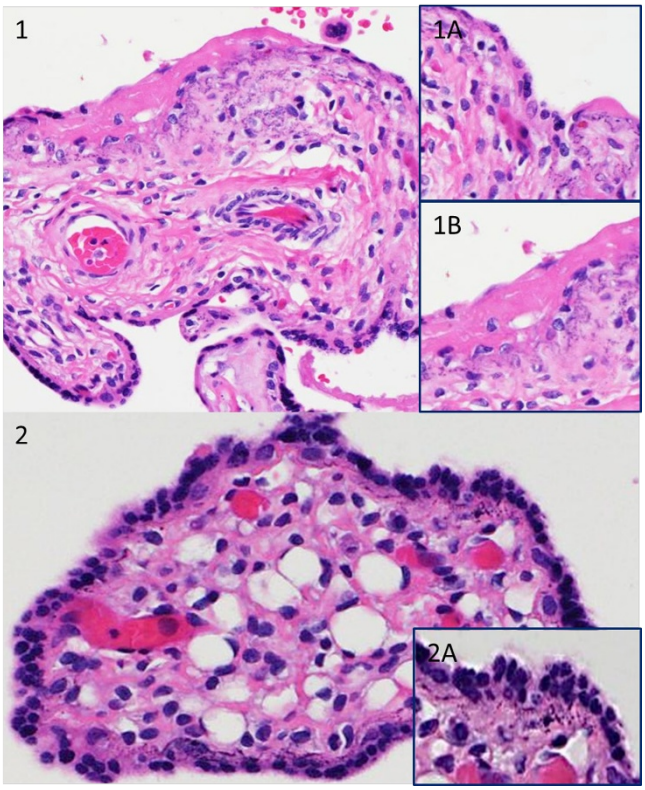
Results: IPMC involved >5% of villi in 11 of 17 placentas (65%) from FD cases, but only 1 of 118 from live births (0.8%, p<0.0001). IPMC involved >10% of villi in 5 of 17 placentas (30%) from FD cases and none from live births (0%, p<0.0001). Clinical data for 11 of the 17 FD cases was available. IPMC in >5% of villi were seen in 3 of the 7 cases where fetus was delivered within 1 day, versus 4 of 4 cases where fetus was retained for >1 days after demise (p<.05). Frequency of IPMC in categories other than fetal demise are shown in table 1.

Percentage of Villi involved by IPMC (%)	Chorioamnionitis (n=19), n(%)	GDM (n=20), n(%)	Post Term Births (n=12), n(%)	IUGR (n=15), n(%)	Chronic Villitis (n=15), n(%)
<1	10(50)	12(60)	5(42)	9(60)	8(53)
1-5	6(30)	6(30)	2(17)	3(20)	2(13)
5-10					1(6)
>10					
None	3	2	3	3	4

Figures 1 and 2: IPMC in the basement membranes of villi with perivillous fibrin and within the perivillous fibrin (1A and 1B). However, IPMC were also present in otherwise seemingly normal villi, without any perivillous fibrin (2A).



Conclusions: Association of IPMC with fetal demise, duration of fetal demise and perivillous fibrin suggests that IPMC may be a response to a local hypoxic environment. Presence of IPMC in more than 10% of villi may be used to support a diagnosis of intrauterine fetal demise in forensic and medico-legal cases.

1256 Immunohistochemical Profile of Pure Endometrial Mucinous Adenocarcinoma

Gloria Zhang, Charles V Biscotti, Tao Wu, Xiangdong Ding, Bin Yang. Cleveland Clinic, Cleveland, OH; Kingmed Diagnostics, Guangzhou, OH.

Background: Most endometrial mucinous carcinomas (EMC) have a major mucinous component (>50%) and minor endometrioid component. Pure EMC occurs rarely. EMC's deceptively bland histopathologic features with low grade nuclear atypia complicate recognition particularly in endometrial biopsy /curetting specimens. We analyzed the clinicopathologic and immunohistochemical features of a series of pure EMC.

Design: Seventeen cases of pure EMC (>95% neoplastic mucinous component), including 8 in-house and 9 consultation cases, were identified from pathology database. These included 17 biopsies/curettings and 10 hysterectomy specimens. 13 cases had tissue blocks available for immunostaining with PAX2, PAX8, ER, PR, p16, p53. Ten cases of benign endometrium and benign endocervix served as controls.

Results: Patients' age ranged from 50 to 81 years (mean 59). Thireen patients including 4 with voluminous mucinous discharge had abnormal uterine bleeding. Histologically, fifteen cases (88%) were FIGO 1 and two cases were FIGO 2. Fourteen cases (82%) had endocervical-type mucinous glands including three cases with a predominant microglandular pattern. Three cases (18%) consisted of either gastric or intestinal-type mucinous glands. All 17 cases had mild to moderate cytologic atypia with minimal or no mitotic activity. Subsequent hysterectomy specimens were available in 10 cases. Six tumors lacked myometrial invasion, 2 tumors invaded 1/3 of the myometrial thickness and 2 tumors had deeper myometrial invasion (85% and 90% respectively). Immunohistochemical study showed consistent loss of PAX2 nuclear staining in 100% cases regardless of endocervical-type or gastrointestinal-type. All cases showed positive PAX8 staining and wild-type p53 staining pattern including those of gastrointestinal type. ER was diffuse (>70%) and strong in eleven cases (85%), focal and moderate in two cases. PR was negative in six cases, focal and moderate in four cases, diffuse and strong (>70%) in three cases. P16 was either negative (5) or focally positive (8).

Conclusions: Pure EMC is diagnostically challenging due to its bland histologic features. Our study demonstrates that loss of PAX2 staining was observed in all cases regardless of endocervical or gastrointestinal cell type. Retaining strong ER expression and variable loss of PR expression occurred in most pure EMC (77%). A panel of immunostains including PAX2, ER and PR can help identify EMC in problematic biopsy/curetting specimens.

1257 Pattern C Invasive Endocervical Adenocarcinomas: Can We Identify the More Aggressive Subset?

Ranran Zhang, Erin E Medlin, Paul S Weisman, Ahmed Al-Niaimi, Aparna Mahajan. University of Wisconsin Hospital and Clinics, Madison, WI.

Background: A recently proposed classification for endocervical adenocarcinoma (EA) has shown that the vast majority of EAs with lymph node metastases (LNM) and/or recurrences display a frankly invasive pattern (pattern C). However, even in pattern C tumors, LNM are seen in less than a quarter of cases (24%) and the factors that predict aggressive behavior in this group remain unclear.

Design: All available resections of usual type EA with negative margins at our institution from 2002-2014 were retrieved. Other histologic subtypes were excluded. Pattern C assignment required agreement by 2 pathologists (AM, PSW). Tumors were stratified as follows: Greatest horizontal extent (GHE) <1 cm vs ≥ 1cm; depth of invasion (DOI) <1 cm vs ≥ 1cm; % cervical wall invasion (CWI) <50% vs ≥50%; presence of lymphovascular invasion (LVI); and presence of microcystic, elongated, and fragmented pattern invasion (MELF). LNM and recurrence data were recorded. Statistical analysis utilized the 2-tailed Fisher's exact test.

Results: 44 cases of EA were available. 14 cases of other histologic subtypes were excluded, leaving 30 cases of usual type EA (15 pattern A or B, 15 pattern C). LN dissection had been performed in all pattern C cases and in 13/15 pattern A or B cases. All LNM (2 cases) and recurrences (2 cases) occurred in pattern C cases. Among pattern C cases, 11/15 (73%) had GHE ≥ 1cm, 6/15 (40%) had DOI ≥ 1cm, 10/15 (67%) had %CWI ≥50%, 3/15 (20%) had LVI, and 10/15 (67%) had MELF. While all 4 cases with LNM and/or recurrences had GHE ≥ 1cm, CWI ≥50%, and MELF, none of these trends reached statistical significance [GHE ≥ 1cm (4/11 vs 0/4, p = 0.52); CWI ≥50% (4/10 vs 0/5, p = 0.23); MELF (4/10 vs 0/5, p = 0.23)].

Conclusions: While limited by its small size, our study demonstrates that large tumor volume (≥ 1cm GHE), invasion into the outer aspect of the cervix (≥50% CWI), and MELF are frequent findings in pattern C tumors with LNM and/or recurrence. Larger studies are required to determine if these features can reliably predict which pattern C tumors are more likely to run an aggressive clinical course.

Head and Neck Pathology

1258 Sinonasal leiomyosarcoma: Analysis of 9 Cases Exploring Their Clinicopathological and Morphological Spectrum with Emphasis on Previous Irradiation and Association with Other Malignancies

Abbas Agaimy, Sarina Muller, Lester DR Thompson. University Hospital of Erlangen, Erlangen, Germany; Woodland Hills Medical Center, Woodland Hills, CA.

Background: Sinonasal tract leiomyosarcoma is exceedingly rare with less than 100 cases reported. Their exact pathogenesis remains unknown and their relationship to retinoblastoma and previous irradiation has not been specifically explored.

Design: Routine and consultation cases were reviewed for histologically and immunohistochemically proven sinonasal leiomyosarcomas. The tumors were tested with antibodies directed against alpha smooth muscle actin, desmin, h-caldesmon, HMB45, Rb1 and MDM2.

Results: The 9 cases included 5 males and 4 females aged 26 to 77 years (median: 48 years). Tumor sites were maxillary sinus (n=4), nasal cavity (n=3) and combined nasal and sinuses (n=2). Three patients had previous irradiation (2 for retinoblastoma, 1 for fibrous dysplasia) and another patient had chemotherapy and stem cell transplantation for Hodgkin lymphoma. All patients with follow-up developed either local recurrences or/and metastases, mainly to lung (time to metastasis: 16-55 months). Histologically, all tumors but one were conventional high-grade leiomyosarcomas indistinguishable from their somatic soft tissue counterparts; one of these had a glycogen-rich clear cell (PEComa-like) morphology. The low-grade primary tumor, showed grade 2 features in the recurrence and grade 3 features in the lung metastases. Two cases showed dedifferentiation to anaplastic pleomorphic (MFH-like) phenotype. Immunohistochemistry (IHC) showed strong diffuse expression for at least two smooth muscle markers and no reactivity for HMB45. None of the cases expressed *MDM2*. RB1 IHC showed inconsistent pattern.

Conclusions: Sinonasal tract leiomyosarcomas are rare aggressive sarcomas that frequently develop in a background of previous cancer therapy, often radiation for retinoblastoma. The frequency of leiomyosarcoma in this particular clinical setting merits further genetic analysis to identify tumors that are *Rb1*-derived. A history of irradiation might have been a confounding factor preventing recognition of hereditary leiomyosarcoma in the setting of retinoblastoma syndrome.

1259 Cutaneous Leishmaniasis Presenting as Facial Midline Lesions: A Series of 15 Cases

Elie Alam, Ossama Abbas, Roger Moukarbel, Ibrahim Khalifeh. American University of Beirut Medical Center, Beirut, Lebanon.

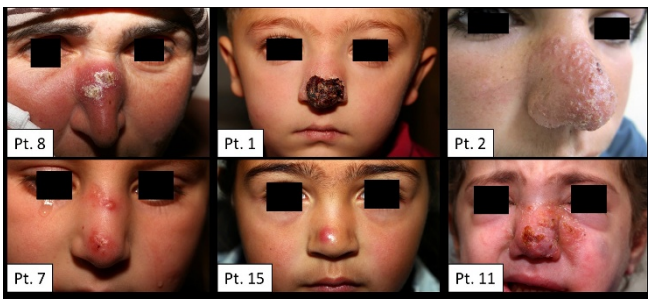
Background: Midline destructive lesions of the face (MDL) have a wide range of etiologies. Cutaneous Leishmaniasis (CL) is rarely reported as a possible cause.

Design: The clinical data, biopsies/scrapings and PCR were collected/performed on patients with solitary CL nose lesions (n=15). Ridley's Pattern (RP) and Parasitic Index (PI) were documented.

Results: Patients' ages ranged from 1 to 60 years including 7 males and 8 females. Lesions duration extend between 1 to 18 months. Clinically, the lesions showed 6 patterns varying from dermal erythematous papulonodular with no epidermal changes to destructive erythematous plaque with massive central hemorrhagic crust.

Patient	Eruption pattern	Favored Diagnosis
Patient 1	EPC	Wegner
Patient 2	Erythematous Plaque with Multiple papular Component	Leishmania
Patient 3	EPC	Leishmania
Patient 4	EPC	Leishmania
Patient 5	SEP	Lupus
Patient 6	CEP	Leishmania
Patient 7	Papulovesicular and Erythematous lesion	Sarcoidosis
Patient 8	CEP	Leishmania
Patient 9	EPC	Leishmania
Patient 10	CEP	Lupus
Patient 11	SEP	Lupus
Patient 12	EPC	Leishmania
Patient 13	CEP	Leishmania
Patient 14	SEP	Lupus
Patient 15	Erythematous Papulonodular with no Epidermal Changes	Sarcoidosis

EPC: Erythematous Plaque with Central Hemorrhagic Crust; SEP: Scaly Erythematous Plaque/ Patch; CEP: Crusted Erythematous Plaque.



The clinical impression ranged from neoplastic to inflammatory processes. RP varied among the cases [RP 3 (n=6), RP 4 (n=3), RP 5 (n=6)]. All cases show low PI [PI 0 (n=7), PI 1 (n=6), PI 2 (n=1), and PI 3 (n=1)]. Higher PI was noted in the pediatric group [average age 24 years for PI 0-1 vs. 6.5 years for PI 2-3]. Molecular speciation showed Leishmania Tropica (n=13) and Leishmania Major (n=2).

Conclusions: Leishmaniasis may cause MDL especially in endemic areas. PCR is instrumental in confirming the diagnosis. MDL caused by CL showed wide spectrum of clinical and microscopic presentation.

1260 Comprehensive Genomic Profiling of Acinic Cell Carcinoma of Salivary Glands

Siraj M Ali, Kyle Fedorchak, Kyle Gowan, Rodolfo Bordoni, Timothy A Jennings, Julia A Elvin, Jo-Anne Vergilio, James Suh, Vincent A Miller, Philip J Stephens, Jeffrey S Ross. Foundation Medicine, Inc., Cambridge, MA; Georgia Cancer Specialists, Marietta, GA; Albany Medical College, Albany, NY.

Background: Acinic cell carcinoma (AciCC) of salivary glands is a rare slow growing malignancy with an overall excellent prognosis, but a tendency for late recurrences and metastases. When AciCC reaches systemic dissemination, conventional treatments are generally ineffective.

