/=100) and very strong (H-score >/=200) in 21% and 12%, respectively. Although CXCR4 was only expressed by 8% of tumors, it was typically strongly so; all CXCR4-positive tumors were ACTH-expressing ($p=0.0007$). Seven of 8 clusterin-negative tumors were prolactinomas ($p<0.0001$). 58% of tumors expressed ISL1 and/or PAX6, while 65% expressed ISL1 and/or PAX6 and/or PR. Detailed expression data are presented in the Table.

	% Positive (any non-zero H-score)	% Positive (H-score >/=10)	Mean (Median) H-score (if positive)
ACTH	27%	23%	205 (228)
GH	24%	20%	119 (105)
ISL1	47%	35%	101 (80)
PAX6	26%	8%	8 (5)
PR	27%	14%	36 (8)
SATB2	2%	0%	3 (3)
Clusterin	88%	88%	268 (300)
SSTR2A	41%	36%	126 (108)
CXCR4	8%	8%	155 (160)

Conclusions: Pituitary carcinoma presenting as a metastasis of occult origin is apt to be mistaken for a pancreatic NET (based on results of NET SOO IHC). Clusterin-negativity correlates with a diagnosis of prolactinoma. ACTH-expressing tumors could be selectively screened for CXCR4 as a biotheranostic target. SSTR2A is frequently expressed, often strongly so, and somatostatin-analogue therapy, including peptide receptor radionuclide therapy, should be considered in highly expressing, clinically aggressive tumors.

550 Malignant tumors of steroid cell origin: Different names with overlapping morphology, immunoprofile and molecular assessment – A small series

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Background: Steroid cells synthesize steroid hormones and share a common ultrastructure. These cells are found in the adrenal gland (adrenal cortical cells), ovary (Hilus cells) and testis (Leydig cells). Malignant tumors arising from these cells, including adrenal cortical carcinoma (ACC), steroid cell tumor of the ovary (SCTO) and malignant Leydig cell tumor (mLCT) have similar histology, immunoprofile and molecular features and can be a source of potential pitfall.

Design: We searched the database of our tertiary care cancer center (2018) for cases of mLCT and SCTO. The histology, clinicopathologic features, immunoprofile and molecular data were analyzed. H&E and IHC stained slides from all the tumors were reviewed.

Results: There were 3 cases of SCTO and 1 case of mLCT. Pertinent features of the tumors are listed in Table 1. Histologically and immunohistochemically all the 4 tumors were similar to ACC; composed of polygonal cells with moderate amount of eosinophilic cytoplasm and a single round nucleus. Case 3 in addition had foci with clear cytoplasm. Strong nuclear beta-catenin immunopositivity (which may correspond to the presence of CTNNB1 mutation as seen in ACC) was performed in 2 cases and present in both (1 and 4). Molecular profiling (NGS) available in one case (4) confirmed CTNNB1 mutation and CDKN2A/B loss.

Case	Age (years)	Sex	Presenting Features	Metastases	Immunoreactivity	Follow up (months)
SCTO (1)	76	F	Incidental finding in endometrial cancer patient	None	Inhibin, calretinin, Melan A, synaptophysin and β catenin (nuclear)	Alive (2)
SCTO (2)	84	F	Hirsutism, loss of scalp hair	Liver	Inhibin, calretinin, SF1	Alive (15)
SCTO (3)	45	F	Weight gain, hirsutism, irregular cycles	Lung, bones, adrenal gland	SF1, calretinin, inhibin, Melan A	Alive (12)
mLCT (4)	76	M	Left groin mass	Lung, retroperitoneal lymph nodes	Inhibin, calretinin, melan A, synaptophysin, β catenin (nuclear)	Alive (11)

Conclusions: Malignant steroid cell tumors of the gonads are aggressive with widespread metastases. They resemble adrenocortical carcinomas (ACCs) histologically and immunohistochemically. Like ACCs, β catenin nuclear positivity (may correspond to the presence of CTNNB1 mutation) was present in 2 cases. CTNNB1 mutation was confirmed by molecular analysis in one of these two cases (case 4). These tumors can be misdiagnosed as ACCs and neuroendocrine tumors.

551 Paraganglioma: a clinical and pathological study of 161 cases

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Disclosures: Ameer Hamza: None; Pheroze Tamboli: None; Camilo Jimenez: None; Miao Zhang: None

Background: Paragangliomas are rare, their clinicopathologic and molecular features are not thoroughly studied. Loss of Succinate Dehydrogenase B (SDHB) expression has been suggested to be associated with malignant behavior without sufficient data to support. We examined the clinicopathological features, and, prevalence and significance of SDHB loss in paragangliomas.

Design: We identified 161 cases of paragangliomas from 1953 to 2014. These cases were analyzed for family history, clinical presentation, location, size, gross and histologic appearance, SDHB status, overall and recurrence free survival.

Results: 53.4% (n=86) were male and 46.6% (n=75) were female. Median age at diagnosis was 43 years (Range:5-81 years). 55.3% (n=89) were malignant with 51 synchronous and 38 metachronous. 8.2% (n=13) patients had family history of paraganglioma. 17.7% (n=28) cases were incidentally found by imaging studies. 34.8% (n=56) cases were in para-aortic location, 25.5% (n=41) were retroperitoneal, 11.8% (n=19) were mediastinal, and 8.2% (n=13) were in urinary bladder. Mean tumor size was 6.7 cm (SD 3.9 cm). Grossly, tumors were firm, well circumscribed with mottled tan-white to grey cut surfaces. Histologically, tumors were composed of nests of round to oval, small to medium sized cells with prominent nucleoli, granular cytoplasm and minimal cytological atypia. 63.4% (n=26) of retroperitoneal, 63.1% (n=12) of mediastinal, 58.9% (n=33) of para-aortic, and 53.8% (n=7) of urinary bladder paragangliomas were malignant. SDHB mutational status was available in 93 cases. Of these, 14 cases (15%, 7 benign and 7 malignant) had SDHB deletion detected by PCR and/or immunohistochemical stain. 96 patients were alive at the end of study period. In malignant cases, 51 patients were dead and 38 were alive with mean overall survival of 6.5 years (SD 8.1 years) while mean recurrence free survival was 3.4 years (SD 6.7 years).

Conclusions: This is the first large scale study to address the prevalence of SDHB loss in paragangliomas. Our data suggest that more than half of paragangliomas are malignant, with highest rate of malignancy for retroperitoneal paragangliomas. Malignant paragangliomas are aggressive, with mean recurrence free survival of only 3.4 years. Considering the 15% prevalence rate of germline SDHB loss in these patients, pathologists may need to report SDHB mutational status when diagnosing paragangliomas. Finally, we did not find a correlation between SDHB loss and malignant behavior in these tumors.

552 Partial loss of SF-1 expression is frequent in recurrent gonadotroph adenomas and may be a predictive biomarker for recurrence

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Background: Immunohistochemical stains against lineage-specific transcription factors are critical in accurately classifying pituitary adenomas and are recommended in the recent WHO Classification of Endocrine Neoplasms. Gonadotroph adenomas (GA) represent the most common pituitary adenoma surgically resected and show specific expression of steroidogenic factor 1 (SF-1). Tumor recurrence is associated with significant morbidity, however, accurate predictors for aggressive behavior are lacking. We sought to review the staining patterns of SF-1 in recurrent and non-recurrent GA in order to assess features that may predict recurrence.

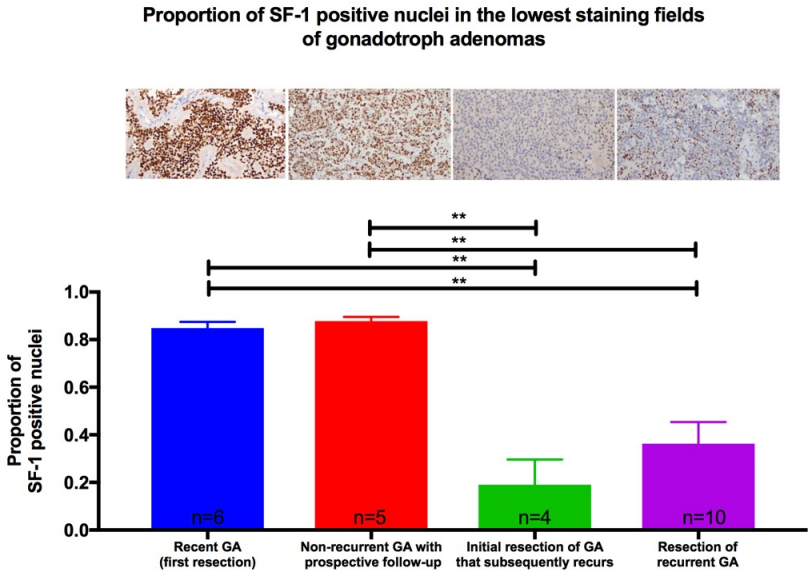
Design: Four groups of GA were examined: 1) Recent first-time resections of GA (n=6), 2) Non-recurrent GA with radiological prospective follow-up times of up to 7 years (n=5), 3) Initial resections of GA that were known to subsequently recur (n=4), and 4) Resections of recurrent GA (n=10), 4 cases of which were the associated recurrence of those in group 3. Formalin fixed paraffin embedded tissue of all 25 GA were immunostained against SF-1. Staining patterns were qualitatively reviewed and the proportion of positive nuclear staining in the lowest staining fields were manually counted out of a total of 1000 cells. Statistical tests were performed using GraphPad Prism v7.0c.

Results: Patient demographics and the mean maximal dimension of the adenoma of each of the four groups are outlined in Table 1. The Ki-67 proliferative indices were available for 18 cases and are also reported in Table 1.

All adenomas demonstrated at least partial staining for SF-1. Strong, diffuse expression of SF-1 was seen in all initial resections of non-recurrent tumors (n=11). Recurrent adenomas, however, demonstrated confluent areas of nuclei that lacked staining in nearly all cases (n=13). Manual counts of the lowest SF-1-positive fields demonstrated a highly significant loss between recurrent and non-recurrent adenoma groups (**P<0.005, Student's t-test) and was independent of age, tumor size and Ki-67 proliferative index.