Design: From a series of 51,238 total cases, DNA was extracted from 40 microns of FFPE sections from 50 cases of AciCC. Comprehensive genomic profiling (CGP) was performed using a hybrid-capture, adaptor ligation based next generation sequencing assay to a mean coverage depth of 669X. The results were analyzed for all classes of genomic alterations (GA), including base substitutions, insertions and deletions, select rearrangements, and copy number changes. Clinically relevant genomic alterations (CRGA) were defined as those identifying anti-cancer drugs on the market or in registered clinical trials.

Results: The median age of the patients was 60 years (range 14 to 85 years). There were 23 (46%) male and 27 (54%) female patients. All (100%) of AciCC were clinically advanced stages III and IV at the time of sequencing. The primary tumor was used for CGP in 22 (44%) and a biopsy from a wide variety of metastatic sites was used in 28 (56%) of cases. 46 (92%) of AciCC featured GA with a median of 2.28 GA per AciCC. 36 (72%) of AciCC featured CRGA with a median of 1.06 CRGA per sample. Inactivation of cell cycle regulators and tumor suppressor genes were the most common GA with losses in *CDKN2A* in 60%; *CDKN2B* in 40% and *PTEN* in 12% of cases. TP53 mutations were seen in 10% of AciCC. Other GA identified at 4% frequency included *NCOR1*, *ARID2*, *ATM*, *BCOR*, *ETV6*, *FBXW7* and *HRAS*. Among the CRGA, alterations in *NF1*, *PIK3CA* and *BRAF* were found in 1 (2%) AciCC each. The *NF1* and *PIK3CA* GA open consideration for MTOR pathway inhibitors. The single case of AciCC with a *BRAF* GA featured a *BRAF* kinase domain duplication in an advanced parotid AciCC, which developed in a 38 year old woman that did not respond to conventional treatment, but achieved a sustained major clinical response to the anti-BRAF drug regorafenib.

Conclusions: The generally low frequency of GA at 2.28 per tumor reflects the slow growing and relatively indolent nature of these tumors even when they disseminate. Given the examples of responses to targeted therapies for patients with advanced stage AciCC demonstrated here, continued study using CGP for relapsed and metastatic AciCC appears warranted.

1261 A Subset of Ectomesenchymal Chondromyxoid Tumors (ECTs) of the Tongue Shows EWSR1 Rearrangement and Is Genetically Linked to Soft Tissue Myoepithelial Neoplasms: A Study of 9 Cases

Prokopios Argyris, Elizabeth Bilodeau, Denise Trochesset, Stefan E Pambuccian, Stephanie Wetzel, Paul Freedman, Michelle M Dolan, Ioannis Koutlas. University of Minnesota, Minneapolis, MN; University of Pittsburgh, School of Dental Medicine, Pittsburgh, PA; Stony Brook Oral Pathology, Stony Brook, NY; Loyola University Medical Center, Maywood, IL; New York Hospital of Queens, Flushing, NY.

Background: ECT is a rare, benign, intraoral neoplasm of possible neural crest origin showing predilection for the anterior portion of the tongue. According to the WHO classification, ECT belongs to the pathologic spectrum of soft tissue myoepithelioma. However, this classification is based on histopathologic observations and lacks cytogenetic proof. *EWSR1* rearrangement is identified in 45% of skin, soft tissue and bone myoepithelial neoplasms. In addition, 37% of the *EWSR1*-negative myoepithelial tumors display *PLAG1* aberrations. The cytogenetic background of ECT has not been hitherto investigated. We aimed to study the presence of *EWSR1* and *PLAG1* rearrangements in a sizeable cohort of ECTs.

Design: Nine ECTs were evaluated for the occurrence of *EWSR1* and *PLAG1* rearrangements using *EWSR1* (22q12) and *PLAG1* (8q12) break-apart FISH probes in FFPE specimens.

Results: Among the 9 ECT cases tested, 22% (2/9) showed *EWSR1* rearrangement, while the remaining cases were negative for this type of genetic abnormality. A mean hyperploidy of 11.3% (range 0-27.9%) was demonstrated. Four cases had >10% hyperploidy, including one positive for *EWSR1* rearrangement. *PLAG1* rearrangement was not detected in any of the successfully hybridized ECTs (5/9). Furthermore, no correlation was observed between the molecular findings and the ECT microscopic features, such as morphology of the neoplastic cells, presence of atypia, properties of the matrix, and muscle or adipose tissue entrapment.

Conclusions: We identified *EWSR1* rearrangement in 2/9 ECTs of the tongue. These results suggest that a portion of ECTs, at least on a cytogenetic base, is linked to myoepithelioma of the soft parts. The biologic significance of tumor-cell hyperdiploidy in ECT in unknown. However, increase in the DNA content appears to be an important underlying event in ECT. Finally, *PLAG1* aberrations do not appear to participate in the pathogenesis of ECT of the tongue.

1262 HPV Genotyping in Head and Neck Cancer: An Institutional Experience

Aileen Grace P Arriola, Joshua Edwards, Vivianna M Van Deerlin. Hospital of the University of Pennsylvania, Philadelphia, PA.

Background: The incidence of human papilloma virus (HPV)-related head and neck squamous cell carcinoma (HNSCC) is rising in developed countries. Such tumors are biologically, epidemiologically, and clinically distinct from HPV negative (HPV-) HNSCC. Distinguishing HPV positive (HPV+) from HPV- tumors is essential, as HPV+ HNSCC has improved survival. There are 14 known high risk (HR) HPV subtypes. Here, we report the frequency of HPV subtypes in HNSCC diagnosed at our institution and correlate results to histology and p16 IHC status.

Design: HPV genotyping was performed on 80 HNSCC PET or FNA samples using the Roche Linear Array HPV Genotyping (LAG) test, a qualitative test that detects and distinguishes 14 HR and 23 low risk (LR) types. Clinical samples sent for the HR Cervista test, LAG test, and samples used in the HR Cervista validation for PET (2009-2014) were genotyped. Pathology reports were reviewed to determine tumor location, histologic type of SCC, differentiation, and p16 IHC, when available.

Results: Of 80 HNSCC samples (71 patients [50 M, 21 F, median age 58]) genotyped, 81% (n=65) were HPV+ and 19% (n=15) were HPV-. Type 16 was the most prevalent (44/57, 77%). Other HR types included: 33 (4/57, 7%), 35 (4/57, 7%), 18 (1/57, 1.8%), 39 (1/57, 1.8%), and 45 (1/57, 1.8%). Two LR types were detected: type 6, in the trachea of a patient with laryngeal papillomatosis and type 11, co-infected with 16 in a pharyngeal biopsy. Two other cases had co-infections, both involving type 16 (+33 & +35). The sole case with a well-differentiated histology involved LR type 6, with the rest showing moderate-poor differentiation. 95% of HPV+ cases were conventional SCCs, with 4 cases displaying other variants: basaloid (type 16), papillary (type 33), spindle cell/sarcomatoid (type 33), and one resembling an inverted Schneiderian papilloma (type 39). Interestingly, most of the variant histologies were not of type 16. Of the HR types, 16, 33, 18, & 45 mainly involved the oropharynx. Though the number of cases with type 35 & 39 were small, the primary tumor sites were typically non-oropharyngeal: sinonasal for type 39 & oral cavity, naso- and oropharynx for type 35. Finally, 93% (41/44) of p16+ and 22% (2/7) of p16- cases had detectable HPV by the LAG test.

Conclusions: HPV type 16 was the most common subtype seen in HNSCC. Other HR types were detected, which may be associated with variant histologies, though the number of cases in this study was small. Genotype profiles provide useful data for clinical trials and further study into genotype-histology associations may be pursued.

1263 HPV-Induced HNSCC, All Locations Combined: Prevalence, Diagnostic Tests and Prognostic Impact of HPV Status in a Heavy-Smoking French Population

Jeremy Augustin, Samah El Naderi, Helene Pere, Helene Roussel, Cecile Badoual. Georges Pompidou Eureopean Hospital, Paris, France, Metropolitan.

Background: There are few data about Human Papillomavirus (HPV) prevalence and prognosis of patients with HPV-induced HNSCC, all locations combined, in a heavy-smoking population like the French one. Besides, there are no consensual recommendations on which tests one should use to detect, routinely, HPV in formalin-fixed paraffin-embedded specimens. Our goals are to evaluate HPV prevalence for 399 HNSCCs, identify clinicopathologic factors associated with HPV infection, discuss the different HPV testing, and evaluate overall survival of patients with HPV-induced HNSCC.

Design: Clinical, radiological and histopathologic features collected from 399 cases of HNSCCs were reviewed. Tumors were screened for p16 expression by immunohistochemistry (p16 IHC), for HPV DNA by chromogenic in situ hybridization (CISH) and for genomic DNA by PCR. For statistical analyses, PCR was used as gold-standard to determine HPV status.

Results: Population characteristics: mean age 63 years, 79% male, 72% (n=286) of heavy-smokers (> 20 packs-years) and 10% (n=39) of non-smokers. Population included laryngeal (42%), oropharyngeal (35%), hypopharyngeal (13%), oral cavity (8%) and nasopharyngeal cases (2%). 26% (n=104) of HNSCCs were HPV+ and 60% (n=62) of these cases were oropharyngeal. In this cohort, absence of tobacco exposure, oropharyngeal location, lymph node invasion and basaloid histologic subtype were significantly associated with HPV-positive status ($p<0.05$). Interestingly, 6/7 nasopharyngeal carcinomas harbored HPV virus. For oropharyngeal locations, sensibility of p16 IHC, CISH, and combined test "IHC or CISH" were respectively 82%, 73% and 89%. For oropharyngeal locations, overall survival of smoking patients with HPV+ carcinomas (smoking/HPV+) and overall survival of non-smoking patients with HPV-positive carcinomas (non-smoking/HPV+) were better than overall survival of non-smoking patients with HPV- carcinomas (non-smoking/HPV-); (p=0,057 and p=0,014 respectively).

Conclusions: HPV prevalence in French patients with HNSCC is comparable to that reported in American studies. Although French population is heavy-smoking, patients with HPV+ oropharyngeal carcinoma still have better overall survival compared to patients with HPV- one. We propose to use p16 IHC and if doubtful or positive, PCR to determine HPV status, because screening with combined p16 IHC and CISH is much more expensive and give low diagnostic value in routine practice.

1264 Reliability of Tumor Depth and Thickness Measurements in T1 Oral Cancer

Saad Baqai, Norbert Sule, Wei Tan, Gregory Wilding, Mihai Merzianu. Roswell Park Cancer Institute, Buffalo, NY.

Background: Tumor thickness (TT) and depth of invasion (DOI) are important prognosticators of oral squamous cell carcinoma (OSCC) and were proposed to be included in the AJCC TNM staging with cutoff values of 4-5 mm suggested for neck management. Uniform measurement guidelines are lacking, differences using various reference points are unclear and interobserver agreement of TT/DOI measurement in OSCC has not been studied.

Design: TT/DOI of 60 previously untreated pT1 OSCC were independently measured by 3 observers using the same methodology and ocular micrometer (Olympus WHN10x) from same deepest point of invasion (DPI) to the tumor surface (TT), adjacent nondysplastic mucosa (NM) surface (DOIs) and NM basement membrane (DOIb). Keratin layer for TT/DOIb and thickest (NMT) and thinnest (NMt) mucosa was recorded. Mean was used for statistical analysis (SAS, Cary NC) including intraclass correlation coefficient (ICC) and compared with pathology reports (pTT/pDOI).

Results: Sixty OSCC of oral tongue(OT; n=36), floor of mouth(FOM; n=11), lip(L; n =5), buccal(B; n=4), hard palate(HP; n=2) and gingiva(G; n=2) were included. Tumor largest diameter (mm) averaged 10.6 (range, 0.2-20). Mean (SD) TT, DOIs and DOIb (mm) were 4.5(2.9), 4.5(3) and 4.2(3). Keratin layer in TTI and DOIs (mm) was 0.08(0.13) and 0.05(0.03). NM thickness (mm) was 0.9(0.5) overall, 0.5(0.2) in B, 0.7(0.2) in G, 0.6(0.2) in HP, 0.6(0.4) in L, thicker in OT 1.0(0.5) than FOM 0.7(0.4) (NS). ICC among the 3 observers was 0.91, 0.90, 0.89, 0.68 and 0.6 for TT, DOIs, DOIb, NMT and NMt. One observer (C) had consistently higher measurements (Figure 1). Observer experience did not play a role. pTT and/or pDOI was reported in 88% cases: ICC of pTT and mTT was 0.76 and of pDOI and mDOIb was 0.92.

FIGURE 1: MEASUREMENTS OF TT/DOI IN ORAL CANCERS BY THREE OBSERVERS (MM)

	OBSERVER A			OBSERVER B			OBSERVER C		
	MEAN	MEDIAN	RANGE	MEAN	MEDIAN	RANGE	MEAN	MEDIAN	RANGE
TT	4.3	3.4	0.4-12.1	4.5	3.7	0.4-13.6	4.8	3.9	0.4-16.0
DOIs	4.3	3.9	0.4-11.7	4.5	3.5	0.4-14.8	4.7	4.0	0.4-16.0
DOIb	4.0	3.6	0.1-11.4	4.1	3.4	0.3-14.5	4.4	3.7	0.1-15.9
NMT	0.8	0.6	0.1-3.1	0.9	0.9	0.2-2.6	0.7	0.6	0.1-2.6
NMt	0.2	0.1	0-1.3	0.2	0.1	0-1.2	0.2	0.1	0-0.9

Conclusions: TT/DOI measurements vary among observers even with predefined DPI, same method and tool. TT does not significantly differ from DOIs but is greater than DOIb. DOIb appears to be overall more reliable regardless of the system used. Keratin layer does not significantly influence TT/DOIs but subsite and selection of outer reference point do. NM thickness varies with subsite and observer and may significantly impact DOI value. Until a uniform, consensus methodology is developed and validated, recording both TT and DOIb in pathology reports is recommended.

1265 Lymphovascular Invasion and Pattern of Invasion in Floor of Mouth Squamous Cell Carcinoma: An Interobserver Variability Study

Caitlin Beggan, Cassie Fives, Gerard O'Leary, Patrick Sheahan, Cynthia Heffron, Linda Feeley. Cork University Hospital, Cork, Ireland; South Infirmary-Victoria University Hospital, Cork, Ireland.

Background: Lymphovascular space invasion (LVI) and pattern of invasion (POI) have previously been shown by our group to be significant predictors of survival on multivariate analysis in a cohort of patients undergoing surgery for squamous cell carcinoma (SCC) of floor of mouth (FOM). Other investigators have also linked LVI and a non-cohesive invasive front to poorer survival outcomes in oral cavity SCC thus providing a possible rationale for adjuvant radiotherapy in these patients. The aim of this study was to evaluate interobserver variability in the assessment of LVI and POI in SCC of FOM given the clinical and potential therapeutic importance of these parameters.