Group	n	Mean age±SD	Male: Female ratio	Mean maximal dimension of the adenoma (mm)	Mean Ki-67 proliferative index (range)
Recent GA (first resection)	6	51.5±13.8	0.83	28.5	1.7% (0.8- 5%)
Non-recurrent GA with prospective follow-up	5	53.0±12.4	0.4	18.4	4.3% (1.8-6%)
Initial resection of GA that subsequently recurs	4	46.5±12.2	1	30.5	1.7% (1.6- 1.8%)
Resection of recurrent GA	10	60.9±13.1	0.7	N/A	1.4% (0.6- 2.5%)

Figure 1 - 552



Conclusions: Although GA are reported to be diffusely SF-1-positive, confluent absence of nuclear staining was repeatedly seen in recurrent GA and was independent of age, tumor size, and Ki-67 proliferative index. This finding may imply a loss of tumor differentiation in recurrent GA and could represent a useful predictive biomarker for recurrence.

553 Genomic Profile of Columnar Cell Variant of Papillary Thyroid Carcinoma

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Disclosures: Tyler Janovitz: None; Kristine Wong: None; Justine Barletta: None

Background: Columnar cell variant (CCV) is a rare papillary thyroid carcinoma (PTC) subtype. The majority of CCV are invasive, aggressive tumors; however, encapsulated/well-circumscribed CCV have been reported and are associated with a clinical course closer to that of classical PTC. Our aim was to molecularly characterize CCV as the genomic profile of this tumor has not been established.

Design: We retrospectively identified 5 CCV with sufficient material to perform a targeted next-generation sequencing panel of cancer-associated genes. Four cases were histologically aggressive. One case arose in a thyroglossal duct cyst. Although this tumor was predominantly well-circumscribed, it had a focally infiltrative edge with associated lymphatic invasion.

Results: All 5 CCV demonstrated activating *BRAF* alterations, most commonly the *BRAF* V600E mutation (3/5), but also an activating *BRAF* in-frame deletion (1/5), and an *AGK-BRAF* fusion (1/5). Four cases possessed multiple copy number alterations, including recurrent gains and losses on chromosomes 1, 6, 7, 9, and 22. Additional single nucleotide variants were detected in 2 cases, and included an *hTERT* promoter mutation and an inactivating *CDKN2A* alteration. The one case without copy number alterations or secondary pathogenic mutations was the tumor arising in the thyroglossal duct cyst.

Conclusions: We found that CCV have *BRAF* alterations and often have multiple chromosomal gains and losses and secondary oncogenic mutations. The one tumor that lacked secondary oncogenic mutations and copy number alterations lacked overtly aggressive histologic features, suggesting that molecular analysis could potentially help risk stratify CCV.

554 Unusual Inflammatory/Hematological Disorders of the Sellar/Suprasellar Region

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Disclosures: Bette Kleinschmidt-DeMasters: None

Background: The finding of inflammatory/hematological cells isolated to the pituitary gland is uncommon and usually prompts consideration of primary lymphocytic, granulomatous, or necrotizing hypophysitis. Recently, at our tertiary pituitary center we have

encountered 4 exceptions: granulomatosis with polyangiitis (GPA) first diagnosed from a pituitary mass, a pituitary adenoma harboring chronic lymphocytic leukemia (CLL), subacute Rathke cleft cyst (RCC) apoplexy with intense lymphoplasmacytic inflammation due to non-hemorrhagic cyst leakage, and neurosarcoidosis (NS) confined to pituitary stalk/hypothalamic region. We detail these unique patients.

Design: Review of all sellar region/pituitary biopsies 1/1/2018-9/15/2018.

Results: A 31-year-old woman presented with panhypopituitarism and a sellar/suprasellar lesion thought to be pituitary apoplexy; biopsy revealed a necrotizing and granulomatous process without adenoma; stains and polymerase chain reaction for organisms were negative. Subsequently, the lesion spread into optic nerves, cavitary lung lesions were found, and c-ANCA (+1:320) and elevated proteinase 3 was identified; GPA was diagnosed. The CLL found in a gonadotroph adenoma from a 62-year-old man proved re-emergence of his supposedly-quiescent leukemia. While pituitary adenoma is one of the more common central nervous system "host" tumors for tumor-to-tumor metastases, donor tumor is usually a solid organ, rather than hematological, malignancy. Subacute/chronic apoplexy occurred in a 37-year-old woman with onset of headaches, nausea, and vomiting 11 months prior to surgery. Biopsy showed intense lymphoplasmacytic inflammation surrounding fragments of RCC cyst wall with squamous metaplasia (negative for BRAF VE1). No organisms were identified on stains or PCR testing. While hemorrhagic RCC apoplexy has been reported by us (1995), and others**,** non-hemorrhagic hypophysitis as a manifestation of RCC apoplexy suggesting slower cyst leakage is unusual (**J Neurosurg 108:**3–8, 2008). NS occurred in a 42-year-old woman presenting with hypersomnolence. Although disseminated sarcoidosis often affects the sellar region, NS isolated to the CNS is rare (<5%) and as a sole suprasellar mass, extremely rare (6th case).

Figure 1 - 554

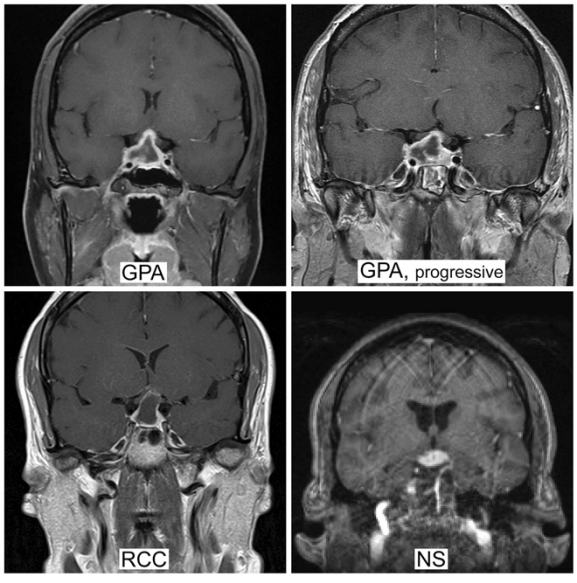
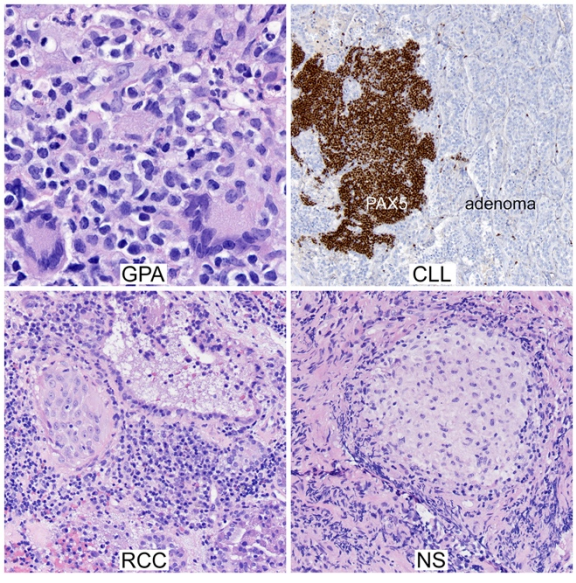


Figure 2 - 554



Conclusions: GPA with first presentation as a pituitary mass and CLL to pituitary adenoma each represents the second reported example; the 2 other cases are rare examples of isolated inflammatory disorders mimicking tumor. All are unique to our 30+ year specialty practice.

555 Multiple cancer risk in rectal neuroendocrine tumors, and it's association with PHLDA3-LOH

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Disclosures: Motohiro Kojima: None; Yu Chen: None; Koji Ikeda: None; Yuichiro Tsukada: None

Background: Rectal neuroendocrine tumors (NETs) are often found as small lesions, which can be indications for endoscopic resection. However, therapeutic strategy in small lesion is not fully established. Rectal NETs are reported to be associated with late recurrences and multiple cancers. On the other hand, management of resectable lesion is not determined. Here we investigated clinicopathological features of 79 rectal NET cases to elucidate risk factors for synchronous LN metastasis, recurrence, and multiple cancers. Recently, we reported that LOH in PHLDA3 was associated with poor prognosis, and double LOH of PHLDA3 and MEN1 frequently occurs in pancreatic NET. Therefore, PHLDA3 and MEN1 LOH in rectal NET were also assessed for associations with these feat

Design: Using pathological data base, we enrolled 79 patients retrospectively diagnosed as rectal NET G1 and G2 according to the World Health Organization (WHO) classification 2010 between January 1, 1999 and March 31, 2014 at National Cancer Center East Hospital.

Results: The distribution of rectal NETs was shown to be male-predominant (73.4%; n = 58); the mean age of the patients was 58.5 ± 12.8 years. Of the 20 patients undergoing surgery, lymph node metastases were found in 10, and the tumor size averaged 9.6 ± 9.1 mm. PHLDA3 and *MEN1* LOH analyses were successful in 55 and 45 cases, and *PHLDA3* and *MEN1* LOH were found in 60.0% (33/55) and 66.6% (30/45) of the cases, respectively. High frequency of double LOH, occurring at both the *PHLDA3* and *MEN1* loci was observed, which suggest that PHLDA3 and MEN1 tumor suppressing pathways both pathways were involved in the development of rectal NETs independently. Although MEN1 and PHLDA3 LOH were not associated with synchronous lymph node metastasis, WHO 2010 classification and vascular invasion were independent risk factor. All three cases with recurrence showed PHLDA3 LOH. And, two of three cases had synchronous lymph node metastasis. Two of three cases recurred over 5-years after the resection. Multiple cancers were detected in 24 of the 79 ca

Conclusions: WHO classification and vascular invasion is important to estimate synchronous lesion in small rectal NETs to assess indication of endoscopic resection. Long-term and systemic management after surgery is recommended especially in the case with lymph node metastasis. Rectal NET with old age and PHLDA3 LOH need for systemic management before and after the treatment.

556 Potential therapeutic Biomarker profiles in Adrenocortical Carcinomas

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Disclosures: Yumi Kojima: None; Miao Zhang: None; Kanishka Sircar: None; Mouhammed Habra: None

Background: Adrenocortical carcinoma (ACC) is an aggressive tumor with less than 50% 5 year survival rate. Current treatment modalities are limited and ineffective. Our preliminary studies indicated that approximately 40% of ACCs are microsatellite Instability-High (MSI-H) tumors and 6% cases are positive for PD-1/PD-L1 by immunohistochemical stains (IHCs). We established a new cohort to validate this frequency and identify other targets to direct therapy.

Design: We constructed a tissue microarray (TMA) with 48 cases of ACCs (24 primary treatment naïve (PTN); 13 primary neoadjuvent treated (PNT); 11 metastasis (M)). Each case was represented by two 1.0 mm cores. 11 adrenal cortical adenomas and 11 normal adrenal tissue were included as controls. Immunohistochemical stains were performed on the TMA with MLH1, PMS2, MSH2, MSH6, PD-1, PD-L1, CD4, CD8, C-MET, and TRK.

Results: There were 33 female and 37 male patients with a mean age of 49 yrs (range: 19-86 yrs). The average tumor size of ACC was 13 cm (range: 3.8-26 cm), significantly larger than the control group (average 3.3 cm; range: 1.0-4.0 cm, $p<0.01$). The Weiss score of ACCs ranged from 4 to 9, significantly higher than the control group (0-2, $p<0.01$). 9 ACC cases (18%) showed loss of at least one MSI marker immunohistochemically (4 PTN, 3 PNT, 2 M); 2 cases (PTN and M) showed loss of two MSI markers (MSH2/MSH6) and 1 case (M) showed loss of all four MSI markers. No loss of MSI markers were seen in the control groups. 2 ACC cases (1 PTN and 1 M) were positive for PD-L1. PD-1/ PD-L1 were negative in the control group. PD-L1 positive lymphocytes were only observed in 1 case of ACC (PNT) while PD-1 positive lymphocytes were observed in 14 ACCs (9 PTN; 3 PNT; 2 M). Staining for CD4/CD8 showed the presence of T cells in ACCs. 2 ACC cases (1 PTN and 1 PNT) were positive for C-Met and 3 cases (1 PTN, 1 PNT, 1 M) were positive for TRK. 21 patients in the ACC group (13 PTN, 5 PNT, 3 M) died of disease with a mean survival of 57 months (range: 7-120 months), while no patient in the control group died of disease (follow up, 60-120 months). A Cox regression analysis found a significant prediction for overall survival when using qKi-67, tumor size, and Weiss score.

Conclusions: This is the first report of using IHCs to address the MSI, PD-1/PDL-1, T cell, CMET, and TRK status in ACCs. We validated that some ACCs are MSI-H tumors with a subset that are positive for C-MET and TRK. These findings warrant new treatment modalities in clinical practice.

557 Prognostic Factors in Merkel Cell Carcinoma of the Skin

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Disclosures: Stefano La Rosa: None; Matteo Bonzini: None; Sofia Asioli: None; Maria Pellilli: None; Roberta Maragliano: None; Silvia Uccella: None; Martina Arrigo: None; Maria Foschini: None; Alberico Motolese: None; Fausto Sessa: None

Background: Merkel cell carcinoma (MCC) of the skin is a rare and aggressive neuroendocrine carcinoma with a reported 5-year overall survival (OS) ranging from 30% to 60%. Although its incidence has largely increased over the last 20 years, specific prognostic factors have not been clearly identified yet.

Design: In the present retrospective study, we analyzed the clinico-pathologic features of 84 cutaneous MCCs with the aim to identify useful markers to stratify patients in different prognostic categories. The prognostic role of several different clinico-pathological factors including age, gender, presence of lymph node metastasis, tumor size and site, depth of tumor invasion, stage, expression of Merkel cell polyomavirus (MCPyV), p63 immunoreactivity, and Ki67 proliferative index (cut-off 55%) has been evaluated using univariate and multivariate analyses.

Results: 50 patients (60%) were men with an average age of 76 years. 32% of cases were at stage I, 27% at stage II, 27% at stage III and 13% at stage IV. The 5-year OS was 52% with 28 patients died of disease during a mean follow-up time of 42 months (range 2-102 months). At univariate analysis, high Ki67 index (>55%) was not associated with prognosis but with recurrence of disease. p63 expression and the lack of MCPyV immunoreactivity were associated with worse prognosis as well as stage IV. At multivariate analysis, only p63 immunoreactivity and stage IV were independent prognostic factors (Table 1).

Table 1. Final model including variable associated with worse prognosis at multivariate analysis.

	OR	95%CI	P value
p63 -	1.00	-	
p63 +	6.77	1.67-27.4	0.007
Female	1.00	-	
Male	3.65	0.84-15.9	0.08
Stage I	1.00	-	
Stage II	0.99	0.16-6.06	0.99
Stage III	2.05	0.45-9.38	0.35
Stage IV	10.5	1.38-79.3	0.02
MCPyV -	1.00	-	
MCPyV +	0.34	0.07-1.67	0.18

Conclusions: p63 immunohistochemistry is strongly suggested in the routine work-up of MCC since it seems the most important prognostic factor together with stage IV. Ki67 is not associated with survival but with recurrence of disease.

558 Investigation of Mismatch Repair Protein, BRAF V600E Mutation, and P53 Expression in Thyroid Anaplastic Carcinoma

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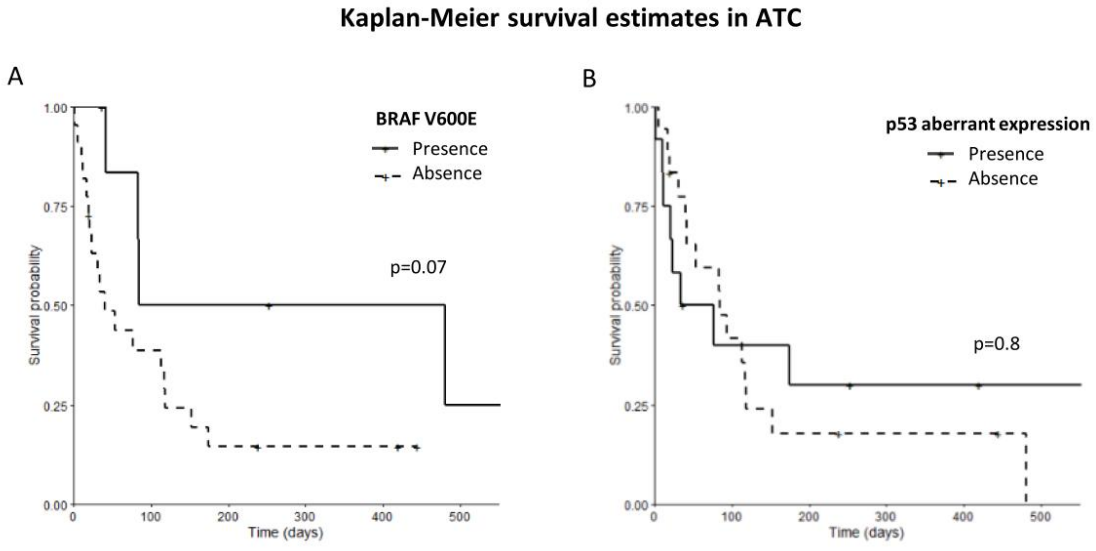
Disclosures: Wei-An Lai: None; Jen-Fan Hang: None

Background: Anaplastic thyroid carcinoma (ATC) is a rare but highly aggressive malignant tumor. There is no effective treatment for ATC to date. Recently, testing for DNA mismatch repair (MMR) deficiency and/or microsatellite instability (MSI) has become increasingly important in malignant tumors due to the emerging role of immune therapy. MMR and MSI status in ATC has not been well investigated. In addition, BRAF V600E is a frequent driver mutation in well-differentiated thyroid carcinoma and p53 mutation is a hallmark of tumor de-differentiation. MMR and MSI status in association with these molecular events are not established. The objective of this study is to investigate MMR status, BRAF V600E mutation, p53 expression and their prognostic effects in ATC.

Design: A retrospective search of our pathology archives for ATC cases from 1997 to 2017 was performed. All pathologic slides were retrieved for morphology review. Tumors with sufficient formalin-fixed paraffin-embedded materials were selected for tissue microarray construction. Immunohistochemical (IHC) stains for MLH1, PMS2, MSH2, MSH6, BRAF V600E (clone VE1), and p53 were performed.

Results: Thirty cases of ATC were identified. The median patient age was 78 years (range 51-91 years). Median survival was 83 days (95% interval 41-152 days). Eight cases showed concomitant ATC and well-differentiated carcinoma, of which 6 were papillary carcinoma and 2 were follicular carcinoma. Of all ATC, only one (3.3%) showed loss of all 4 MMR proteins. The patient is a 75-year-old man and had died 5 days after biopsy due to disease-related cardiopulmonary arrest. The tumor had no BRAF V600E mutation or p53 aberrant expression. BRAF V600E mutation was detected in 7 (23.3%) ATC by IHC. ATC with and without such mutation had a median survival of 283 and 41 days respectively (p=0.07). Aberrant p53 expression was noted in 12 (40%) ATCs (overexpression in 9 and complete loss in 3). Survival analysis found no significant difference between ATC with and without aberrant p53 expression.

Figure 1 - 558



Conclusions: MMR protein deficit is a rare event in ATC and has been seen only in 3.3% of cases in this study. BRAF V600E mutation was noted in 23.3% of ATC and it was associated with advantageous patient survival. Aberrant p53 expression was present in 40% of ATC and it was not related to patient survival. Microsatellite analysis at the DNA level remains the gold standard for detection of a high MSI phenotype. Further molecular characterization of MSI status in ATC will be conducted.

559 Clinicopathologic Features and Prognosis of Papillary Thyroid Carcinoma with High-Grade Features

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Disclosures: Lei Li: None; Kristine Wong: None; Justine Barletta: None

Background: The 2017 Endocrine WHO defines poorly differentiated thyroid carcinoma (PDTC) as a tumor with solid growth, a lack of nuclear features of papillary thyroid carcinoma (PTC), and increased mitotic activity or necrosis. However, it has previously been recognized that PTC with high-grade features, i.e., increased mitotic activity or necrosis, may also pursue an aggressive clinical course. Our aim was to evaluate the histopathologic features, molecular findings, and clinical behavior of PTC with high-grade features.