Design: The study cohort comprised of 52 patients with SCC of FOM who underwent surgery. All H&E stained slides of the primary tumour were re-reviewed independently by 3 pathologists and evaluated for LVI and POI. LVI was classified by each pathologist using their own criteria to reflect routine practice. POI at the deep aspect of the tumour was qualitatively classified as cohesive (broad cohesive sheets of cells or strands of cells >15 cells across) or non-cohesive (narrow strands, non-cohesive small groups or single cells) as per the Royal College of Pathologist's (RCPath) guidelines. As the RCPath do not provide quantitative criteria we chose to apply 3 different cut-offs with cases classified as non-cohesive if (1) >50% of the tumour, (2) >20% of the tumour or (3) any of the tumour (worst pattern of invasion) showed a non-cohesive invasive front. Interobserver variability was analysed using Fleiss kappa statistics.

Results: Interobserver agreement was moderate for the assessment of LVI (K =0.59, 95% CI 0.55-0.64). Interobserver agreement was also moderate for the evaluation of POI when using both a 50% (K =0.56, 95% CI 0.52-0.60) and 20%(K =0.54, 95% CI 0.49-0.58) cut-off, but dropped to fair when classified by worst pattern of invasion (K =0.41, 95% CI 0.37-0.45).

Conclusions: Interobserver reproducibility for LVI and POI in a cohort of SCC of FOM across three pathologists was moderate. These two parameters have been shown to be of prognostic significance with potential management implications for individual patients. This study highlights the need for improved and internationally accepted criteria for the histological diagnosis of both LVI and POI, without which interobserver agreement is unlikely to be improved upon.

1266 Role of CRTC1/MAML2 Translocation in Determining Prognosis and Clinical Outcomes in Mucoepidermoid Carcinoma Patients: The MD Anderson Experience

Diana Bell, Rami E Saade, Joaquin J Garcia, Dianna Roberts, Randal S Weber. University of Texas MD Anderson Cancer Center, Houston, TX; Mayo Clinic, Rochester, MN.

Background: The *CRTC1/MAML2* fusion transcript, which arises from the *CRTC1/MAML2* translocation, is a molecular marker unique to mucoepidermoid carcinoma (MEC), the most common salivary gland malignancy. The extent to which the transcript influences disease features and patient survival is unclear.

Design: OBJECTIVE: To determine whether the *CRTC1/MAML2* fusion transcript correlates with disease stage, tumor grade, or survival outcomes in MEC patients.

PARTICIPANTS: Ninety patients with MEC treated between 1995 and 2011 for whom archived formalin-fixed, paraffin-embedded tumor specimens were available.

MAIN OUTCOMES AND MEASURES: Patients' medical records were reviewed for clinical, demographic, and survival data, and patients' archived tumor specimens were subjected to fluorescence in situ hybridization (FISH) to determine *CRTC1/MAML2* fusion transcript status. Statistical analyses were used to determine whether transcript status was correlated with disease stage, tumor grade, and/or overall survival and/or disease-free survival.

Results: FISH revealed a *CRTC1/MAML2* translocation in 50 patients (56%). The translocations were more prevalent in intermediate-grade tumors (63%) than in high-grade (22%) and low-grade (15%) tumors. Similar proportions of translocation-positive patients had T1, T2, or T4a disease. The majority of translocation-positive patients had N0 disease. The translocation-positive and translocation-negative patients' rates of 5-year overall survival (76.8% vs 75.5%; p=0.165) and disease-free survival (65.2% vs 57.4%; p=0.284) did not differ significantly.

Conclusions: Detection of the *CRTC1/MAML2* fusion transcript provides useful information for MEC diagnosis but is not by itself a powerful predictor of outcomes.

1267 Primary Cutaneous Mammary Analogue Secretory Carcinoma: Series of 4 Cases Harboring ETV6 Gene Rearrangements

Justin A Bishop, Janis Taube, Albert Su, Scott Binder, William H Westra. Johns Hopkins, Baltimore, MD; University of California Los Angeles, Los Angeles, CA.

Background: Mammary analogue secretory carcinoma (MASC) is recently described salivary gland tumor that is defined by its striking similarity to secretory breast cancer at the histologic, immunophenotypic, and genetic levels, with both tumors harboring the *ETV6-NTRK3* translocation. Rare cases of purported secretory carcinoma of the skin adnexa have been reported, but to date they have all been negative for *ETV6* rearrangements, calling into question whether they are truly related to secretory breast carcinoma or salivary MASC.

Design: Cases of cutaneous neoplasms with histologic features identical to salivary MASC were identified from the consultation files of two academic medical institutions. The tumors were examined with routine hematoxylin and eosin staining, immunohistochemistry for S100 and mammaglobin, and break apart fluorescent in situ hybridization (FISH) for *ETV6*.

Results: Four cases of cutaneous MASC were identified. The tumors arose in two men and two women patients ranging from 24 to 71 in age (mean, 49 years). The cases presented in the axillary skin (n=2), ventral neck (n=1), and skin of the cheek (n=1). The tumors arose in the superficial dermis in association with adnexal structures, with no breast or salivary tissue within the specimen. Moreover, none of the patients had a history of precedent breast or salivary gland tumors. The neoplasms exhibited histologic features classic for MASC: circumscribed but unencapsulated proliferations of bland, eosinophilic cells arranged in microcysts and follicles. Intraluminal secretions were seen in all cases, and 3 of 4 demonstrated prominent intratumoral sclerosis. By immunohistochemistry, all cases were diffusely positive for S100 and mammaglobin. Finally, all cases harbored rearrangements of *ETV6* as demonstrated by FISH. All tumors were treated by simple excision alone. Follow up was available in 2 of 4, with no reported recurrences or metastases.
Conclusions: True MASC may rarely occur in the skin, where it likely arises from adnexal structures. Cutaneous MASC appears to be histologically, immunophenotypically, and even genetically identical to their mammary and salivary counterparts, complete with *ETV6* rearrangements. An awareness of this cutaneous tumor type is needed to avoid diagnostic confusion, as it may unfamiliar to many dermatopathologists. Additional cases with follow-up are needed to determine the prognostic significance of cutaneous MASC.

1268 Human Papillomavirus and Activating EGFR Mutations: Alternative Oncogenic Mechanisms in Inverted Sinonasal Papilloma

Noah Brown, Aaron Udager, Jonathan McHugh, Thomas E Carey. University of Michigan Health System, Ann Arbor, MI.
Background: Inverted sinonasal papillomas (ISP) are benign tumors of the sinonasal tract. The oncogenesis of these tumors is currently unknown, however, human papillomavirus (HPV) infection has been proposed to play a role. Recently, we identified activating somatic *EGFR* mutations in nearly 90% of ISP, suggesting that EGFR pathway activation is central to ISP oncogenesis. Interestingly, HPV infection can also stimulate EGFR pathway activation via E5 oncoprotein activity. Thus, we sought to explore the relationship between HPV infection and somatic *EGFR* mutations in ISP.
Design: 21 cases of ISP were identified retrospectively from the pathology records database at a single large academic institution, and after central review by an experienced head and neck pathologist, representative formalin-fixed, paraffin-embedded tissue from each case was selected for sequencing. Sanger sequencing of *EGFR* exons 18-21 was performed with nested sequencing primers. Detection of HPV DNA was performed using two methods: 1) Sanger sequencing with the PGMY 09/11 L1 consensus primer set; and, 2) PCR-based mass spectrometry for high risk subtypes (i.e., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 73).
Results: *EGFR* mutations were identified in 19 (90.5%) cases. HPV DNA was detected in 3 (14.3%) cases, including 2 cases with HPV subtype 11 and 1 case with HPV subtype 6; no high risk subtypes were detected. 19/19 (100%) of HPV-negative cases harbored an *EGFR* mutation, and 2/3 (66.7%) of HPV-positive cases were *EGFR* wild type; only one case had both HPV DNA (subtype 11) and an *EGFR* mutation (E746_S752delinsT). Overall, the detection of HPV DNA and *EGFR* mutations showed strong, negative correlation (phi coefficient = -0.79, $P = 0.014$).
Conclusions: This is the first report to investigate HPV infection and somatic *EGFR* mutations in ISP, and our data demonstrate strong, negative correlation between HPV DNA and *EGFR* mutations in these tumors. These results suggest that either somatic *EGFR* mutation or HPV infection is a primary oncogenic event in the vast majority of ISP, although rare tumors (<5%) may harbor both HPV DNA and an *EGFR* mutation. Furthermore, our data support the hypothesis that EGFR pathway activation is a central event in ISP oncogenesis, which may have important implications for treatment of advanced, surgically unresectable tumors.

1269 Detection of HPV-DNA from May-Grünvald-Giemsa Stained Fine-Needle Aspiration Specimens Using Polymerase Chain Reaction

Hani I Channir, Christian G Larsen, Lise Ahlborn, Thomas van Overeem Hansen, Thomas A Gerds, Birgitte W Charabi, Ben Vainer, Christian von Buchwald, Christel B Lajer, Katalin Kiss. Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; University of Copenhagen, Copenhagen, Denmark.
Background: Human Papillomavirus (HPV)-related non-keratinizing oropharyngeal squamous cell carcinomas (NKOPSCC) often present with cystic cervical metastasis, and can be diagnostic challenging for the pathologists. In addition, the detection of HPV-DNA on fine-needle aspiration (FNA) specimens could potentially be a useful tool in the diagnostic workup of patients with metastases from unknown primary to the neck. The objective of this study was to assess the ability to detect HPV-DNA using Polymerase Chain Reaction (PCR) essay on scraped cells from previously May-Grünvald-Giemsa (MGG)-stained FNA smears and their corresponding histological specimens.
Design: We collected archived MGG stained FNA smears and the corresponding surgical specimens from metastases and primary tumors from 51 patients with NKOPSCC, 12 with oral squamous cell carcinomas (OSCC), and 20 with branchial cleft cysts and 20 with Warthin tumors. A single representative FNA slide from each case was chosen. The coverslips from FNA smears were removed and all material from the object glass was scraped off with a sterile scalpel. The scraped cell material and the corresponding formalin fixed paraffin embedded histological specimens were analyzed for HPV-DNA by PCR. p16 immunohistochemistry was performed on the surgical specimens of the carcinomas.
Results: The surgical specimen from all primary NKOPSCC and their metastases were both p16 and HPV-DNA positive. HPV-DNA was found in 49 of the corresponding FNA from the metastases. The two HPV negative FNA-specimens contained less than 50 well preserved epithelial cells. The 12 OSCCs and the FNA from their metastases were HPV-DNA negative. All histologic samples from these tumors were p16-negative. There was no detectable HPV-DNA neither in the FNA nor the corresponding surgical specimens from the Warthin tumors and the branchial cleft cysts.
Conclusions: HPV-DNA detection by PCR-essay from previously MGG stained FNA-specimens is a useful diagnostic tool and can improve the work-up program for patients presenting with metastasis to the neck.

1270 PSMA Expression in Non-Neoplastic and Neoplastic Salivary Gland

Esther Cheng, Neil H Bander, Brian D Robinson, Theresa Scognamiglio. Weill Cornell Medical College, New York, NY.
Background: Prostate specific membrane antigen (PSMA) is expressed in benign and malignant prostate and the neovasculature of most solid tumors. As such, it has become a novel target for therapy in prostate cancer and solid tumors. PSMA also shows low levels of expression in small intestine, renal tubular cells, and salivary gland. In this study, we aimed to analyze the distribution and expression of PSMA in salivary gland tumors and normal salivary gland and evaluate the use of PSMA as a potential diagnostic and therapeutic marker.
Design: 117 tumors (48 malignant and 69 benign) and 6 normal salivary glands were examined for PSMA staining by immunohistochemistry using previously constructed tissue microarrays. The cases included: 27 mucoepidermoid carcinomas (MEC),17 adenoid cystic carcinomas (AdCC),2 acinic cell carcinomas (AcCC),2 mammary analogue secretory carcinomas (MASC),7 basal cell adenomas (BCA),13 Warthin tumors (WT), and 49 pleomorphic adenomas (PA). The presence or absence of PSMA staining was noted as well as distribution (cell type and localization) and intensity (score: 0 negative, 1+ weak, 2+ moderate, 3+ strong).
Results: All normal salivary gland showed weak to moderate apical PSMA staining in intercalated duct epithelium. 12/17 (71%) AdCC showed PSMA staining predominantly in ductal cells in an apical pattern and rarely in myoepithelial cells where it showed cytoplasmic staining. 1/2 (50%) AcCC showed moderate diffuse cytoplasmic staining. 5/7 (71%) BCA showed moderate to strong PSMA staining in ductal cells only. All MEC and MASC were negative for PSMA. 21/40 (53%) PA showed weak to moderate PSMA staining in ductal cells in an apical pattern and myoepithelial cells in the cytoplasm. 10/13 (77%) WT showed weak cytoplasmic staining in the oncocytic epithelium. PSMA staining was observed in the neovasculature of 29/48 (60%) malignant tumors only. 25/27 (93%) MEC and 4/17 (24%) AdCC showed PSMA staining in the neovasculature. Of the 25 positive MEC, 9 showed weak staining and 16 moderate to strong staining. PSMA staining in AdCC was predominantly weak. Differences in PSMA expression did not correlate with grade or other clinicopathologic characteristics.
Conclusions: PSMA staining is only present in the neovasculature of malignant salivary gland tumors, similar that described previously in other solid tumor types. As such, PSMA could be explored as a novel anti-angiogenic therapeutic target. Additional cases are being analyzed to explore the potential diagnostic role of PSMA in salivary gland tumors with intercalated duct differentiation.

1271 Clinicopathologic Characterization of Mammary Analogue Secretory Carcinoma

Simion I Chiosea, Raja R Seethala, Lindsay Williams, Adel M Assaad, Lester DR Thompson, Madalina Tuluc, Bibianna Purgina, Chi K Lai, Nasir Ud Din, Alena Skalova. University of Pittsburgh, Pittsburgh, PA; Virginia Mason Medical Center, Seattle, WA; Southern California Permanente Medical Group, Woodland Hills, CA; Thomas Jefferson University, Philadelphia, PA; University of Ottawa, Ottawa, Canada; Aga Khan University Hospital, Karachi, Pakistan; Faculty of Medicine, Plzen, Plzen, Czech Republic.
Background: The clinicopathologic understanding of the mammary analogue secretory carcinoma (MASC) is still evolving.
Design: Multi-institutional review of patients with MASC (n = 185) confirmed by ETV6 fluorescence in situ hybridization (n=179) or real time polymerase chain reaction (n=6). Immunohistochemistry (IHC) for mammaglobin, GCDFP15, DOG1, S100, p63/p40 was performed and follow-up obtained.
Results: Clinicopathologic features are summarized in Table 1.