Design: We retrospectively identified cases that were diagnosed as PTC with high-grade features. These tumors had maintained nuclear features of PTC in the presence of increased mitotic activity ($\geq$ 5 mitoses per 10 HPFs) and/or coagulative necrosis, but lacked findings that would meet WHO criteria for PDTC or anaplastic thyroid carcinoma. Histopathologic characteristics, targeted next generation sequencing results, and clinical outcome data were recorded.

Results: We identified 9 cases of PTC with high-grade features from 5 men and 4 women (mean age of 69 years at diagnosis). The mean tumor size was 4.8 cm, with 6 (67%) cases demonstrating significant extrathyroidal extension (T4a or T4b). All cases had at least 5 mitoses per 10 HPFs (average: 9; range: 5-25), and 2 cases had necrosis. Two cases had a columnar cell morphology, 1 had extensive solid growth, 1 had a tall cell morphology, and 5 had a mixed tall cell, hobnail, and/or columnar cell morphology. Of the 5 cases with molecular data, 3 cases had a *BRAF* V600E mutation, and 1 case had a *BRAF* activating in-frame deletion. A putative driver mutation was not detected in the last case. Additionally, 3 cases had secondary pathogenic mutations, and 4 cases had copy number alterations. Of the 8 patients with at least one-year follow-up, 3 (38%) died of disease (mean survival 19 months), 2 (25%) developed distant metastases, 1 (13%) developed a local recurrence, and 2 (25%) had no evidence of disease at last follow up (mean follow up 21 months).

Conclusions: PTC with high-grade features should be identified as aggressive thyroid tumors based on histopathologic features, molecular characteristics, and clinical outcome. Although high-grade features were identified in PTC subtypes known to pursue an aggressive clinical course, categorizing them as a group may help pathologists identify these tumors and increase clinical awareness of the prognostic implications of the diagnosis.

560 Utility of TROP-2 by RNA In Situ Hybridization in Diagnosing Papillary Thyroid Carcinomas

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Disclosures: Haiyan Liu: None; Jianhui Shi: None; Robert Monroe: *Employee*, Bio-Techne; Fan Lin: None

Background: Our previous study reported that TROP-2, a paralog of epithelial specific cell adhesion molecule (EpCAM)/Trop-1, can serve as a biomarker to identify papillary thyroid carcinomas (PTC) (H Liu et al., Appl Immunohistochem Mol Morphol 2016). However, the anti-TROP-2 antibody (Sc-376181/F5, Santa Cruz Biotechnology) is unstable and produces significant background stains, which limits its utility in daily practice. Recently, a new generation of RNA in situ hybridization (RNA ISH) assay has been developed. In this study, we investigated TROP-2 expression by RNA ISH in a series of normal and neoplastic thyroid tissues.

Design: RNA ISH using a specific RNA probe to TROP-2 (Advanced Cell Diagnostics) was performed on 188 thyroid neoplasms on tissue microarray (TMA) sections, including 100 PTCs (65 classic, 35 follicular variant), 51 follicular adenomas (FA), and 37 follicular carcinomas (FC); in addition, including 15 normal thyroid tissues. The stained tissues were examined using bright-field microscopy, and semi-quantitatively scored as negative (0-1 dots/tumor cell or 2-3 dots/tumor cell in <5% of tumor/targeted cells), 1 + (2-3 dots/ tumor cell in >5% of tumor/targeted cells), 2+ (4-10 dots/tumor cell in >5% of tumor/targeted cells), 3+ (>10 dots/ tumor cell in >50% of tumor/targeted cells), and 4+ (>10 dots/tumor cell in >50% of tumor/targeted cells with clusters of signal).

Results: The staining results are summarized in Table 1. Ninety-eight cases of PTCs (98/100, 98%) showed overexpression of TROP-2 by RNA ISH; 91% (89/98) were diffuse (3+ or 4+) (Figure 1A&B). Of the 51 cases of FA, 3 cases (3/51, 6%) revealed focal expression (2+); on H&E, two cases showed focal PTC morphology (Figures 1C&D). All normal thyroid tissues (n=15) lacked expression of TROP-2.

Table 1. TROP-2 Expression in 188 Cases of Thyroid Neoplasms

Diagnosis (n)	0 (neg.)	1+	2+	3+	4+	Total positive cases (%)
PTC, FV (35)	1	0	3	6	25	97% (34/35)
PTC, classic (65)	1	0	5	11	48	98% (64/65)
FA (51)	48	0	3	0	0	6% (3/51)
FC (37)	36	0	1	0	0	3% (1/37)

PTC: papillary thyroid carcinoma; FV: follicular variant; FA: follicular adenoma; FC: follicular carcinoma

Fig.1. 1A, classic PTC with 3+ positivity; 1B, follicular variant PTC with 4+ positivity; 1C, one of the follicular adenomas shows focal PTC changes, H&E; 1D, the same case showing focal 2+ positivity.

Figure 1 - 560

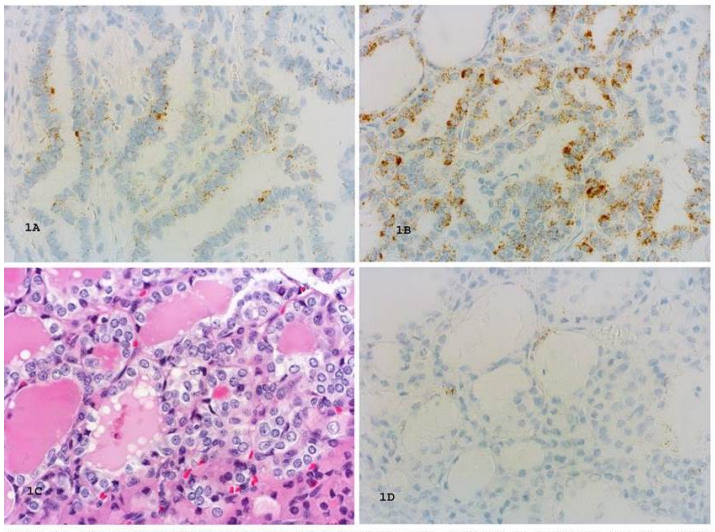

Fig.1. 1A, classic PTC with 3+ positivity; 1B, follicular variant PTC with 4+ positivity; 1C, one of the follicular adenomas shows focal PTC changes, H&E; 1D, the same case showing focal 2+ positivity.

Conclusions: The current study confirms our previous finding that T ROP-2 overexpression can serve as an indicator for PTCs. The findings of rare cases of FA or FC with focal TROP-2 expression and showing features of PTC on H&E raise the possibility that TROP-2 may identify early PTC changes. RNA ISH assay overcomes TROP-2 antibody instability, therefore, can serve as a diagnostic tool for identifying both classic and follicular variant PTCs. Future studies are needed to validate these findings.

561 Ki-67 identifies two prognostic classes of Lung Large Cells Neuroendocrine Carcinoma (LCNEC)

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Disclosures: Massimo Milione: None; Patrick Maisonneuve: None; Giovanni Centonze: None; Luigi Rolli: None; Alessio Pellegrinelli: None; Cinzia Paolino: None; Giovanna Garzone: None; Luisa Bercich: None; Andrea Tironi: None; Elisa Roca: None; Diego Gavezzoli: None; Mauro Roberto Benvenuti: None; Alfredo Berruti: None; Ugo Pastorino: None; Giancarlo Pruneri: None; Carlo Capella: None

Background: The 2015 World Health Organization (WHO) classification defines large cells lung neuroendocrine carcinoma (LCNEC) as Non Small Cells Lung Carcinoma (NSCLC) with neuroendocrine features, >10 mitoses and necrosis. In order to distinguish LCNEC from other NSCLC, WHO recommends to assess p40 and napsin; however, whether the expression of these proteins influences prognosis of LCNEC patients remains unclear. In LCNEC, the prognostic role of Ki-67 has been poorly investigated, although this marker proved to be a powerful prognostic factor for neuroendocrine neoplasms (NENs) of the gastro-entero-pancreatic (GEP) tract including poorly differentiated neuroendocrine carcinoma (NEC). Likewise, several clinicopathologic studies on GEP-NECs showed that, a Ki-67 >55% is a biomarker of poor prognosis in GEP-NEC patients.

Design: In the present study, we interrogated the prognostic relevance of Ki-67 and traditional clinico-pathological characteristics in a well annotated series of LCNEC patients.

Results: In order to identify LCNEC patients, 400 neuroendocrine lung tumors diagnosed between 1975 and 2015 in two referral Italian centers were analyzed. The surgical specimens from all 400 patients were evaluated, in a blinded fashion, by a panel of NEN's experts Pathologist: 70/400 surgical specimens (17,5%) were classified as LCNEC according to WHO 2015 guidelines. In all 70 LCNEC cases, Ki-67, p40, napsin and synaptophysin expression were investigated. The prognostic role of Ki-67 was investigated also in order to search for the best cut-off value in predicting LCNEC patients' survival. Median cancer specific survival (CSS) was 3.1 years in patients with Ki67 ≤55% (n=23) and 1.2 years in those with Ki67 >55% (n=47). At multivariable analysis, after adjustment for center, age, and stage, only Ki-67 (>55% vs ≤55%; HR 8.41, 95% CI 3.70-19.1, p<0.0001) and expression of p40 (present vs absent; HR 3.54, 95% CI 1.34-9.36, p=0.01), but not napsin expression were associated with survival.

Conclusions: In LCNEC, a Ki67 cut-off of 55% identifies two prognostic classes with different prognosis.

562 Validation of Fascin-1 as Predictor of Tumour Invasiveness in Adrenocortical Carcinoma

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Background: The identification of prognostic factors would be beneficial for accurate prediction of survival and treatment selection in adrenocortical cancer (ACC) patients, thereby improving outcome. The purpose of this study was to assess the prognostic value of the actin-bundling protein fascin-1 (FSCN1) in adrenocortical tumours.

Design: A local monocentric series of 37 ACC cases and two independent validation ACC cohorts, from the European Network for the Study of Adrenal Tumours (ENS@T), were studied. FSCN1 expression on ACC specimens was quantified by immunohistochemistry, Western Blot and quantitative RT-PCR analyses. Its prognostic power was assessed by Kaplan-Meier analysis and compared to that of tumour stage, Weiss score and Ki67 labelling index.

Results: FSCN1 immunohistochemical expression proved to be an independent prognostic factor, also refining results obtained with staging and Ki67 labelling index. Kaplan-Meier curves, obtained by stratifying patients into low and high expression levels of FSCN1 transcript, revealed correlation with disease-free (DFS) and overall survival (OS) (DFS: Log Rank p=0.013, HR=5.93[1.19-28.99], p=0.029; OS : Log Rank p=0.019, HR=8.60[0.99-74.20], p=0.049). Consistency of FSCN1 levels in prognostication was confirmed in two independent ACC cohorts. Both FSCN1 and Steroidogenic Factor-1 (SF-1) transcript levels showed a significantly higher expression in ACCs at advanced stages, with at least one of the three Weiss score parameters associated with invasiveness (i.e. sinusoidal, venous and capsular invasion). Moreover, we demonstrated the role of FSCN1 in promoting cell invasion in a human ACC cell line exclusively in the case of increased SF-1 dosage.

Conclusions: These findings show that FSCN1 is a promising independent prognostic marker in ACC and may serve as a potential therapeutic target to block tumour spread.

563 SPOP Mutations are Found in Thyroid Tumors with Unusual Histopathological Features

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Background: The *SPOP* gene encodes an E3 ubiquitin ligase adaptor, which binds to its substrates via the MATH domain. Mutations affecting the MATH domain were reported in prostate and several other cancer types including papillary thyroid carcinoma. The prevalence of *SPOP* mutations in various types of malignant and benign thyroid tumors and histopathological features of thyroid tumors associated with such mutations have not been studied.

Design: We analyzed 317 papillary thyroid carcinomas, 41 follicular carcinomas, 36 Hürthle cell carcinomas, 29 follicular adenomas, 34 Hürthle cell adenomas, 19 poorly differentiated/anaplastic carcinomas and 114 hyperplastic nodules using Sanger sequencing for mutations in exon 2 (P94R) and exon 6 (F133C) of the *SPOP* gene. Positive cases were genotyped for all common molecular alterations found in thyroid cancer by targeted next-generation sequencing.

Results: *SPOP* mutations were identified in 5/317 (1.6%) papillary carcinomas and 2/29 (6.8%) follicular adenomas and in none of the other tumors or hyperplastic nodules studied. All mutations were P94R. Among 5 papillary carcinomas, 3 (60%) were follicular variants of PTC and two could be re-classified as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Three (60%) tumors showed pronounced adipose metaplasia which is rarely seen in thyroid tumors. Among two *SPOP* mutation-positive follicular adenomas, one was follicular adenoma with papillary hyperplasia. Despite pronounced papillary growth, the tumor cells showed no nuclear features of papillary carcinoma. Tumors harboring *SPOP* P94R mutation had no *BRAF*, *RAS*, or other known driver mutations or fusions, suggesting that *SPOP* mutation is a driver event in these thyroid tumors.

Conclusions: Our results indicate that *SPOP* P94R mutations occur in follicular variant PTC and NIFTP and these tumors frequently have pronounced adipose metaplasia. However, *SPOP* mutations are not specific for thyroid cancer and pre-cancer (NIFTP) tumors and can also be found in follicular adenomas, including follicular adenoma with papillary hyperplasia.

564 Pituitary adenomas share a neuroendocrine transcription factor, Insulinoma-associated protein1(INSM1): An immunohistochemial study

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Background: Insulinoma-associated protein1 protein (INSM1) is a transcription factor which promotes neuroendocrine differentiation in the normal and neoplastic cells of various organs such as pituitary, pancreas, gastrointestinal tract, lung, thyroid, central and peripheral nervous systems (AJSP 2018). The study on the pituitary tumors has been very limited. This immunohistochemical study is aimed at to elucidate the expression of INSM1 in the pituitary adenomas and to explore its role in the pituitary differentiation and tumorigenesis.

Design: Total 36 adenomas, 5 somatotroph adenomas: SAs, 5 lactotroph adenomas: LAs, 5 thyrotroph adenomas: TAs, 5 corticotroph adenomas: CAs, 5 gonadotroph adenomas: GAs, 5 null cell (hormone: H-negative, transcription factor: TF-positive) adenomas: NAs, 1 true null cell (H-negative,TF-negative) adenoma: true NA, and 5 cases of pituitary adenomas with typical morphology of well differentiated neuroendocrine tumor(WDNET), were subjected to the immunohistochemistry using anti-INSM1 antibody (Santa Cruz biotechnology,#sc-271408 ,1:300) and LSAB method on the formalin-fixed paraffin embedded(FFPE) sections. The results were interpreted as negative (-), weak (+ positive), strong (++ positive). A normal pituitary gland was also stained similarly.

Results: 30 of 36 cases (83%) of pituitary adenomas were immunohistochemically positive for INSM1 in their nuclei. The staining in each group(WHO 2017) of the adenomas is as follows. SAs: -(3/5), +(2/5), LAs: -(2/5), +(2/5), ++(1/5),TAs: +(3/5), ++(2/5), CAs: +(2/5), ++(3/5), GAs: -(1/5), +(1/5), ++(3/5), NAs: ++(5/5), True NAs: +(1/1). In 5 cases of WDNET, the staining was +(1/5), ++(4/5). In the normal gland, the majority of the hormone producing cells were positive for INSM1 and a small proportion of them were negative for INSM1.

Conclusions: Nuclear localization of INSM1 in high proportion of the pituitary adenomas suggests the role of INSM1 in maintaining the neuroendocrine function of the normal and neoplastic anterior pituitary cells. This role appears to be intensified in the cases of null cell adenomas(NAs) and in the cases of WDNET. The INSM1-negative pituitary adenomas remain to be further investigated. In conclusion, our immunohistochemical study elucidated the pituitary adenomas of various types share a neuroendocrine transcription factor INSM1 and suggests its role in maintaining the neuroendocrine differentiation in both function and morphology.

565 Clinicopathologic features of well-differentiated lung neuroendocrine tumors

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Background: There are controversies in the classification and diagnostic workup of well-differentiated lung neuroendocrine tumors (NETs). We reviewed the clinicopathologic features of a series of these tumors.

Design: Retrospective review of endocrine pathology records from 2013-2018 identified 167 patients (142 resections and 25 biopsies) with lung NETs. Clinicopathologic variables were collected and reviewed. In resections, tumors were classified as Typical (TC) or Atypical Carcinoids (AC) using mitosis- and necrosis-based WHO criteria. For biopsy specimens, immunohistochemical data other than the Ki67 (MIB-1) labeling index (LI) were analyzed.

Results: The mean age was 60.29 years with a female predominance (2.15:1). The 142 resections included 9 with a second tumor; 4 of those and an additional 17 had tumorlets. Among the 102 TC and 49 AC, average tumor size was 2.35 cm. Age, tumor size, and tumor location were not significantly different between TC and AC. Synchronous neuroendocrine cell hyperplasia was more frequent in peripheral (27%) than central (13%) tumors. Vascular invasion (VI) was seen in 9% with a higher frequency in central tumors and in ACs. Thirty-two (24.8%) of 129 patients with available pN status had nodal metastasis originating from 14 (15%) TCs and 18 (47%) ACs. Six (3 TC, 3 AC) of 66 patients with follow-up data had recurrent/metastatic disease. All tumors were positive for chromogranin, synaptophysin, and CAM5.2. TTF-1 (SPT24) was positive in 79% of tumors; negative TTF-1 was more common in central (28%) than peripheral tumors (4%) and in ACs (30%) than TCs (16%). No tumor had diffuse reactivity for mCEA; 35% had focal staining for mCEA. Stains for pulmonary

neuroendocrine hormones included calcitonin, CGRP, and serotonin; positivity for at least one of these was present in 89.7% and was more frequent in peripheral than in central tumors. The mean Ki67 LI was 5.04% in TCs (range: 0.9-10.2) and 11.18% in ACs (range: 3-29.8), 11.62% in tumors with nodal disease and 12.25% in tumors with recurrent disease. Tumors with a Ki67 LI >10% had VI in 30%, whereas those with a Ki67 <5% had VI in 4.5%. Hormone-negative tumors had no VI, lower frequency of nodal spread (8.3%) and absence of recurrent disease compared to hormone-positive tumors.

Conclusions: Lung NETs show different characteristics depending on the tumor location. This series underscores the role of Ki67 LI, hormone expression and VI as important risk modifiers in these tumors.

566 Clinicopathologic Characteristics of Thyroid Nodules Harboring EIF1AX, THADA, or DICER1 Gene Alterations

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Background: Molecular panels used to evaluate thyroid nodules with indeterminate cytology continue to expand and some report uncommon thyroid cancer-associated genes, including EIF1AX, THADA, and DICER1. We describe the clinicopathologic features of our cohort of thyroid nodules with these gene alterations.

Design: Cases with EIF1AX, THADA, or DICER1 alteration were retrieved from our cohort of 360 Bethesda III/IV thyroid nodules evaluated by ThyroSeq v2/v3 since 2014. H&E slides were reviewed and clinical data collected.