Male/Female	101/78
Age, years, average (range)	47 (7-88)
Site, parotid	119/185
Submandibular	21/185
Buccal mucosa	17/185
Tumor size, cm, average (range)	2.1 (0.1 - 5.8)
pT1	77/137
pT2	29/137
pT3	24/137
pT4	6/137
pN0	48/67
pN1-3	19/67
Perineural invasion, present	38/147
Angiolymphatic invasion, present	22/145
Growth pattern, papillary cystic	47/166
Growth pattern, microfollicular	62/166

Unusual sites included base of tongue (n=2), retromolar trigone (n=2), trachea (n=1), and thyroid (n=1). Among patients with lymph node sampling, the nodal metastatic rate was ~29%. Three patients presented with distant metastases (lung, bones, thyroid). Nine patients received radio- or chemoradiotherapy. Of 64 patients with available

follow-up, 13 developed recurrence. Tumors were characterized by invasive (n=75) or pushing (n=66) border, or were encapsulated (n=13). Sclerosis was noted in 81/142 and lymphoid stoma in 32/131 cases. High grade transformation (HGT; n=10) was defined by nuclear pleomorphism and necrosis. Variant features included chondromyxoid stroma, prominent mucous, clear, or spindle cells. IHC findings are summarized in Table 2.

IHC Marker	Positive	Number of Tested cases
Mammaglobin	119	120
GCDFP15	28	35
DOG1	21	112
p63 or p40 (basal cells)	49	137
S100	158	159

Conclusions: It appears that MASC is more common than initially thought and affects male patients slightly more commonly. Among patients whose surgical treatment included lymph node sampling, the rate of regional lymph node metastases is ~29%. The clinically aggressive cases and expanded morphologic spectrum of MASC may require a formal grading scheme and criteria for HGT-MASC.

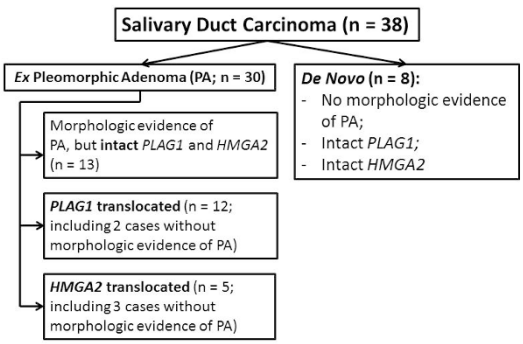
1272 Salivary Duct Carcinoma: Relationship between Morphologic Evidence of Pleomorphic Adenoma, PLAG1, HMGA2 Translocations and Mutations/Copy Number Changes in 50 Cancer-Related Genes

Simion I Chiosea, Alyssa M Luvison, Caitlyn Miller, Lester DR Thompson, Ilan Weinreb, William E Gooding. University of Pittsburgh, Pittsburgh, PA; Southern California Permanente Medical Group, Woodland Hills, CA; University Health Network, Toronto, Canada.

Background: A histogenetic classification of salivary duct carcinoma (SDC) would consider SDC origin (*de novo versus ex* pleomorphic adenoma [PA]). Both morphologic and molecular evidence (ie, *PLAG1, HMGA2* status) of pre-existing PA should be accounted for. The relationship between SDC origin and alterations in 50 cancer-related genes is unknown.

Design: SDC (n=38) were reviewed for morphologic evidence of PA. *PLAG1* and *HMGA2* translocations were detected by break-apart fluorescence *in situ* hybridization probes (Empire Genomics, Buffalo, NY). All cases were technically successfully analyzed by Ion Ampliseq Cancer HotSpot panel v2 (Life Technologies, Carlsbad, CA) for mutations and copy number variation in 50 cancer-related genes. Overall survival (OS) was the primary endpoint.

Results: Most patients were males (30/38, 79%) and presented with Stage IV (28/38, 74%) disease involving parotid. The probability of 3 year OS was 68% (95% confidence interval [CI], 54-87%). Based on morphologic and molecular evidence of PA, 4 groups of SDC were identified. (Figure 1)



The relationship between the 4 groups and molecular findings are summarized in Table 1.

SDC Group	*PIK3CA* mutated, n=14	*HRAS* mutated, n=12	*Her2* amplified, n=11	p53 abnormality, n=18	*p16* Loss, n=7
Morphologically ex PA, n=13	6	4	4	6	1
PLAG1 positive, n=12	2	1	5	9	2
HMGA2 positive, n=5	0	2	2	4	0
De novo, n=8	6	5	0	1	4

Further analysis to account for overlapping alterations, types of mutations, mutant allelic frequency, and response to anti-Her2 therapy is pending. Rare (n<2) events included *PTEN, BRAF, ATM, Her2,* and *FGFR3* mutations.

Conclusions: Seventy-nine percent of SDC in our series are *ex* PA (95% CI, 63-89%). Most patients present with advanced disease and there is no correlation between OS and origin of SDC. *PIK3CA* mutations are observed in *de novo* SDC more commonly than expected under the null hypothesis (false discovery rate [FDR]<.067). Conversely, p53 alterations are more common than expected in SDC with *PLAG1* translocation (FDR<.067).

1273 PS100 and Mamoglobin Coexpression Are Not Sufficient to Affirm the Diagnosis of Mammary Analogue Secretory Carcinoma (MASC)

Valerie Costes, Mathieu Gallo, Ariane Tempier, Vanessa Szablewski, Valere Cacheux, Assia Hafidi Benammar. CHU Montpellier, Montpellier, France.

Background: Mammary analogue secretory carcinoma (MASC) is a recently described low-grade carcinoma characterized by a recurrent t(12 ;15)(p13 ;q25) translocation which results in the ETV6-NTRK3 fusion transcript.

Design: We reviewed 35 salivary glands tumors entering in the differential diagnosis of MASC (19 acinic cell carcinomas, 3 low-grade polymorphic adenocarcinomas and 13 NOS adenocarcinomas) and 4 cases initially diagnosed as MASC in our institution. Complementary immunochemistry and FISH were performed in all these cases.

Results: We identified 15 cases of MASC (7 with a previous diagnosis of ACC, 4 with a previous diagnosis of NOS adenocarcinoma). The median age was 46 and the male:female ratio was 8/7. 57% developed into the parotid gland and the papillary-cystic and solid pattern were the most frequent pattern (10/15). Mammoglobin and PS100 were respectively expressed (> 25% positive cells) in 12/15 and13/15 of the cases. These 2 markers were co-expressed in 12/15 cases.

Three cases without ETV6 rearrangement coexpressed PS100 and mammoglobin (1ACC and 2 PLGA). On the contrary ETV6 rearrangement was found positive in a case which stayed negative for PS100 and mammoglobin. Among the 14 ETV6 FISH positive cases, 7 showed a standard ETV6 rearrangement and 8 presented a more complex anomaly including 3 with duplication of the 3' or 5' ETV6 gene , 2 with complete ETV6 gene deletion of the other allele, 2 with a 3' deletion of the ETV6 gene and 1 with a complete ETV6 deletion). Four of these 8 cases showed nerve infiltration and 3 had a pejorative outcome (2 recurrences and 1 metastatic case). We did not observed recurrence or metastasis in the cases with simple rearrangement.

Conclusions: In conclusion the PS100/mammoglobin co-expression is not sufficient to affirm the diagnosis of MASC. Complex rearrangements of ETV6 gene could be associated with a more aggressive course.

1274 Mammary Analog Secretory Carcinoma (MASC) with a Predominant Cystic Intraductal Component: A Report of 3 Cases

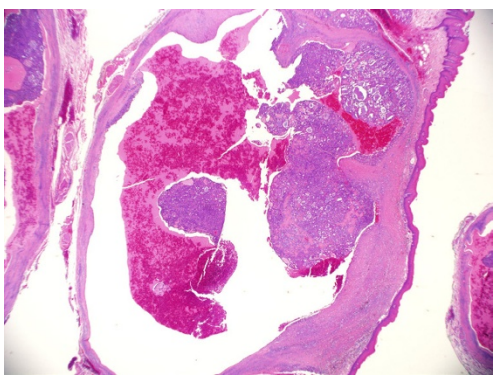
Jennifer L Dettloff, Justin A Bishop, Marino E Leon. Moffitt Cancer Center, Tampa, FL; Johns Hopkins University, Baltimore, MD.

Background: Mammary Analog Secretory Carcinoma (MASC) is a recognized type of salivary gland carcinoma characterized by a t(12;15)(p13;q25) resulting in an ETV6-NTRK3 fusion gene. A focal intraductal component has been described in MASC tumors.

Design: We identified 3 MASC cases where the principal tumor was a cystic intraductal (CID) carcinoma; the clinical and pathologic findings were reviewed. Assessment for rearrangement of the ETV6 (12p13) locus was conducted by FISH on representative FFPE sections using the Vysis LSI ETV6 break apart probe (Abbott Molecular, Des Plaines, IL, USA).

Results: The patients were two males (50 and 69 yo) and 1 female (23 yo). All tumors showed a CID component resulting in an intracystic tumor with microcystic, cribriform, and papillary patterns; these tumors were composed of bland polygonal eosinophilic cells with vesicular nuclear chromatin and conspicuous nucleoli. One case was only intraductal and two cases showed a minor invasive component. Myoepithelial cells in the dilated duct were seen in all cases; these myoepithelial cells were positive for smooth muscle myosin heavy chain and p63 in 2 tested cases. Rearrangement of the ETV6 locus was confirmed in all cases.

Case	Age/ Sex	Size (cm)	Site	Pattern	Mamma-globin	S-100	ETV-6 FISH
1	23 / F	0.4	Soft palate	CID, microcystic, cribriform, and papillary	+	+	+
2	50 / M	1.3	Upper lip	CID / invasive, microcystic, cribriform and papillary	+	+	+
3	69 / M	1.6	Right buccal mucosa	CID / invasive microcystic, cribiform and papillary	+	+	+



Conclusions: Predominant intraductal pattern should be recognized in MASCs and may represent a feature of an early MASC lesion. This could be interpreted as an intracystic pattern. It is important to differentiate these lesions from the low grade cribriform cystadenocarcinoma as these lesions have overlapping histologic (basal/myoepithelial

layer) and immunophenotypic features (S100, SOX10, mammaglobin positivity). Awareness of this intraductal pattern is essential to avoid a misinterpretation of cystic MASCs and FISH can be helpful in differentiating these lesions.

1275 The Great Mimicker - Metastatic Breast Carcinoma to the Head and Neck with Emphasis on Unusual Clinical and Pathologic Features

Dikson Dibe Gondim, Rebecca Chernock, Samir K El-Mofty, James Lewis. Washington University in St. Louis, Saint Louis, MO; Vanderbilt University, Nashville, TN.

Background: Although distant metastases are relatively common in breast cancer, spread to the head and neck (HN) region is rare and can be diagnostically challenging. This study describes the clinical and pathologic features of patients with breast carcinoma metastatic to the HN region from two academic hospitals. To the best of our knowledge, this is the largest case series on this subject.

Design: Pathology databases of two academic hospitals were searched for breast cancer metastases to the HN region. The diagnoses were made by morphologic comparison with the primary breast specimen (when available) or through the use of immunohistochemical stains characteristic of breast carcinoma (excluding primary tumors at the respective sites). Cases of brain metastasis were excluded.

Results: Of the 22 cases identified, 19 (86%) had a known history of breast carcinoma with metastatic disease to other sites. The time from primary diagnosis to HN metastasis ranged from 1 to 33 years (mean=9.2 years). In 3 patients (14%), the metastasis was the first diagnostic specimen for their tumors. The most common locations were neck lymph nodes (7 cases) and orbital soft tissue (5 cases), followed by oral cavity (3), skull base (2), mastoid sinus (2), nasal cavity (1), palatine tonsil (1), and facial skin (1). Clinical presentations were highly variable, ranging from cranial nerve palsies without a mass lesion to oral cavity erythema and swelling to bone pain. Histologically, three cases showed mucosal (or skin)-based lesions with associated pagetoid spread in the adjacent epithelium, a feature normally associated with primary carcinomas. Further, several of the lesions (mucosal and bone-based) had associated cervical nodal metastases, also mimicking primary HN tumors. The facial skin tumor was initially misdiagnosed as basal cell carcinoma, and one of the oral cavity tumors as primary adenosquamous carcinoma.

Conclusions: This series demonstrates the extreme variability in clinical and pathologic features of breast cancer metastatic to the HN. Lack of a known cancer diagnosis, pagetoid spread in the adjacent epithelium, and regional adenopathy do not exclude metastatic breast carcinoma. Further, the interval between diagnosis and metastasis can be extremely long (average 9 years, maximum 33 years). Clinicians and pathologists must be keenly aware of the spectrum of findings and consider metastasis in unusual adenocarcinomas in the HN region.

1276 Head and Neck Presentation of Cutaneous Leishmania in Syrian Refugees

Gabriel Dunya, Robert Habib, Roger Moukarbel, Ibrahim Khalifeh. American Univeristy of Beirut, Beirut, Lebanon.

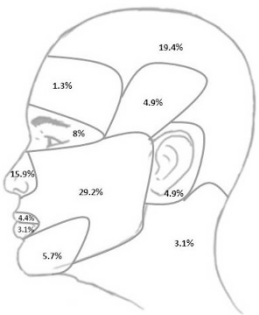
Background: Lebanon, nonendemic area for cutaneous leishmania (CL), is suffering from a CL epidemic brought by the massive population influx from endemic Syria. CL affects mainly exposed areas; therefore the head and neck (HN) region is highly susceptible.

Design: Individuals diagnosed and speciated with CL (n=168) using molecular and microscopic analysis on punch biopsy/scrapings were studied. Clinical data, parasitic index (PI) and Ridley's Parasitic Index (RP) were recorded. The HN was divided into 11 anatomic locations.

Results: Of 168 patients, 96 patients (57.1%) had HN involvement and 72 (42.9%) had no HN involvement. Lesions from the HN were more common in younger patients and were more prone for ulceration, had larger size, higher PI and more advanced RP. There was no difference in the anatomic distribution of lesions between age groups and genders in the HN group. Lesions were less commonly encountered in the veiled area in women.