Results: ThyroSeq was positive in 134/360 (37%) nodules of which 27 had EIF1AX (17/134, 13%), THADA (9/134, 7%) or DICER1 (1/134, 0.7%) alterations. Cases included 22 women and 5 men, with a mean age of 56 years (range 34-74). In total, 21 patients (78%) underwent surgery and had available histology. Among nodules with EIF1AX alterations, concomitant mutations in RAS, TERT and/or TSHR were frequent (8/17, 47%); and A113_splice was the most common mutation (9/17, 53%). Of 12 operated EIF1AX nodules 11 (92%) were benign (7 hyperplasic nodules (HN) and 4 follicular adenomas (FA)) and 1 (8%), with coexisting NRAS and TERT mutations, was a widely invasive follicular carcinoma (FC) with high-grade features characterized by 2 mitoses per HPF, focal solid growth, but no necrosis. This patient had distant metastases at diagnosis, was treated with radioactive iodine (RAI) and remains alive with stable disease after 27 months of follow-up. All 9 nodules with THADA alterations had (n=7) or were suspected to have (due to overexpression of IGF2BP3, n=2) a THADA/IGF2BP3 fusion. Eight of the 9 THADA nodules were resected: seven (88%) were benign (3 HNs and 4 FAs); and 1 (12%) was a minimally invasive follicular carcinoma with capsular invasion, one focus of angioinvasion and no regional/distant metastasis. This patient did not receive RAI and has no evidence of disease after 24 months follow-up. The resected DICER1 nodule was diagnosed as HN.

Conclusions: In our study most (90%) cytologically indeterminate thyroid nodules with EIF1AX, THADA, or DICER1 alterations proved benign. It is notable that almost half of the resected nodules did not appear neoplastic (clonal) on histologic evaluation. The prevalence of surgical disease (either cancer or NIFTP) was lower than commonly estimated, perhaps in part due to a high diagnostic threshold for NIFTP in our institution. As previously reported, the presence of concomitant EIF1AX, RAS and TERT mutations was associated with a high-risk of malignancy.

567 Tyrosine Hydroxylase is Superior to GATA-3 for the Diagnosis of Pheochromocytoma/Paraganglioma Among Neuroendocrine Neoplasms

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Background: Pheochromocytoma (PHEO) and paraganglioma (PARA) must be distinguished from well-differentiated neuroendocrine tumors (NET). We have typically employed GATA-3 as the positive PHEO/PARA marker in this diagnostic setting. We often observe weak and heterogenous staining, particularly in resection specimens, which we have attributed to delayed and incomplete fixation. Tyrosine hydroxylase (TH) converts L-tyrosine to L-DOPA in the rate limiting step of catecholamine biosynthesis--a hallmark of the sympathoadrenal lineage. Endocrine pathology colleagues have recommended it as a PHEO/PARA marker, though, to our knowledge, it has not been systematically studied in a large cohort of neuroendocrine neoplasms.

Design: We performed GATA-3 (mouse monoclonal L50-823) and TH (mouse monoclonal from ImmunoStar) IHC on tissue microarrays (tumors arrayed as triplicate 1 mm cores) of the following tumors: 131 PHEOs, 150 PARAs (113 head and neck, 31 thoracoabdominal), 58

pancreatic NETs, 46 jejunoileal NETs, and 4 gangliocytic paragangliomas (GCP). IHC was assed for intensity (0-3+) and extent (0-100%) of staining, and an H-score was calculated. Fisher's exact and Mann-Whitney tests were used with $p<0.05$ considered significant.

Results: TH IHC was diffusely, strongly positive in nearly all PHEOs; it was expressed by a subset of PARAs, more frequently in thoracoabdominal than head and neck tumors ($p=0.0020$). When PARAs were positive, they were typically strongly so ($p=0.053$ compared to H-score in PHEOs). Rare NETs were weakly TH-positive and GCPs were negative. Only 21% of PHEOs were GATA-3-positive, with staining typically much weaker than TH ($p<0.0001$). GATA-3 was similarly sensitive to TH in PARA ($p=1$), but, again, staining tended to be much weaker ($p<0.0001$). NETs and GCPs were all GATA-3-negative. Among PARAs, 32 were TH+/GATA-3+, 27 were TH+/GATA-3-, 27 were TH-/GATA-3+, and 61 were TH-/GATA-3-. Thus, performing both markers increased the sensitivity for the diagnosis of PARA from 40 to 59%. Detailed results are presented in the Table.

Tumor Type	GATA-3 Positive	GATA-3 Mean (Median) H-score (if positive)	TH Positive	TH Mean (Median) H-score (if positive)
Pheochromocytoma	21% (27/131)	37 (5)	98% (127/129)	274 (300)
Paraganglioma (all)	39% (59/150)	54 (23)	40% (59/149)	225 (300)
Paraganglioma (head and neck)	39% (44/113)	45 (21)	33% (37/112)	209 (300)
Paraganglioma (thoracoabdominal)	42% (13/31)	90 (85)	65% (20/31)	249 (300)
Pancreatic neuroendocrine tumor	0% (0/58)	NA	12% (7/57)	12 (15)
Jejunoileal neuroendocrine tumor	0% (0/46)	NA	2% (1/46)	5 (5)
Gangliocytic paraganglioma	0% (0/4)	NA	0% (0/3)	NA

Conclusions: TH IHC boasts superior sensitivity to GATA-3 in the diagnosis of PHEO, and it provides a strong, uniform signal. TH and GATA-3 are similarly sensitive for the diagnosis of PARA, though, again, when PARAs are TH-positive, they demonstrate strong staining. TH-negativity in a majority of PARAs, especially in head and neck tumors, suggests they are of non-sympathoadrenal (i.e., parasympathetic) lineage.

568 Distinguishing Parathyromatosis and Parathyroid Neoplasms Utilizing Clinical and Histologic Features

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Background: Parathyromatosis (PTM) is the presence of ectopic parathyroid tissue in the neck & mediastinum thought to be related to prior parathyroid surgery. PTM is difficult to confidently distinguish from atypical adenoma (AA) and parathyroid carcinoma (PTC) on histologic grounds. All often include multiple local structural and biochemical recurrences. However, PTM and AA should not manifest distant metastases. The aim of this study is to evaluate clinical and morphologic features that may differentiate PTM, AA, and PTC.

Design: Cases of PTM, AA, and PTC were identified. The index case was reviewed for the presence of a peripheral fibrous capsule (FC), capsular invasion (CI), intralesional fibrous bands (FB), nuclear atypia (coarse chromatin with nucleoli (CCN) vs random endocrine atypia (REA)), solid growth (SG), necrosis (Nec), soft tissue invasion (infiltrative (STI) vs circumscribed (STC)), and lymphovascular (LVI) or perineural invasion (PNI). Gland size, weight, serum parathyroid hormone (PTH) and calcium (Ca), and disease progression (local or biochemical recurrence (LR) vs distant metastasis (DM)) were recorded. Ki67 proliferation index (KI) was performed using Adsay technique.

Results: 4 PTM, 17 AA, and 6 PTC were included (Table 1). LVI ($p<0.05$) and necrosis were only observed in PTC. CCN, STI, and DM were more likely in PTC ($p<0.05$). CI, REA, and PNI were only seen in PTC and AA. AAs with PNI and eventual DM were likely underdiagnosed PTC. STC was present in all PTM ($p<0.01$). There was no difference in FC, CI, FB, SG, size, weight, PTH, Ca, LR, or KI. There was no difference in KI between cases with (2.98%) and without (3%) recurrence ($p=0.9$).

	FC (p=0.6)	CI (p=0.7)	FB (p=0.4)	CCN (p=0.04)	REA p=0.4	SG (p=0.2)	Nec (p=0.2)	STI (p=0.01)	STC (p<0.01)
PTM	33%	0%	67%	0%	0%	33%	0%	0%	100%
AA	54%	33%	77%	17%	20%	55%	0%	13%	7%
PTC	33%	0%	100%	67%	33%	83%	17%	83%	0%
	LVI (p=0.03)	PNI (p=0.6)	Size (cm, p=0.9)	Weight (gm,p=0.7)	PTH (pg/mL, p=0.9)	Ca (mg/dL, p=0.4)	LR(p=0.5)	DM (p=0.02)	KI (average, p=0.2)
PTM	0%	0%	N/A	N/A	615	13.2	50%	0%	8.2%
AA	0%	8%	2.9	7263	601	11.5	24%	6%	2.8%
PTC	33%	17%	2.8	4399	957	11.8	17%	50%	4.3%

Conclusions: Overlapping clinical and histologic features among PTM, AA, and PTC make definitive diagnosis difficult. Presence of capsule, fibrous bands, solid growth, gland size/weight, serum PTH/Ca, and Ki67 index were not different among groups. Circumscribed soft tissue nodules were present in all PTM. Soft tissue infiltration, capsular invasion, nuclear atypia (random endocrine and coarse chromatin with nucleoli) were only present in PTC or AA. LVI, PNI, and necrosis were only found in lesions that metastasized. Therefore, these features may be most specific for PTC. Close clinical follow-up is warranted for all patients with histologic features suggestive of AA and PTC.

569 Neuroendocrine Tumors of the Minor Duodenal Papilla/Ampulla: Clinico-Pathologic and Immunophenotypic Analysis of 10 Cases

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Background: Tumors of the minor papilla/ampulla (MIPA) region are rare and poorly defined. A variety of epithelial neoplasms have been reported to occur in the MIPA such as adenocarcinomas, intraductal papillary mucinous neoplasms, and neuroendocrine tumors (NETs), including somatostatin (SST)-producing tumors and gangliocytic paragangliomas (GPs). However, unlike their major ampulla counterparts, the literature on MIPA-NETs is so far limited to a few individual case reports; thus, their pathologic features and biologic behavior are not yet well-established.

Design: The aim of this study was to analyze the clinico-pathologic, immunophenotypic and prognostic features of 10 clinically and histologically ascertained MIPA-NETs. Immunoreactions for synaptophysin, chromogranin A, Ki67, SST, gastrin, pancreatic polypeptide, serotonin, MUC1 and type 2A somatostatin receptor (SSTR2A) were performed.

Results: The median age at diagnosis was 58.5 years and six patients were females. Six patients underwent pancreatoduodenectomy, while four had minor ampullectomy. No case was clinically functioning or had evidence of hereditary predisposing syndrome. Median NET size was 1.5 cm (range 0.6-2.5 cm); seven NETs involved the duodenal submucosa and three the muscularis propria. Lymph node metastases were present in three patients. All but one were grade (G) 1; no G3 NET nor NEC was identified. One case was classified as GP. Among the other nine NETs, seven cases expressed SST in >50% of tumor cells and showed tubulo-acinar formation and/or psammoma bodies, while the remaining two NETs had no reactivity for tested hormones. Most (86%) SST-producing NETs showed MUC1 reactivity and lacked SSTR2A membranous expression. No tumor-related death was recorded after a mean follow-up of 56 months.

Conclusions: MIPA-NETs are generally indolent, usually G1, tumors; however, lymph node metastases are detected in about one third of cases. Most (70%) MIPA-NETs have histology, immunophenotype and behavior closely resembling SST-expressing tumors of the major ampulla.

570 Up-regulated Long Noncoding RNAs (lncRNAs) in Anaplastic Thyroid Carcinomas

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Background: Long non-coding RNAs (lncRNAs) participate in transcription and in epigenetic or post-transcriptional regulation of gene expression; they also have roles in epithelial to mesenchymal transition and in carcinogenesis. LncRNAs may also play a role in thyroid tumor progression. We examined a group of thyroid tumors which included papillary thyroid carcinomas (PTCs) and anaplastic thyroid carcinomas (ATCs) to determine the specific lncRNAs that were upregulated during thyroid tumor progression.

Design: An RT^2 Profiler PCR Array Human Cancer Pathway Finder consisting of 84 lncRNAs (Qiagen) and fresh tissues of normal thyroid (NT), PTCs and ATCs with gene expression profiling were used to determine genes up-regulated and down-regulated in ATCs. Two of the most highly up-regulated genes (prostate cancer antigen 3 (PCA 3) and HOTAIRM1) were selected for further studies using a thyroid tissue microarray (TMA) with formalin-fixed paraffin-embedded tissues of normal thyroid (NT, n=10), nodular goiters (NG, n=10), follicular adenoma (FA, n=32), follicular carcinoma (FCA, n=28), papillary thyroid carcinoma (PTC n=28), follicular variant of papillary thyroid carcinoma(FVPTC, n=28), and anaplastic thyroid carcinoma (ATC, n=10). TMA sections were analyzed by in situ hybridization (ISH) using RNAscope technology. (Advanced Cell Diagnostics). The results of ISH analyses were imaged with Vectra imaging technology and quantified with Nuance® and inForm ® software. The TMA analysis was validated by qRT-PCR using FFPE tissues for RNA preparation. Cultured thyroid carcinoma cell lines (n=5) were also used to analyze for lncRNAs by qRT PCR.

Results: There were 31 lncRNAs up-regulated and 6 down-regulated more than two-fold in the ATCS compared to PTCs. We then used a thyroid carcinoma TMA to examine the two most up-regulated lncRNAs: PCA3 and HOTAIRM1. There was increased expression of both lncRNAs in ATCs and PTCs compared to NT after TMA analysis. qRT-PCR analyses showed increased expression of both lncRNAs in ATCS compared to NT and PTCs. Analyses of these lncRNAs from cultured thyroid carcinoma cell lines by qRT-PCR also showed the highest levels of lncRNA expression in ATCs.

Conclusions: The lncRNAs PCA3, and HOTAIRM1 are up-regulated during thyroid tumor development and progression from NT to well differentiated PTCs and ATCs and may function as oncogenes during thyroid tumor progression.

571 Prognostic Significance of Extent of Invasion in Poorly Differentiated Thyroid Carcinoma

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Disclosures: Kristine Wong: None; Justine Barletta: None

Background: Poorly differentiated thyroid carcinoma (PDTC) is defined as a tumor with solid growth, a lack of nuclear features of papillary thyroid carcinoma, and increased mitotic activity or necrosis. Our aim was to evaluate how extent of invasion impacts clinical outcome for cases of PDTC.

Design: We retrospectively identified 47 consecutive cases diagnosed as PDTC that were resected between 2005 and 2018. All cases were reviewed to confirm that the tumors met the 2017 Endocrine WHO criteria for PDTC. Additionally, tumors were categorized as follows: encapsulated with capsular penetration only, encapsulated with focal angioinvasion (<4 foci), encapsulated with extensive angioinvasion (4 or more foci), or widely invasive. Histopathologic characteristics and clinical outcome data were recorded.

Results: Forty-seven cases of PDTC, including 14 oncocytic tumors, were identified from 28 (60%) women and 19 (40%) men (mean age of 57 years at diagnosis). The mean tumor size was 4.3 cm, with T4 disease in 6 (13%) cases. Mitoses numbered 8 per 10 HPFs on average (range: 1-34) and necrosis was present in 21 (45%) cases. Eight (17%) cases were encapsulated with capsular penetration only, 5 (11%) were encapsulated with focal angioinvasion, 18 (38%) were encapsulated with extensive angioinvasion, and 16 (34%) were widely invasive. Of the 39 patients with follow-up data, 7 (18%) died of disease (with a mean survival of 6.5 years), 11 (28%) had distant metastatic disease, and 21 (54%) patients had no evidence of disease (mean follow-up of 5.3 years). The 5-year survival for patients with encapsulated PDTC with capsular invasion only or focal vascular invasion was 100% (n=4). In contrast, the 5-year survival of patients with encapsulated PDTC with extensive angioinvasion and widely invasive PDTC was 77% (n=13) and 43% (n=7), respectively.

Conclusions: Extent of invasion is an important parameter that affects clinical outcome for patients with PDTC. In our cohort, patients with encapsulated PDTC with capsular invasion only or focal vascular invasion had an excellent outcome.

572 Diagnosis of non-invasive follicular thyroid neoplasm with papillary-like nuclear features in thyroid core needle biopsy and its impact on the risk of malignancy

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Disclosures: Ji Won Woo: None; Hee Young Na: None; So Yeon Park: None

Background: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is a recently adopted diagnostic term indicating a neoplasm formerly classified as non-invasive encapsulated follicular variant of papillary thyroid carcinoma due to its indolent clinical behavior. This study aimed to evaluate diagnostic categories of NIFTPs in thyroid core needle biopsy (CNB), and to analyze its impact on the risk of malignancy (ROM).

Design: A total of 2746 consecutive cases of thyroid CNBs which were consecutively diagnosed between 2013 and 2015, were reviewed and classified into six diagnostic categories based on the pathologic reporting system proposed by the Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group, a similar system to Bethesda system for reporting thyroid cytopathology. Diagnostic categories on CNB were compared with final surgical diagnoses, and the ROM in each category was calculated both including and excluding NIFTP from the malignant diagnosis.

Results: Thyroid CNBs yielded 171 non-diagnostic (6.2%), 1054 benign (38.4%), 486 indeterminate (17.7%), 276 follicular neoplasm (10.1%), 101 suspicious for malignancy (3.7%) and 658 malignant lesions (24.0%). Of the 2746 thyroid CNB cases, 963 cases underwent surgical resection. In the resected specimens, 690 cases were revealed as papillary thyroid carcinoma, and 34 cases (4.9%) were re-classified as NIFTP. The CNB diagnoses for NIFTP were follicular neoplasm in 21 cases (61.8%), indeterminate lesion with nuclear atypia in 10 cases (29.4%), indeterminate lesion with architectural atypia in 2 cases (5.9%) and suspicious for malignancy in 1 case (2.9%). On the contrary, the most common CNB diagnosis for conventional papillary thyroid carcinoma was malignant (511 cases, 78.3%) followed by suspicious for malignancy (61 cases, 9.3%). The decrease in ROM after excluding NIFTP from malignant diagnosis was most prominent in follicular neoplasm category, but with marginal statistical significance.

Conclusions: The decrease in the ROM when excluding NIFTP from malignant diagnosis was not significant. In thyroid CNBs, most NIFTPs were diagnosed as follicular neoplasm and indeterminate lesion with nuclear atypia. Thus, it would be possible to separate NIFTP from conventional PTC on thyroid CNBs to guide conservative clinical management for patients with NIFTP.

573 Steroid Receptor Coactivator-1 (SRC-1) Expression in Pheochromocytoma: Clinicopathologic Correlation and Potential Diagnostic Pitfall

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Disclosures: Meng-Jun Xiong: None; Adeboye O. Osunkoya: None

Background: SRC-1 (steroid receptor coactivator-1) is a tyrosine kinase that mediates transcriptional activity. Cell signaling research in animal models of pheochromocytoma (PCT) have shown that SRC-1 is a downstream target of RET and have also suggested that SRC-1 may be involved in hypoxic pathways to PCT tumorigenesis. SRC-1 is used in routine practice as a marker of adrenocortical carcinoma (ACC). SRC-1 expression in human PCT is novel. Thus, we evaluated the correlation between SRC-1 expression and clinicopathological features that may predict malignant behavior and metastasis.

Design: All PCT cases were retrieved from our Urological Pathology database and senior author consult files, 2015-2018. Clinicopathological data was collected. SRC-1 IHC was performed and scored in a step-wise procedure: 1) Nuclear expression 2) Focal or diffuse positivity 3) Intensity of staining >75% (strong) or <25% (weak) of viable tumor cells.

Results: Thirty-eight PCT cases were included (26 female;12 male). Age range was 16-75 years (mean:52 years). In our cohort, >50% of the subset of resected PCTs under the age of 40 had a heritable mutation. These 7 cases included mutations of: RET (n=3), VHL (2), SDHB (1), and ATM and PDGFRA (1). Mean tumor size was 4.7 cm (range:1.5-14.5 cm). Two cases (5%) were malignant with clinical metastasis. About 50% of patients had >1 year of follow-up, ranging up to 16 years. No patients died of disease. All but 1 case showed some degree of SRC-1 expression. All 7 cases with genetic mutations showed positive staining, 86% with a diffuse pattern. All VHL cases had diffuse pattern-strong intensity positivity for SRC-1, while RET cases showed diffuse positivity but ranged in staining intensity. Mean tumor size and PASS scores showed an inverse correlation with SRC-1 expression as follows: focal positivity subset was 6.8 cm (PASS=3.6), diffuse pattern-weak intensity subset was 4.2 cm (PASS=3.5), and diffuse pattern-strong intensity subset was 4.2 cm (PASS=2.7).

Conclusions: SRC-1 in human PCT has never been explored. Diffuse positivity was seen in most of our heritable cases, providing evidence for a putative link between RET and downstream SRC-1 signaling. An inverse relationship was observed between SRC-1

expression and PASS-tumor size, suggesting that SRC-1 phenotype becomes muted with increasing PCT malignancy potential. Given that SRC-1 is often expressed in PCT, one must cautiously evaluate SRC-1 in an adrenal mass in primary or metastatic settings to avoid misdiagnosis as an ACC.