		Head & Neck	Non Head & Neck
Number of Cases		96 (57.1%)	72 (42.9%)
Gender	*Male*	48 (50.0%)	32 (44.4%)
Age average (years)*		14 ± 14.3	27.2 ± 15.8
Lesion type	*Papule*	2 (2.1%)	2 (2.8%)
	*Plaque & Nodule**	41 (42.7%)	43 (59.7%)
	*Ulcer & Verrucous**	53 (55.2%)	27 (37.5%)
Dry/Wet	*Dry*	75 (78.1%)	58 (80.6%)
	Wet	7 (7.3%)	6 (8.3%)
	Both	14 (14.6%)	8 (11.1%)
Average Size (cm)*		4.31± 2.33	3.58 ± 2.65
Lesion Duration (average in months)		5.8 ± 5.5	6.9 ± 6.3
Lesion Chronicity (>12 months)		8 (8.3%)	6 (8.2%)
Recollection of Insect Bite		49 (51.0%)	34 (47.2%)
Number of Lesions (average)		3.4 ± 3.6	3.1 ± 3.1
PI	*0-1*	42 (52.5%)	45 (66.2%)
	2-3	11 (13.8%)	12 (17.6%)
	*4-6**	27 (33.8%)	11 (16.2%)
RP	*2**	1 (1.3%)	8 (11.8%)
	3	20 (25.0%)	18 (26.5%)
	*4**	34 (42.5%)	13 (19.1%)
	5	25 (31.3%)	29 (42.6%)
Molecular Speciation	*L. Tropica*	93 (96.90%)	67 (93.10%)
	L. Major	3 (3.10%)	5 (6.90%)
*** Designate statistically significant difference (p<0.05)**			

Head and neck distribution



Conclusions: In the community we studied, HN is commonly involved by CL. Lesions with HN involvement were more encountered in pediatric age group and showed more extensive features.

1277 The Effect of MGMT and p16 on Prognosis in Oropharyngeal Squamous Cell Carcinomas Is Independent of Tumor Grade and Lymphovascular Invasion

David Fink, Sameer Jhavar, Marcus Volz, Kimberly L Walker, Arundhati Rao. Baylor Scott and White, Temple, TX.

Background: Prognostic indicators in oropharyngeal squamous cell carcinomas (SCC) include genetic and epigenetic alterations, such as hypermethylation of the promoter region of O6-methylguanine DNA methyltransferase (MGMT) as well as inactivation of the cell cycle inhibitor p16 gene which are associated with increased tumor size, stage, nodal metastasis, and increased risk for disease recurrence. Lymphovascular invasion by itself has been demonstrated to also be a poor prognostic indicator. There have been no studies to identify if hypermethylation of MGMT or p16 inactivation is associated with lymphovascular invasion and tumor or if these are independent prognostic factors.

Design: 122 cases of oropharyngeal SCC with follow up were identified from our pathology database for a 15 year period. After morphological examination to assess for grade and lymphovascular invasion, MGMT pyrosequencing using a commercial kit (Qiagen) was performed to quantitatively measure the methylation of four CpG sites in exon 1 of the human MGMT gene after tumor enrichment. Immunohistochemistry with p16 antibody (Ventana) was evaluated in all cases.

Results: 19/122 (16%) of oropharyngeal squamous cell carcinoma cases were MGMT/p16 positive, 21/122 (17%) were MGMT positive/p16 negative, 40/122 (33%) were MGMT negative/p16 positive, and 42/122 (34%) were negative for MGMT/p16. Using the four point Broder's scale for grading oral squamous cell carcionma, the average tumor scores were the following: 2.315 for MGMT/p16 positive, 2.38 for MGMT positive/p16 negative tumors, 2.575 for MGMT negative/p16 positive, and 2.285 for MGMT/p16 negative tumors. There was no statistical difference between tumor grades for these groups (p-value=0.115).

Lymphovascular invasion was present in 1/19 (5%) MGMT/p16 positive tumors, 2/21 (10%) MGMT positive/p16 negative, 6/40 (15%) MGMT negative/p16 positive, and 10/42/ (24%) MGMT/p16 negative tumors. MGMT methylation and p16 positivity did not predict lymphovascular invasion (p-value=0.235).

Conclusions: Despite its known impact on prognosis, MGMT and p16 status are not associated with high tumor grade or increased lymphovascular invasion, suggesting their effect on prognosis and outcome is independent of these factors.

1278 Next Generation Sequencing of Olfactory Neuroblastoma Nominates Potential Oncogenic Drivers Including Wnt/Beta-catenin Signaling, FGFR3, and Cyclin D1

Paul W Harms, Lorena Lazo de la Vega, Andi K Cani, Jonathan McHugh, Daniel H Hovelson, Michaela J Haller, Komal Kunder, Chia-Jen Liu, Scott A Tomlins. Department of Pathology, Ann Arbor, MI; Michigan Center for Translational Pathology, Ann Arbor, MI.

Background: Olfactory neuroblastomas (ONB), also known as esthesioneuroblastomas, are malignant round-cell tumors that represent up to 5% of sinonasal malignancies. Despite their aggressive course, molecular studies of ONB have been limited, and targeted therapies are lacking.

Design: In order to identify potential oncogenic drivers and targetable pathways in ONBs, we characterized a cohort of 23 ONBs from 21 patients for mutational events and copy number alterations (CNAs) via targeted, multiplexed PCR based sequencing of the entire coding sequence of over 400 cancer-relevant genes.

Results: Mutational analysis identified 14 prioritized, high confidence somatic non-synonymous mutations in 8/22 tumors (36%). Most mutations were not previously described in ONB, and included a beta-catenin (*CTNNB1*) stabilizing mutation in 1 tumor, inactivating mutation of *PTEN* in 1 tumor, and inactivating mutations affecting genes in the KMT2 histone methyltransferase family of putative tumor suppressors in 2 tumors. CNAs were detected in 16/18 (89%) tumors suitable for CNA analysis. In agreement with previous cytogenetic studies of ONB, we detected multiple CNAs per tumor (average: 6.5, range: 0-12). The most recurrent copy number alterations included gains involving all or part of chromosome 20 in 14/18 (78%), chromosome 5 in 13/18 (72%), and chromosome 11 in 10/18 (56%). Recurrent focal gains affected *CCND1* (chromosome 11q13), *BCL2L1* (chromosome 20q11), and *FGFR3* (chromosome 4p16), among others.

Conclusions: Based on a 409 cancer-related gene panel, ONBs display low mutation rates and few recurrent mutations. However, tumors harbor multiple highly recurrent copy number alterations. Our data also nominate specific candidate genes and pathways as oncogenic drivers in subsets of ONBs, including Wnt/beta catenin signaling, PI3K signaling, FGFR3, and cyclin D1.

1279 Macrocystic Mammary Analogue Secretory Carcinoma: An Unusual Architectural Variant of a Recently Described Salivary Gland Tumor

Juan C Hernandez-Prera, Alessandro Valentino, Carlos E Bacchi, Fredrik Petersson, Vesna Najfeld, Bruce M Wenig. Mount Sinai Beth Israel, New York, NY; Ospedale S. Andrea, La Spezia, Italy; Bacchi Lab/Consultoria em Patologia, Botucatu, Brazil; National University Health System, Singapore, Singapore; Mount Sinai Hospital, New York, NY.

Background: MASC is a recently described low-grade salivary gland adenocarcinoma characterized by a recurrent *ETV6-NTRK3* gene fusion. The majority of tumors show an admixture of microcystic, solid and tubular growth patterns. Only a few cases with macrocystic (oligolocular) growth have been reported as part of larger case series. To the best of our knowledge, a series wholly focusing on this unusual architectural variant of MASC has not been previously reported.

Design: Seven cases of MASC characterized by a macrocystic (oligolocular) growth pattern were retrieved and reviewed. Representative sections were subject to immunohistochemical staining for S-100 protein, mammaglobin and DOG1. Fluorescence in situ hybridization (FISH) analysis for ETV6 break-apart probe was performed in all cases. Clinical parameters were obtained.

Results: There were 5 men and 2 women ranging in ages from 17 to 65 years (avg., 41 years). The patients presented with a painless cystic mass in the region of the parotid gland (5), submandibular gland (1) and neck (1). All tumors were circumscribed measuring 1 to 4 cm in greatest diameter (mean: 2 cm). Five tumors were unilocular, while two were multilocular. The cystic spaces were predominantly lined by a single epithelial cell layer with focal areas in which the epithelium was multilayered with papillary and hobnail features. Two cases had larger intraluminal microcystic and papillary growths. The neoplastic cells were round to oval with hyperchromatic to vesicular nuclei with a centrally located nucleoli and lightly eosinophilic or vacuolated cytoplasm. Tumor cells show strong positivity for S100 protein and mammaglobin, while DOG-1 was uniformly negative. ETV6 gene rearrangement was successfully identified in 5 cases.

Conclusions: Macrocystic MASC can present diagnostic difficulties simulating benign and other malignant salivary gland lesions. This histologic variant of MASC needs to be included in the differential diagnosis of cystic lesions in the head and neck. Identification of the characteristic cytomorphological features in conjunction with immunohistochemical reactivity and molecular analysis are key in rendering the correct diagnosis.

1280 Three-Dimensional Histology: Spatial Envisioning of Pattern of Invasion

Yan Hu, Elliot Yu, Claudia Velosa, Jessica Xu, Qiuying Shi, John Tomaszewski, Scott Doyle, Margaret Brandwein. University at Buffalo, Buffalo, NY; Allegheny Health Network, Pittsburgh, PA; University of Kentucky, Lexington, KY.

Background: Pathology quantifies disease through interpretion of planar images of complex processes. We think that 3D models will enhance interpretation. Worst pattern of invasion (WPOI), a prognosticator for oral squamous cell carcinoma (OSCC) represents specific patterns at tumor advancing edge. We introduce a framework for spatial visualization of WPOI using serial sections.

Design: Serial slides (20 - 60) from 7 T1 OSCC were scanned at high-resolution (0.25 μ/pixel). Scale-Invariant Feature Transform aligned images to occupy the same coordinates using keypoints. Elastic image registration (bUnwarpJ, Fiji) optimized keypoint alignment. Manual annotations (5 slides/case) established training sets. A two-pass classifier was used to develop tumor masks on a pixel-wise basis, first tissue vs. background, then tumor vs. non-tumor. 156 texture-based features were extracted; features were selected for retention in modeling based on minimum redundancy and maximum relevance. A classifier was trained to produce cancer likelihood masks. To ensure a smooth model, we interpolated between the image masks. 3D Object Counter plugin created whole objects.

Results:

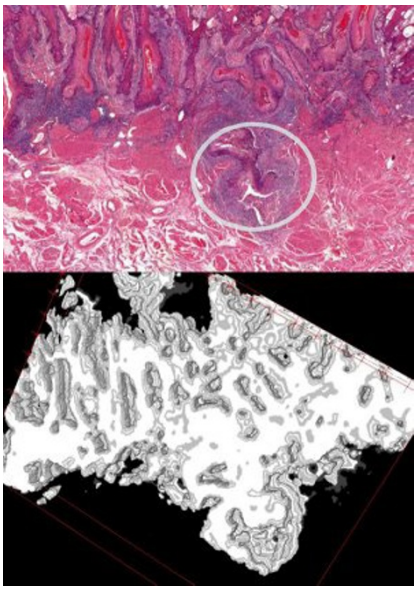


Fig 1, top, shows nonaggressive WPOI with finger-like pushing borders. A deep protrusion (circle) is interpreted as not separated from the main mass. This assumptions is confirmed on the 3D model (bottom).

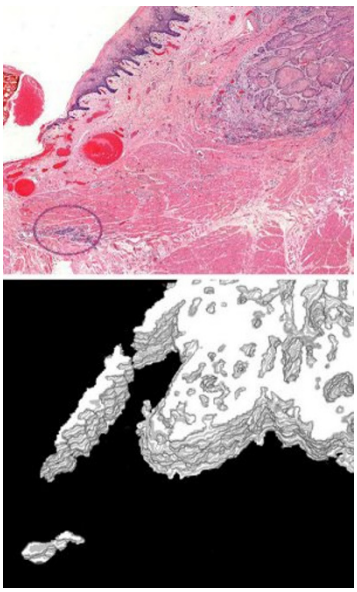


Fig 2 (top) shows a WPOI-5 OSCC with dispersed satellites (circle). The 3D model (bottom) confirmed the lack of connection between satellite and main mass.

Conclusions: The decision point for classifying WPOI is whether a tumor satellite is separated from the main tumor. Tangential sectioning is known to mimic separation. A series of visual context-dependent assumptions are necessary to interpretation. We present proof of concept the 3D modeling can confirm inherent assumptions necessary in interpretation of planar morphology.

1281 Abstract Withdrawn

1282 Population-Based 30-Year Retrospective Review of Major Salivary Gland Carcinomas Identifies 22 Mammary-Analogue Secretory Carcinomas (MASC)

Martin Hyrcza, Gareth Ayre, Alena Skalova, Amir Rahemtulla, Eric Berthelet, Jonn Wu, Thomas Thomson. University of British Columbia, Vancouver, BC, Canada; British Columbia Cancer Agency, Vancouver, BC, Canada; Charles University, Faculty of Medicine, Plzen, Czech Republic.

Background: The molecular and morphological aspects of MASC are now well described; however the frequency and the clinical outcomes are still unclear as no population-based studies of this tumour have been reported to date.

Design: Retrospective chart review over the 30-year period identified 1012 major salivary gland malignancies treated at the provincial oncological center. Review by two of the authors identified 244 cases that could represent MASC. 140 cases were retrieved and included on the tissue microarray (TMA). TMA was stained with H&E, S100, mammaglobin, GATA3, keratin 5, and p63, and was probed with ETV6 break-apart FISH. All cases showing S100 and mammaglobin positivity and / or presence of ETV6 rearrangement by FISH were tested by PCR for the presence of ETV6 translocation.

Results: The original diagnoses of the 140 cases included 93 acinic cell carcinomas, 22 adenocarcinomas NOS, 19 mucoepidermoid carcinomas, 2 mucinous adenocarcinomas, and 1 each of papillary cystadenocarcinoma, clear cell adenocarcinoma, cystadenocarcinoma, and carcinoma NOS.

31 tumours showed dual positivity for mammaglobin and S100, with 28 also showing nuclear GATA3 staining. 8 of the 31 cases showed some positivity of p63 and / or keratin 5 and none of these tumors showed ETV6 translocation by FISH or PCR. Of the remaining 23 cases, 22 showed ETV6 rearrangement by FISH and 15 by PCR.

The 22 MASC cases all occurred in the parotid gland. 14 cases occurred in men and 8 in women (M:F 1.8:1). The ages ranged from 17 to 74 years with a mean of 45 years and a bimodal age distribution with minor peak in 3rd decade and a major peak in the 6th decade. 16 tumours were originally diagnosed as acinic cell carcinoma, 3 as adenocarcinoma NOS, 2 as mucoepidermoid carcinoma and 1 as papillary adenocarcinoma. 15 tumours were originally graded as low grade and 7 as intermediate grade.

Mean clinical follow up was 63.6 months; mean survival follow up was 101.9 months. All tumours were treated surgically. Two patients experienced recurrences. 21 of 22 patients (95%) were disease free while one patient died of the disease 42 months after diagnosis.