574 The Prognostic Impact of Percentage of Papillae in Unifocal Encapsulated Papillary Thyroid Carcinoma: Implications for Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) Diagnosis

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Background: Since the publication of the consensus statement on noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), two studies have shown that the presence of any papillae may be associated with nodal metastasis, which led to modification of NIFTP criterion from <1% papillae to no true papillae allowed. The aim of this study was to establish the association between architectural patterns and nodal metastases in unifocal encapsulated/well-circumscribed papillary thyroid carcinoma (U-EPTC).

Design: A meticulous clinicopathologic review was conducted in 232 patients harboring U-EPTC operated between 1982 and 2015. The primary outcome was lymph node status at the time of initial surgery.

Results: The distribution of tumor according to percentage of papillae was: 0% papillae - 147 patients (63%), 0.1-0.9% - 15 (5%), 1-9% 6 (3%), 10-24% 6 (3%), 25-49% 5 (2%), and ≥ 50% 53 (23%). In our cohort, 27 patients (12%) had lymph node metastases (N1) at the time of initial resection. The tumors in N1 group contained a significant higher proportion of papillae (85%) compared to the N0 group (14%) (**Figure 1**). Among the 71 tumors with capsular and/or vascular invasion, nodal metastases were only present in tumors with at least 1% of papillae. In noninvasive U-EPTC (n=161), N1 disease was seen only in tumors with ≥10% papillae. In our cohort, 216 patients had follow-up with a median period of 5.7 years (range 0.1-28.1). Three patients (1.5%) had distant metastases, all of which detected at initial presentation. All three tumors displayed 100% follicular growth, and capsular or extensive vascular invasion. There was no locoregional recurrence in the entire cohort.

Figure 1. Risk of lymph node metastasis in unifocal encapsulated papillary thyroid carcinoma according to percentage of papillae (A) and architectural pattern (B).

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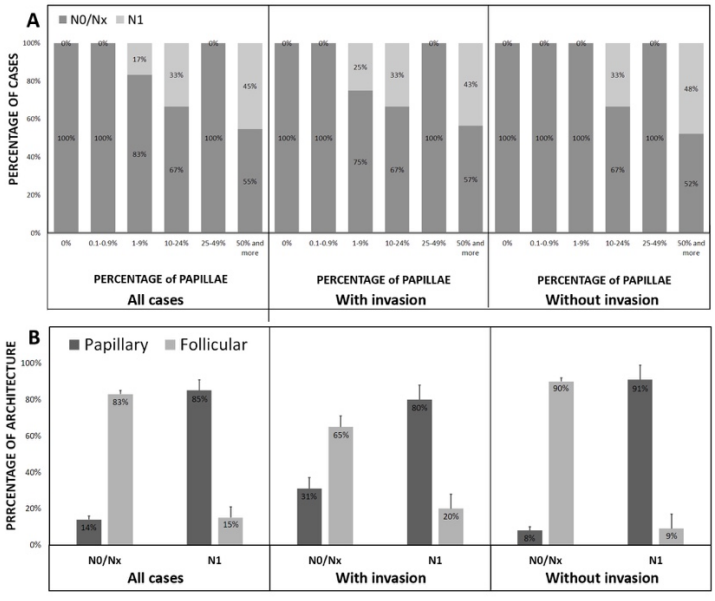

Conclusions: There was a strong correlation between high percentage of papillary growth and risk of nodal metastases in encapsulated papillary thyroid carcinoma, regardless of invasive status. No nodal metastasis or recurrence was observed in noninvasive encapsulated PTC with less than 10% papillae. Consideration should be given to change the percentage of papillary threshold needed to exclude NIFTP.

575 Ki67, p21 and MET as Prognostic Markers in Mediastinal Neuroendocrine Carcinomas

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Background: Mediastinal neuroendocrine carcinomas (MNC) represent approximately 5% of all mediastinal tumors. Unlike neuroendocrine tumors of the lung, prognostic markers for the MNC have not been well characterized in the literature. In the lung neuroendocrine carcinomas, Ki-67 labeling index has emerged as a reliable marker for clinical decision-making. P21 and p27 are cyclin-dependent kinase inhibitors acting at the G1/S cell cycle checkpoint and their expressions are associated with outcomes in various tumors. The MET tyrosine kinase signaling pathway is upregulated in many cancers, including lung cancer. To study the prognostic markers for MNC outcome, we performed Ki67 analysis, p21, p27 and C-MET IHC stains in 31 MNCs and correlated our findings with the clinical outcome data of these patients.

Design: Thirty one mediastinal/thymic neuroendocrine carcinomas (low and intermediate grade) were evaluated. The patient's age, gender, tumor size, mitosis, necrosis, and clinical follow-up data were recorded. Ki67, C-MET, p21 and p27 IHC stains were performed on formalin fixed paraffin embedded tissue sections. Moderate to strong cytoplasmic and/or membrane stain for C-MET in > 50% cells, and >5% nuclear stain for p21 or p27 were considered positive. Ki67 labeling index was obtained in hot spot regions with the highest stain and counting a total of at least 2000 cells by imaging analysis. Prognostic analysis of patient's gender, tumor necrosis, p21, p27 and C-MET expression was performed by Kaplan-Meier survival analysis. Prognostic analysis of age, tumor size, mitosis and Ki67 index was performed by univariate Cox proportional-hazards regression analysis. $P<0.05$ was considered statistically significant.

Results: The survival data of this cohort of MNC cases show significant correlation with tumor size, p21, C-MET and Ki67 index. Ki67 index has the strongest statistical correlation with a P value <0.0006. The patient's gender, age, p27, mitosis and necrosis have no significant statistical correlation with survival. There is no significant statistical correlation between Ki67 index and mitotic count.

Conclusions: Ki67 index, p21 and C-MET are potential prognostic markers for MNCs with C-MET being a potential target of therapy in personalized medicine.

576 Predisposition of Adrenocortical Carcinoma by Loss of Function of Mismatch Repair Genes and The Role of TP53 In Cancer Development

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Background: Adrenocortical carcinoma (ACC) is an uncommon endocrine malignancy with poor prognosis. Recently, aberrance of DNA mismatch repair (MMR) system was identified in ACC, opening a new revenue to investigate ACC tumorigenesis. Here we aims to investigate the genetic predisposition of ACC by MMR deficiency and potential tumorigenesis mechanisms in a Chinese sample cohort.

Design: Forty-two consecutive cases of ACC from 1999 to 2016 were studied. Personal and family cancer history was collected. Immunohistochemistry and next generation sequencing (NGS) for MMR-related genes were performed. The deleterious effect of a novel MSH2 mutation was investigated in Hela cell lines.

Results: Five cases (11.9%) of ACC manifested loss of one or more MMR proteins. Germline mutations of *MSH2* and/or *MSH6* were detected in two cases, including a novel MSH2 (c.2032T>G), whose deleterious effect was confirmed in Hela cells, including resultant loss of MSH6 protein expression. The other one case mimicking lynch syndrome was found that harbored MUTYH germline mutation. Interestingly, *TP53* mutations were found in all five cases with deficient MMR with proportional mutation allele frequencies to that of MMR genes. Aberrant P53 expression was also significantly associated with deficient MMR in the whole sample cohort (p=0.018).

Conclusions: MMR deficient caused by germline mutation is frequent in ACC patients in the Chinese population, indicating the need for Lynch syndrome screening and therapy selection for ACC patients. The close association of *TP53* with MMR gene mutations provide novel insight into ACC tumorigenesis.

577 Parathyroid Neoplasms: Immunohistochemical Characterization and Long Noncoding RNA (lncRNA) Expression

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Disclosures: Qiqi Yu: None; Heather Hardin: None; Ying-Hsia Chu: None; William Rehrauer: None; Ricardo Lloyd: None

Background: Parathyroid adenomas are slow growing benign neuroendocrine neoplasms associated with hypercalcemia, while atypical parathyroid adenomas and parathyroid carcinomas are uncommon tumors and their histologic features may overlap with parathyroid adenomas. LncRNAs participate in transcription and in epigenetic or post-transcriptional regulation of gene expression, and also have a role in carcinogenesis. We analyzed a group of normal, hyperplastic and neoplastic parathyroid lesions to determine the best immunohistochemical markers for these lesions and to determine the role of selected lncRNAs in tumor progression.

Design: A tissue microarray (TMA) consisting of 111 cases of normal parathyroid (n=14), primary hyperplasia (n=15), secondary hyperplasia (n=10), tertiary hyperplasia (n=11), adenomas (n=50), atypical adenomas (n=7) and carcinomas (n=4) was used. Immunohistochemical staining with antibodies against chromogranin A (CGA), synaptophysin (SYN), parathyroid hormone (PH) and insulinoma-associated protein 1 (INSM1), a new transcription factor that is a highly sensitive broad spectrum neuroendocrine marker, was used on the TMA. Expression of lncRNAs including Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1), HOX transcript antisense intergenic RNA (HOTAIR), and Regulator of Reprogramming (ROR) was also analyzed by in situ hybridization (ISH) on the TMA and by RT-PCR. The results of ISH analyses were analyzed with Vectra imaging technology, Nuance® and inForm ® software.

Results: All of the parathyroid tissues were positive for PH, while most cases were positive for CGA (98%). SYN was expressed in only 7 cases (6%) and INMS1 was negative in all cases. Analysis of the three lncRNAs in the normal parathyroid and parathyroid tumors showed that there was significant upregulation of ROR lncRNA in normal parathyroid and parathyroid adenomas as compared to parathyroid carcinomas by ISH ($P<0.05$). MALAT1 and HOTAIR were also expressed in normal, hyperplastic and neoplastic parathyroid tissues, but there were no significant differences between the various tissue types. RT-PCR analysis supported the ISH findings.

Conclusions: Parathyroid tumors can be reliably detected with PH and CGA while SYN and INSM1 are not commonly expressed in parathyroid tissues. ROR may be functioning as a tumor suppressor gene during tumor progression in parathyroid tumors.