Conclusions: MASC is an uncommon carcinoma in the major salivary glands with a low rate of recurrence. S100 and mammaglobin positivity are sensitive and specific markers of MASC **in the absence** of p63 and keratin 5 staining.

1283 LEF-1 Expression in Basaloid Tumors of the Salivary Gland

Reuben P Jacob, Shannon O'Brien, Cynthia Cohen, Momin T Siddiqui. Emory University School of Medicine, Atlanta, GA.

Background: Immunohistochemistry (IHC) maybe useful in separating basal cell adenoma (BCA), pleomorphic adenoma (PA), and adenoid cystic carcinoma (ACC) in some cases. Lymphoid enhancer binding factor 1 (LEF-1) is a nuclear transcription factor that is involved in the Wnt signaling pathway and influences cellular division and migration. We evaluated its expression in surgical resections (SP) and fine needle aspiration (FNA) specimens of BCA, PA and ACC as well as benign salivary gland tissue (BSG) to determine its diagnostic utility.

Design: IHC for LEF-1 was performed on 62 PA (35 SP, 27 FNA), 17 cases of BCA (11 SP, 6 FNA) and 46 ACC (35 SP, 11 FNA). Nuclear staining was graded by intensity (0-3) and percentage of positive cells. Positivity in this study was defined as 1+ intensity and greater than 5% of tumor cell positivity or intensity of 2-3+ regardless of percentage.

Results: Table 1: LEF-1 analysis in SP cases

Type (n)	Positive (%)	Negative (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PA (35)	31/35 (88.6)	4/35 (11.4)	88.6	76.5	72.1	90.7
BCA (11)	10/11 (91.0)	1/11 (9.0)	91	56	23.3	97.7
ACC (35)	2/35 (5.7)	33/35 (94.3)	5.71	19.6	4.62	23.3
BSG (5)	0/5 (0)	5/5 (100)	0	46.9	0	88.4
Benign (PA+BCA) (46)	41/46 (89.1)	5/46 (10.9)	89.1	94.3	95.3	86.8
Malignant (ACC) (35)	2/35 (5.7)	33/35 (94.3)	5.71	10.9	4.65	13.2

Table 2: LEF-1 analysis in FNA cases

Type (n)	Positive (%)	Negative (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PA (27)	23/27 (85.2)	4/27 (14.8)	85.2	81.8	85.2	81.8
BCA (6)	3/6 (50)	3/6 (50)	50	44.2	11.1	86.4
ACC (11)	1/11 (9.0)	10/11 (91.0)	9	31.6	3.7	54.5
BSG (5)	0/5 (0)	5/5 (100)	0	38.6	0	77.3
Benign (PA+BCA) (33)	26/33 (78.8)	7/33 (21.2)	78.8	91.0	96.3	58.8
Malignant (ACC) (11)	1/11 (9.0)	10/11 (91.0)	9.0	21.2	3.7	41.2

Conclusions: This study identified a strong role for LEF-1 as a diagnostic marker in distinguishing basaloid tumors of the salivary gland, especially when comparing benign (PA + BCA) and malignant (ACC) lesions. LEF-1 is a useful marker for diagnosing PAs and BCAs in SP specimens and for PAs in FNA's. However with 90% of ACCs in SP and FNAs being LEF-1 negative, it can also be very helpful in excluding it as a diagnosis. LEF-1 expression was negative in all BSG. In conclusion, LEF-1 is most useful in the diagnosis of benign salivary gland basaloid tumors.

1284 Prognostic Significance of Histologic Features in HPV-Associated Tonsillar Squamous Cell Carcinoma

Jian Jing, Indu Varier, Joanna Dong, David Zhang, Andrew G Sikora, Elizabeth G Demicco. Icahn School of Medicine at Mount Sinai, New York, NY; Baylor College of Medicine, Houston, TX.

Background: HPV-associated oropharyngeal squamous cell carcinoma (SCC), typically arising within tonsillar epithelium, are often described having "basaloid", "non-keratinizing" or "poorly differentiated" morphology. However, there is a wide spectrum of histological patterns, and the correlation between histological features and patient outcomes has not been well-established. The aim of this research was to identify histologic features associated with aggressive behavior of tonsillar SCC.

Design: H&E slides from 129 patients with primarily resected tonsillar SCC were evaluated for histologic features, including tumor architectural pattern, degree of keratinization, host reaction, and cytological features. Medical record was reviewed for clinicopathologic features including LVI, PNI, stage, patient age, sex, risk factors and outcomes including local recurrence (LR), distant metastasis (DM) or survival (OS). Outcomes were evaluated using the Kaplan-Meier method. P values of < 0.05 were considered statistically significant.

Results: HPV status was known, and positive in 91.5%. 89% of patients were male, and mean age at diagnosis was 60 yrs. (range 41-89). Mean follow-up was 34 months (range 1 to 86). All tumors arose in tonsillar tissue from base of tongue (37.2%), palatine tonsil (49.6%) or other oropharyngeal sites. Nonsmokers accounted for 48.8% and 48.8% had no history of alcohol abuse. 15% of patients were Stage I-II at diagnosis. There were 8 LRs, 9 DM and 10 deaths. As expected, lower T stage was associated with improved survival ($p = 0.03$), while lymph node status was not significant.

Morphologic features associated with improved OS included tumors with any areas of spread along crypt epithelium (mimicking in situ carcinoma) ($p = 0.03$), and papillary

architecture (p= 0.05). Lymphoepithelial morphology (p= 0.05), presence of frequent monster tumor nuclei (p= 0.03), and high overall nuclear pleomorphism (p= 0.0001) portended worse OS.
Nuclear pleomorpism and desmoplasia were associated with DM ($p<0.05$), while lymphoepithelial morphology and monster nuclei were associated with LR ($p<0.04$).
Conclusions: Among tonsillar SCC, specific histological patterns are associated with aggressive behavior and poor outcomes. These features may be useful to develop a meaningful histologic grading system for tonsillar tumors. Validation in additional cases is underway.

1285 β-catenin Expression Is Frequent in Sinonasal Hemangiopericytoma and Its Mimics

Vickie Y Jo, Christopher Fletcher. Brigham and Women's Hospital and Harvard Medical School, Boston, MA.
Background: Sinonasal hemangiopericytoma (HPC) is a tumor showing pericytic myoid differentiation that is unique to the sinonasal tract. *CTNNB1* mutations appear to be a consistent aberration in sinonasal HPC, and nuclear expression of β-catenin has been reported. Our aim was to evaluate the frequency of β-catenin expression in sinonasal HPC and its histologic mimics in the upper aerodigestive tract.
Design: Cases were retrieved from the authors' files. All tumors were located in the sinonasal tract or oral cavity, and diagnoses were based on standard and widely accepted diagnostic criteria. Immunohistochemical staining for β-catenin was performed using a mouse monoclonal antibody (BD Bioscience, #610154) at a 1:1000 dilution with antigen retrieval by citrate buffer and pressure cooker. Appropriate positive and negative controls were used throughout. Nuclear staining was recorded semiquantitatively by extent (0/negative, no staining; focal, <10% of cells; multifocal, 25%-75%; diffuse, >75%) and intensity (graded as weak, moderate, and strong).
Results: Nuclear reactivity for β-catenin was found in 19/20 cases of sinonasal HPC; 17 showed moderate-to-strong multifocal or diffuse staining, and 2 had moderate focal nuclear reactivity. All solitary fibrous tumors (SFT) (10/10) showed focal-to-multifocal staining varying from weak to strong in intensity. Most cases of synovial sarcoma (9/10) showed β-catenin expression in the spindle cell component, ranging from focal-weak to strong-multifocal. No cases of myopericytoma (0/10) showed nuclear β-catenin expression.
Conclusions: β-catenin expression is prevalent in sinonasal HPC, but is also frequent in SFT and synovial sarcoma. No expression is present in myopericytoma. Our findings indicate that β-catenin is not a useful differential diagnostic tool in the evaluation of spindle cell tumors with a prominent hemangiopericytoma-like vasculature in the sinonasal tract and oral cavity.

1286 Characterization of Inflammatory Infiltrates and Programmed Death Ligand 1 (PD-L1) Expression in Squamous Carcinoma Precursor Lesions in Organ Transplant Recipients

D Anand Rajan Kanagasabapathy, Samir K El-Mofty. Washington University School of Medicine, St Louis, MO.
Background: Perilesional inflammation plays an important role in the evolution of head and neck cutaneous squamous carcinoma (SCC). Studies have shown reduced inflammation in cutaneous SCC in organ transplant recipients (OTR). We identified two distinct SCC precursor lesions in a cohort of OTRs, bowenoid and nonbowenoid dysplasia (BD and NBD), exhibiting differential but low-level HPV β mRNA expression (in BD). Here we characterize the composition of the perilesional inflammatory infiltrate and investigate programmed cell death 1 ligand 1 (PD-L1) expression in the two types by immunohistochemistry.
Design: We assembled 60 paraffin embedded tissue cores (1.5 mm) from skin biopsies of 40 organ transplant recipients (OTR) in two tissue microarrays (TMA). These included BD (n=33) and NBD (n=17) lesions and controls from adjacent skin (n=10). Immunohistochemistry for CD20, CD3, CD4, and CD8 and CD56 were performed on TMA sections using standard techniques. Perilesional infiltrating lymphocytes (PIL) and marker expression were graded on an ordinal scale from 0 to 4, representing absent-0, rare-1, scattered-2, aggregates-3 and dense bandlike-4 infiltrates. Additionally we classified marker expression on a binary scale as sparse/absent (0) or present (1). PD-L1 expression was studied using a monoclonal antibody (clone SP142, Spring Biosciences); tonsillar crypt epithelium served as positive controls. Frequency and amount of expression were compared using χ^2 and Student t-tests.
Results: Inflammation was present in BD as lymphoid aggregates or a lichenoid band, compared to NBD and controls, which exhibited sparse scattered lymphoid cells. PILs were predominantly CD3+ve T-cells, and CD20+ve B-cells were sparse-to-absent in the cores including controls ($p<<0.05$). CD4+ve PILs were both more frequent (p=0.04), and significantly increased in number in BD compared to NBD (p=0.02). CD8-positive PILs were frequent in BD compared to NBD (p=0.02). CD56-expressing lymphocytes were not seen and PD-L1 expression was negative in both lesional types.
Conclusions: Here we show a preserved CD4/CD8+ve inflammatory response in one type of precursor SCC (BD) but not in others (NBD) in OTRs. However, PD-L1 expression is negative in both types. The biologic behavior of precursor SCC associated with HPV β may be different and influenced by host inflammation. Delineation of molecular differences may eventually be used in different therapeutic methods to prevent progression in these distinct entities.

1287 Comprehensive Genomic Profiling of Esthesioneuroblastoma Reveals a Relatively Low Overall Genomic Alteration Frequency, but Identifies Numerous Potential Opportunities for Targeted Therapies

Sungeun Kim, Kyle Fedorchak, Siraj M Ali, Julia A Elvin, Jo-Anne Vergilio, James Suh, Vincent A Miller, Philip J Stephens, Jeffrey S Ross. Albany Medical College, Albany, NY; Foundation Medicine Inc., Cambridge, MA.
Background: Esthesioneuroblastoma (ENB), known as olfactory neuroblastoma, is a rare malignant neoplasm of the olfactory mucosa. Despite surgical resection combined with radiotherapy and adjuvant chemotherapy, ENB often relapses and pursues an aggressive clinical course. We queried whether comprehensive genomic profiling (CGP) of relapsed/refractory ENB could uncover genomic alterations (GA) that could potentially lead to targeted therapies for these patients.
Design: DNA was extracted from 40 microns of FFPE sections from 30 consecutive clinical cases of relapsed/refractory ENB. CGP was performed using a hybrid-capture, adaptor ligation based next generation sequencing assay to a mean coverage depth of 561X. The results were analyzed for short variant genomic alterations (GA) including base substitutions, insertions and deletions and select rearrangements as well as for copy number changes (amplifications and homozygous deletions). Clinically relevant GA (CRGA) were defined as GA linked to drugs on the market or under evaluation in mechanism driven clinical trials.
Results: The 20 male (67%) and 10 female (33%) ENB patients had an age of 49.5 years (range 16 to 70 years). All tumors were stages III and IV at the time of CGP. The sample used for sequencing was from the primary or recurrent ENB in the head and neck or nasal cavity in 14 (47%), brain in 6 (20%), lymph node in 5 (17%), bone in 4 (13%) and liver in 1 (3%) on the ENB cases. 22 (73%) of ENB featured GA with an mean of 1.9 GA/sample. 16 (53%) ENB featured at least one CRGA with a mean of 0.73 CRGA/sample. The most frequent GA at 23% of ENB were mutations in *TP53* with GA in *CDKN2A*, *CDKN2B, CDKN2C, CTNNB1, HGF, NF1, PIK3CA, SMARCD1 and TET2* all occurring at 7% on ENB. In addition to the relatively low frequency of GA in ENB were the infrequent mutations in RB1 at 3%. Noteworthy potential targetable GA in ENB included *HGF* at 7% and *ERBB2*, *KIT* and *PTCH1* all at 3% frequencies. CRGA impacting the MTOR pathway and potentially selecting the use of MTOR inhibitors included *NF1* and *PIK3CA* at 7% of ENB and *PTEN, TSC1/2* and *RICTOR* each at 3%.
Conclusions: Current multi-modality non-targeted therapy for relapsed ENB is of limited clinical benefit. CGP revealed potential new therapy targets for the disease including GA in *HGF, ERBB2, KIT* and *PTCH1*. Based on these findings, further study of CGP for ENB patients appears warranted.

1288 Clinicopathological Features of Extranodal Follicular Dendritic Cell Sarcoma of Head and Neck Region: Report of 18 Cases of an Uncommon Entity

Rajiv Kumar, Anuja Pradhan, Munita Bal, Asawari Patil, Prathamesh Pai, Sarbani Laskar, Jai P Agarwal, Anil D'Cruz, Shubhada Kane. Tata Memorial Hospital, Mumbai, India.
Background: Extranodal follicular dendritic cell sarcoma(FDCS) of Head and neck (H &N) region are extremely rare. Till date, less than 80 cases are reported in literature. We hereby, report the clinico-pathological spectrum of extranodal FDCS of H&N region, reported from a single institution.
Design: Eighteen cases of extranodal FDCS of H&N region were retrieved from pathology archives diagnosed over last 15-years(2001-2015)**.** Clinico-radiological information was obtained from patient's charts. Histopathological and immunohistochemical (IHC) features were reviewed. Risk stratification into low risk and high risk malignant potential was done based on following parameters; growth pattern, cellular atypia, necrosis(-/+) and mitotic count/10hpf(<5 or >5) and tumour size (<5 or >5cms).
Results: The study group was formed by 14 males and 4 females, between 17-79 years of age (median, 50 years). Common clinical symptoms were intra-oral and nasal discomfort, swelling and odynophagia. Imaging revealed lobulated soft-tissue masses, ranging in size from 1-7 cms (median, 4.7cm). Primary site were tonsil (n=8),pharyngeal region(n=5) and larynx(n=2). Parotid, scalp and thyroid had one case each. The tumor was characterized by spindled to ovoid cells arranged in varying growth patterns i.e. storiform, fascicular, whorled and solid. Sprinkling of lymphocytes within tumour was common finding. A wide IHC panel for epithelial, melanoma and lymphoma markers was negative. Variable expression for FDC markers was seen i.e.CD23(18/18),CD21(13/17) and CD35(5/9)]. Risk stratification based on histology findings was possible in 16 cases and their correlation with clinical outcomes was showed in table.

Parameters	Low Risk Malignant Potential	High Risk Malignant Potential
Number(Primary lesion)	8/16	8/16
Lymph Nodal metastasis	1/7	6/7
Recurrences	3/4	1/4
Mean follow up(Months)	41.39	9.13

Treatment modalities were only surgery in 5, surgery plus adjuvant chemo-radiotherapy in 9 and only chemo-radiotherapy in 4 cases. Median follow-up was 26 months(range 4-120 months) and 9 patients were alive with disease. Local recurrence, lymph node and distant metastasis were noted in 4, 7 and 2 patients respectively. Late recurrence after 8 and 10 year was noted in 2 cases. Recurrent tumours were high grade on histomorphology.
Conclusions: Extranodal FDCS of the H&N region is an uncommon tumour and high index of suspicion with wide IHC panel is required for diagnosis. Histopathological risk stratification may determine the prognosis of the tumour.

1289 Clinicopathological, Immunohistochemical and Molecular Approach of a Series of Multiple Primary Oral Carcinomas

Ana Larque, Jorge De la Oliva, Marta Bodalo, Lara Nonell, Carles Marti, Alfons Nadal, Llucia Alos. Hospital Clinic, Barcelona, Spain; Institut Hospital del Mar d'Investigacions Mediques, Barcelona, Spain.

Background: Oral cancer is difficult to control even after treatment because of the high propensity to develop multiple primary tumors. The aim of the study is to characterize the clinicopathological and immunohistochemical characteristics, as well as the cytogenetic alterations of a series of multiple primary oral carcinomas (MPOCs).

Design: Twenty-three patients with MPOCs were included in the study. Clinicopathological data were recorded and lesions were histologically assessed. All cases were analyzed for HPV analysis by in situ hybridization (GenPoint HPV DNA Cocktail, Biotinylated, Dako) and p16, p53 and cyclin D1 expression by immunohistochemistry. In addition, the genomic profile of six tumor samples from three patients (two different carcinomas and one dysplastic lesion of each patient) were analized by using Affymetrix genomic arrays through Cytoscan HD array (3 samples) and OncoScan array (3 samples).

Results: The patients were 12 males (52.2 %) and 11 females (47.8%) with a median age of 58 (range, 36-80). Twelve (52.2%) patients were smokers, and 8 (34.8%) consumed alcohol. Six (26.1%) patients met the proliferative verrucous leukoplakia condition and two (8.7%) had oral lichen planus. MPOCs were most prevalent in the lower gingiva followed by the floor of mouth. Two out of 23 patiens (8.7%) had synchronous MPOC, whereas the rest of tumors were metachronous. Fourteen patients had 2 tumors (60.9%); 3 (13%) had 3 tumors and 4 (17.4%) had 4 tumors. The median interval between onset of metachronous MPOCs was 31 months (range, 7- 109). p53 and cyclin D1 showed similar expression in different MPOCs of the same patient in over 50% of cases. p16 and HPV were negative in all tumors.

Losses on 3p, 6p and 9p, as well as gains on 3q, 4p, 8q, and 11q were the most frequent genetic alteration found in dysplasias and carcinomas. Dysplasias and concomitant tumors shared cytogenetic alterations, whereas metachronous/synchronous tumours showed different molecular alterations.

Conclusions: These results suggest that dysplastic changes and carcinomas that developed from them are clonally related, but we have not been able to confirm this in metachronous/synchronous tumors.

1290 Arrested Pneumatization of the Skull Base: A Sheep in Wolf's Clothing

Jean Lewis, Carrie Y Inwards, Kirk M Welker. Mayo Clinic, Rochester, MN.

Background: Arrested pneumatization of the skull base (APSB) is an uncommon developmental variant characterized by failure of normal aeration following fatty marrow transformation, affecting the sphenoid and/or adjacent accessory sinus sites. Its apparently lytic nature may lead to the clinical impression of osteomyelitis or malignancy. Although characteristic imaging features have been reported, APSB remains poorly recognized by general radiologists. In addition, APSB has not been previously described in the pathology literature. We have recently encountered several consultation cases in which biopsy was performed for a supposedly aggressive skull base process. Because of bland histologic features, submitted images were reviewed with our neuroradiologists, who interpreted the findings as those of APSB. We describe the pathologic features of 5 such cases.

Design: Consultation files were reviewed to identify possible cases of APSB. Accepted cases had benign histology without another specific diagnosis, and review of images by one of our experienced neuroradiologists to confirm the interpretation.

Results: There were 3 males and 2 females ranging in age from 17 – 54 years (mean, 41). A skull base lesion was detected at the time of imaging for unrelated symptoms. The sphenoid bone was involved in 3 cases, the clivus in 1, and both in 1. Submitting pathologists considered the diagnoses of infection, inflammatory process, storage disease, fibrous dysplasia, histiocytosis, mastocytosis, granular cell tumor, xanthoma, and lipoma. Biopsy specimens showed fragments of sclerotic bone (3 cases) admixed with mature fat (5), foamy histiocytes (4), irregular strands of fibrosis (4), mild chronic inflammation (5), and coarse calcifications (4). These features correlated with imaging findings of sclerotic margins, internal fat and soft tissue densities, and curvilinear calcifications. Special stains were limited due to small specimen size. Histiocytes were positive for CD163 or CD68 (3/3 cases) and negative for S-100 (4/4). Keratin immunostain was negative in all cases (3/3), as were special stains for microorganisms (2/2).

Conclusions: APSB is a developmental variant that may be found incidentally during investigation of another condition. Imaging features may appear alarming to those unaware of this phenomenon. The head and neck pathologist should be familiar with its characteristic histology, in order to avoid excessive special stains or further work-up including potential rebiopsy of this critical anatomic site. The diagnosis of APSB emphasizes the importance of radiologic-pathologic correlation in the evaluation of skull base lesions.

1291 JAK2 Overexpression Is a Prognostic Indicator for Worse Outcome in Nasopharyngeal Carcinoma and Is Independent of JAK2 Exon 12 and JAK2 V617F Mutation

Peir-In Liang, Chien-Feng Li. Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung City, Kaohsiung, Taiwan; Chi Mei Foundation Medical Center, Tainan City, Tainan, Taiwan; Southern Taiwan University of Science and Technology, Tainan City, Tainan, Taiwan; National Health Research Institutes, National Institute of Cancer Research, Tainan City, Tainan, Taiwan.

Background: The nasopharyngeal carcinoma (NPC) has distinct incidence in various races and different geographical regions. It is endemic in southern China, Southeast Asia, and the Middle East. The etiology of NPC is likely multifactorial, which include genetic susceptibility, infection by Epstein-Barr virus (EBV), and environmental factors. There are several molecular pathways involved in the pathogenesis of NPC. JAK2 is one of the four members of the Janus kinase (JAK) family, and its mutation is an important oncogenic driver in myeloproliferative neoplasms and certain hematopoietic malignancies. By using public domain datasets and our well-characterized cohort, we intended to analyze the association of JAK2 expression in NPC.

Design: Two datasets from GEO (GSE12452 and GSE34573) were used to analyze the significance of *JAK2* transcript expression between tumor and non-tumor specimen. JAK2 immunostain was performed on 124 cases of NPC and interpreted using H-score. The result was then correlated with clinicopathological features, disease-specific survival (DSS), distal metastasis-free survival (DMeFS), and local recurrence-free survival (LRFS). Twenty NPC cases with JAK2 overexpression were also submitted for *JAK2* exon 12 and *JAK2* V617F mutation analyses using PCR followed by direct sequencing.

Results: Validation of the datasets in public domain showed that, in contrast with non-tumor specimens, there is an up-regulation of *JAK2* transcript in NPC. In the immunohistochemical study, JAK2 overexpression significantly associated with advanced disease stage (stage I-II vs stage III-IV, $p = 0.019$). Its overexpression also independently predict poor DSS ($p = 0.005$), DMeFS ($p = 0.036$), and LRFS ($p = 0.012$). None of the 20 JAK2 overexpressed NPC cases have *JAK2* exon 12 and *JAK2* V617F mutation.

Conclusions: JAK2 overexpression is associated with advanced disease stage and conferred poor clinical outcome, justifying that JAK2 is a potential prognostic biomarker of NPC. Its overexpression is also independent of *JAK2* exon 12 and *JAK2* V617F mutation.

1292 Diagnostic and Prognostic Utility of Mastermind-Like 2 (MAML2) Gene Rearrangement Detected by Fluorescent In-Situ Hybridization (FISH) in Mucoepidermoid Carcinoma

Peter P Luk, James Wykes, Christina I Selinger, Rafael Ekmejian, Jessica Tay, Kan Gao, Timothy J Eviston, Trina Lum, Sandra A O'Toole, Jonathan R Clark, Ruta Gupta. Royal Prince Alfred Hospital, Sydney, NSW, Australia; Chris O'Brien Lifehouse, Sydney, NSW, Australia; University of New South Wales, Sydney, NSW, Australia; The University of Sydney, Sydney, NSW, Australia.

Background: Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignancy. A proportion of MECs have been shown to harbor MAML2 translocation. This study evaluates the diagnostic and prognostic utility of *MAML2* rearrangement in MEC.

Design: 190 salivary gland malignancies at the Sydney Head and Neck Cancer Institute (1989-2014) were reviewed to identify MECs. Histopathologic evaluation, immunohistochemical and fluorescent in-situ hybridization (FISH) studies were performed on MECs and their morphologic mimics.

Results: 41 cases of MEC were identified with most tumors arising within the parotid gland (71%). The age range was 15 to 79 years (mean: 47 years). The tumor size ranged from 4-70mm (mean: 21mm). 7 locoregional recurrences and 5 MEC related deaths were seen over a 22-year follow-up period. 38 cases were suitable for FISH and 31 (82%) cases were positive for *MAML2* translocation, including oncocytic and clear cell variants of MEC. None of the morphologic mimics of MEC showed *MAML2* rearrangement. Only 3% of patients with *MAML2* rearrangement died of MEC as opposed to 43% of patients without *MAML2* rearrangement.

Conclusions: *MAML2* rearrangement is common and specific for MEC. It is a useful diagnostic tool, particularly in cytology cell blocks and cases with limited material or variant morphology. *MAML2* status also provides prognostic information.

1293 Salivary Duct Carcinoma: Clinicopathologic Features, Morphologic Spectrum and Somatic Mutations

Peter P Luk, Jared D Weston, Bing Yu, Christina I Selinger, Rafael Ekmejian, Timothy J Eviston, Trina Lum, Kan Gao, Michael Boyer, Sandra A O'Toole, Jonathan R Clark, Ruta Gupta. Royal Prince Alfred Hospital, Sydney, NSW, Australia; Westmead Hospital, Sydney, NSW, Australia; The University of Sydney, Sydney, NSW, Australia; University of New South Wales, Sydney, NSW, Australia; Chris O'Brien Lifehouse, Sydney, NSW, Australia.

Background: Accurate diagnosis of salivary duct carcinoma (SDCa) requires a high index of suspicion and clinicopathologic correlation. Hallmark genetic changes that may provide novel therapeutic options are being explored.

Design: 190 salivary gland malignancies at Royal Prince Alfred Hospital (1989-2014) were reviewed. HER2 and androgen receptor status were determined along with multigene profiling.

Results: 23 SDCa were identified, predominantly in men in 5th-9th decade. Facial nerve palsy (12%) and cervical lymph node metastases (82%) were present, and 96% received post-operative adjuvant therapy. Histologically, the tumors resembled high-grade invasive and in-situ ductal carcinoma of breast. Micropapillary, papillary, sarcomatoid,

oncocytic and mucinous variants were seen. The tumours showed androgen receptor (70%), *HER2* amplification (30%) and *HRAS*, *AKT1*, *PIK3CA* and *NRAS* mutations (22%; cumulative). The five-year disease free survival was 36%.
Conclusions: SDCa demonstrate a wide histopathologic spectrum. Treatment strategies need to take androgen receptor, *HER2* amplification and *PIK3CA* mutation into account.

1294 Sinonasal Tract Cribriform Adenocarcinoma of Minor Salivary Glands (CAMSG): Description of a Recently Recognized Neoplasm in a Previously Unrecognized Anatomic Location

Abul Ala Syed Rifat Mannan, Juan C Hernandez-Prera, Cristina Antonescu, Carlos E Bacchi, Giovanni Falconieri, Palmina Cataldi, Bruce M Wenig. Mount Sinai St.-Luke's Roosevelt Hospital Center, New York, NY; Mount Sinai Beth Israel Medical Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Bacchi Lab/Consultoria em Patologia, Botucatu, Brazil; University of Trieste, Trieste, Italy; University of Udine, Udine, Italy.
Background: CAMSG is a distinctive low-grade adenocarcinoma characterized by recurrent gene rearrangements in *PRKD1-3* that shows morphological overlap with polymorphous low-grade adenocarcinoma (PLGA). Majority of cases have been described to arise in minor salivary glands of the oral cavity. Herein, we describe three cases of CAMSG arising in the sinonasal tract.
Design: 3 cases of primary sinonasal CAMSG were retrieved from our files and reviewed. Cases were subject to immunohistochemical (IHC) staining for CK8/18, CK7, S100, p63, SMA, calponin, CD117, and TTF1. Fluorescence in situ hybridization (FISH) analysis using custom BAC probes for *PRKD1*, *PRKD2* and *PRKD3* was performed. Available clinical parameters were obtained.
Results: The patients were all women ranging in age from 75 to 89 years (mean, 82 years). One case presented with destruction of the left maxillary, frontal and ethmoid sinuses; one case arose in the left sphenoid sinus with invasion into the ipsilateral orbit and middle cranial fossa; and one case arose in the right maxillary sinus with osseous invasion and nodal metastasis. All tumors were characterized by an invasive carcinoma with cribriform, microcystic, tubular/glandular and papillary growth. The neoplastic cells were rather uniform and showed cytomorphologic features reminiscent of those seen in papillary thyroid carcinoma. IHC staining included variable expression for CK8/18, CK7, p63 and S-100 protein; all cases were negative for calponin, TTF1, SMA and CD117. FISH revealed *PRKD* gene rearrangements in 2 cases, including *PRKD1* and *PRKD2*; 1 case was negative.
Conclusions: To the best of our knowledge, these are the first reported cases of CAMSG arising in the sinonasal tract. Our cases expand the current knowledge of CAMSG, a tumor primarily arising in the oral cavity and validate the utility of *PRKD* gene rearrangements in the diagnosis of this tumor.

1295 Incidence of Recently Described Salivary Gland Carcinoma Types Presenting in an Urban Population: A Retrospective Analysis

Mena Mansour, Juan C Hernandez-Prera, G K Haines, Elizabeth G Demicco. Mount Sinai Hospital, New York, NY.
Background: Malignant salivary gland tumors (SGCA) comprise a diverse and diagnostically challenging group of tumors. With the advent of molecular diagnostics, a number of new entities have been recently described and reclassified, which were not recognized in previous classification systems, such as the 2005 WHO. The goal of this study is to determine the incidence of these tumors in a large, diverse metropolitan population.
Design: All available SGCA specimens diagnosed at our institution between 1994 and 2014 were retrieved from the pathology archives. H&E slides were reviewed and reclassified, taking into account recently described entities, including cribriform adenocarcinoma of minor salivary glands (CAMSG), mammary analogue secretory carcinoma (MASC), clear cell carcinoma (CCCA) and sinonasal adenoid cystic like carcinoma. Cases with equivocal diagnoses were grouped in a separate category for further workup by immunohistochemical and/or molecular studies.
Results: Of 596 patients diagnosed with SGCA, 495 (83%) had slides available for review. Initial diagnoses were confirmed in 322 (65%) of cases, changed in 97 (20%) and required further diagnostic workup in 76 (15%). 8 cases were reclassified as benign, and 15 as not of salivary gland origin. After reclassification, SGCA diagnoses included: 18/472 (4%) MASC, 18 (4%) CCCA, 6 (1%) CAMSG and 1 sinonasal adenoid cystic like carcinoma. Mucoepidermoid carcinoma was the most common diagnosis (n=132, 28%), followed by adenoid cystic carcinoma (n=74, 16%), SGCA NOS (n=36, 8%, including 13 carcinoma ex-pleomorphic adenoma), acinic cell carcinoma (n=29, 6%), polymorphous low grade adenocarcinoma (n=24, 5%) high grade salivary ductal carcinoma (n=23, 5%), myoepithelial carcinoma (n=13, 3%), epithelial-myoepithelial carcinoma (n=12, 3%), and basal cell adenocarcinoma (n=4, 1%), with rare entities including neuroendocrine carcinoma, and cases requiring additional workup accounting for the remainder of cases.
Conclusions: Recently described entities accounted for 9% of SGCA in a preliminary morphologic assessment of salivary gland carcinomas. Further immunohistochemical, molecular, and clinicopathologic studies are pending to confirm diagnoses in equivocal cases and determine the significance of reclassification on tumor prognosis.

1296 Ameloblastoma: Twenty Five Year Experience at a Single Institution

Tatyana Milman, Wei Pan, Virginia LiVolsi. Perelman School of Medicine, Philadelphia, PA.
Background: Ameloblastoma is a rare, locally aggressive odontogenic neoplasm, accounting for 1% of head and neck tumors. Recent literature suggests that the surgical approach and histologic growth patterns are the most important prognostic determinants in ameloblastoma. The aim of this study was to compare the clinical presentation, surgical management, and outcomes of patients with ameloblastoma, spanning the course of 2 decades at a single institution, with the data reported in the literature.
Design: Following the IRB approval, the institution's database was searched for all patients with pathologically confirmed ameloblastoma, diagnosed between 1990 and 2015. The data collected included sex, age, tumor location, management, recurrence, time to recurrence, disease-related mortality, length of follow-up, histologic pattern, and clearance of surgical margins. The potential risk factors of recurrence were evaluated using log-rank test and proportional hazard model for calculating hazard ratio and its 95% confidence intervals (95% CI). The statistical analyses were performed in SAS V9.4 (SAS Institute Inc, Cary, NC) and two-sided $p<0.05$ was considered to be statistically significant.
Results: Review of the database yielded 54 patients with pathologically-confirmed ameloblastoma and a sufficient follow-up. There was male predominance (39 males, 15 females). Ameloblastoma was diagnosed at a median age of 57.5 years (range 13-88). Nineteen tumors were localized to the maxilla (35%) and the remainder involved the mandible. Radical resection (total or radical maxillectomy or mandibulectomy) was performed in 33 (61%) of the patients, while the remainder were managed with limited surgery. The average length of follow-up was 6.4 years (range 0.1 – 30). Recurrence was noted in 13 (24%) patients. Surgical approach was strongly associated with the risk of recurrence (RR=11.1, $p = 0.002$). There was a trend toward higher recurrence rate in the group with pathologically documented positive margins, but it reached borderline statistical significance (42.1% vs, 14.8%, p=0.054). There was no significant association between the recurrence and the patient age, sex, tumor location, or histologic pattern. Malignant transformation into ameloblastic carcinoma was identified in one follicular ameloblastoma. None of the patients succumbed to their disease.
Conclusions: Our study confirms the recent data regarding the importance of complete surgical resection in management of ameloblastoma. Surgical approach appears to be the strongest predictor of tumor clearance.

1297 Prognostic Significance of Histological Tumor Regression at Primary Site and Nodal Metastases in Patients with Oral Squamous Cell Carcinoma, Treated by Neo-Adjuvant Chemotherapy Followed by Surgery

Ashwini N, Kumar Prabhash, Shubhada Kane, Anil D'Cruz, Munita Bal, Rajiv Kaushal, Asawari Patil. Tata Memorial Centre, Mumbai, Maharashtra, India.
Background: Neoadjuvant chemotherapy (NACT) may help in successful resection and prolonged overall survival (OS) in advanced oral squamous cell carcinoma (OSCC). Histological assessment of the tumor regression in post NACT specimens has not been studied in detail in OSCC. This study focuses on assessing types of response in primary tumor (PT) and lymph node metastasis (LNM) in OSCC after NACT and devising a tumor regression grading (TRG) system for prognostication.
Design: 200 OSCC cases that underwent resection after NACT (2009-2012) were selected. Tumor regression was evaluated in PT and LNM on histopathology by evaluating percentage of viable tumor (PVT) and percentage of treatment response (including fibrosis, inflammation, foreign body giant cell reaction, dystrophic calcification, keratin flakes and necrosis). TRG was assigned to PT using PVT on basis of Mandard grading system (TRG 1-5: 1 = 0%, 2 = <5%, 3: 5 = 5-50%, 4 = 51-95%, 5 = >95%). A modified TRG (MTRG) was also assigned by combining TRG as: MTRG 1 = TRG 1+2, MTRG 2 = TRG 3, MTRG 3 = TRG 4+5. Additional parameters studied include: Tumor grade (TG), lymph node status (N stage), disease free survival (DFS) and OS. Statistical analysis was done using SPSS version 20.00.
Results: The distribution of TRG and MTRG is as follow:

TRG	Number of cases	Percentage
1	17	8.5
2	21	10.5
3	32	16.0
4	83	41.5
5	47	23.5

MTRG	Number of cases	Percentage
1	38	19.0
2	32	16.0
3	130	65.0

The most common response at PT was fibrosis, followed by inflammation in contrast to that in LNM being keratin flakes and calcification TRG was significantly associated with TG in PT (p 0.000) and PVT in LNM (p 0.003). In addition, MTRG, but not TRG, was seen significantly associated with N stage (p 0.043) and DFS (p 0.037). No significant association of OS was seen with TRG or MTRG. On multivariate analysis, OS was significantly associated with PVT in LNM (p 0.015), in addition to time tested parameters: TG in PT (p 0.000) and N stage (p 0.001).
Conclusions: Modified TRG in PT and PVT in LNM prove to have prognostic significance and warrant inclusion of these parameters while reporting post NACT specimens. This will help us to identify and study biology subset of tumors not responding to therapy and individualize the NACT regimen.

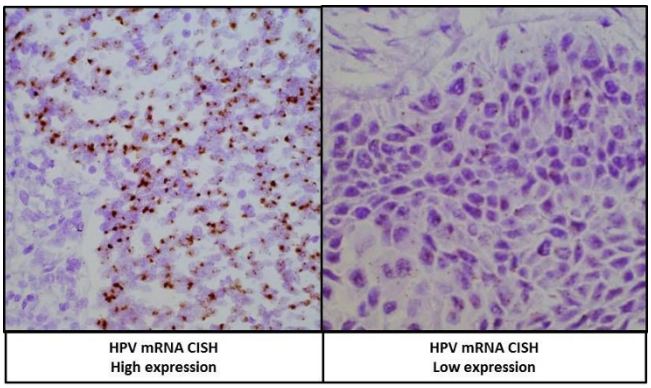
1298 Investigation of High Risk HPV E6/E7 mRNA Transcriptional Activity by In Situ Hybridization in Sino-Nasal Inverted Papilloma with Associated Dysplasia and Malignant Transformation

Shobha Parajuli, Rashmi Tondon, Amy Ziober, Kathleen Montone, Kumarasen Cooper. Hospital of the University of Pennsylvania, Philadelphia, PA.

Background: Schneiderian inverted papilloma comprises 0.5% nasal tumors and affects males in 6th decade with a recurrence rate of 12.8-34%. Malignant transformation is a poorly understood complication seen in 5-15%. HPV 6/11 has been implicated in benign papilloma while oncogenic types 16/18 are associated with malignant transformation. Previous HPV detection rates of 37.8-100% depended on histological type, sample size and methodology. A recent study examining HPV E6/E7 mRNA transcripts in inverted papilloma suggested a higher sensitivity than PCR. (Stoddard, 2105)

Design: We evaluate the high-risk HPV E6/E7 mRNA expression in inverted papilloma with malignant transformation. We performed a retrospective study of 19 patients with inverted papilloma and dysplasia with or without malignant progression from 2005 to 2015 at Hospital of the University of Pennsylvania. After review, FFPE specimens were evaluated for HR HPV E6/E7 mRNA transcription using chromogenic in situ hybridization.

Results: Of 19 cases of inverted papilloma with dysplasia, 14 cases (70%) demonstrated malignant transformation into invasive squamous cell carcinoma. 70% were male, with average age of 67 years (range 53-90 years). RNAscope detected HPV mRNA transcripts in 10 patients (71%) with malignant transformation and 4 patients (80%) without malignant transformation. Invasion in 2 cases of inverted papilloma was cut through. High level of expression of mRNA transcripts was noted in 5 cases (36%) with malignant transformation and 3 cases (60%) without malignant transformation. Low level of expression of mRNA transcripts was noted in 5 cases (36%) with malignant transformation and 1 case (20%) without malignant transformation. Benign inverted papilloma was present in 13 cases with high level of expression in 3 cases (23%) and low level of expression in 8 cases (61%).



Conclusions: This study demonstrates a high prevalence of HR HPV in sino-nasal inverted papilloma with dysplasia, and an equally strong correlation with malignant transformation. These findings are highly suggestive of an etiological role for HPV in the transformation of IP to dysplasia to squamous cell carcinoma.

1299 Use of p40, p63, and Ki-67 in the Differential Diagnosis of Polymorphous Low-Grade Adenocarcinoma, Cellular Pleomorphic Adenoma, and Adenoid Cystic Carcinoma

Vatsal Patel, Tina Woods, Larry J Fowler, Donald Cohen. University of Florida, Gainesville, FL.

Background: Polymorphous low-grade adenocarcinomas (PLGA) can have a wide variety of histologic architectural patterns, hence the name "polymorphous." This leads to difficulties in distinguishing this entity from many other salivary gland neoplasms, in particular cellular pleomorphic adenomas and adenoid cystic carcinomas. Accurate diagnosis is essential since PLGA and adenoid cystic carcinomas are malignant while pleomorphic adenomas are benign. Thus far, immunohistochemical stains haven't been helpful. However, recently Rooper et al. reported an immunophenotype of p63+/p40- in 100% of PLGA, and p63+/p40+ for 90% of adenoid cystic carcinoma.

Design: We reviewed H&E slides from 16 PLGA, 9 cellular pleomorphic adenomas, and 10 adenoid cystic carcinoma within the department archives. The diagnosis on H&E was confirmed by the investigators. IHC for p40, p63, and Ki-67 was performed for each case. The IHC stain results were independently reviewed by the two faculty pathologists. For p40 and p63, positivity or negativity was reported along with whether staining pattern was "diffuse" or "patchy." The Ki-67 mitotic index was estimated by only one faculty Pathologist.

Results: Of the PLGAs, 13/16 had the p63+/p40- immunophenotype while 8/10 adenoid cystic carcinoma had the p63+/p40+ immunophenotype. The staining pattern for cellular pleomorphic adenoma was variable with 4 cases displaying the p63+/p40+ immunophenotype and the remaining 5 cases displaying the p63-/p40- immunophenotype. Of the 13 PLGAs with the p63+/p40- immunophenotype, 5 cases had a p63 which was positive only in a patchy distribution. The average Ki-67 mitotic index was 4.93 ± 2.49 for PLGAs, 5.11 ± 2.14 for cellular pleomorphic adenoma, and 15.20 ± 10.67 for adenoid cystic carcinoma.

Conclusions: A p63+/p40- immunophenotype is specific for the diagnosis of PLGA as 13/14 cases with this phenotype were PLGAs. However, these immunostains may not be reliable when making the diagnosis on small biopsy since the pattern of p63 staining was considered "patchy" in 5 of 13 of the PLGAs with the p63+/p40- immunophenotype. Overall, both p63 and p40 has value when these entities are in the differential diagnosis. The Ki-67 mitotic index was noticeably higher in the adenoid cystic carcinomas when compared to cellular pleomorphic adenomas and PLGAs. However, there was no significant statistical difference, likely due to the small sample size.

1300 Sinonasal Carcinoma Arising in Schneiderian Papilloma: Clinicopathological Review of 27 Cases

Asawari Patil, Tanvee Kulkarni, Ashwini Natu, Munita Bal, Rajiv Kumar, Swapnil Rane, Shubhada Kane. Tata Memorial Centre, Mumbai, Maharashtra, India.

Background: Scheiderian papilloma (SP) are uncommon benign epithelial neoplasms of sinonasal tract. Malignant transformation in SP (CA-ex-SP) is exceedingly rare (11%). Very few series in literature provide comprehensive review of Ca-ex-SP. This study describes clinico-pathological profile of 27 cases of sinonasal Ca-ex-SP diagnosed at a tertiary cancer care centre.

Design: Cases of sinonasal Ca-ex-SP or sinonasal carcinoma with prior history of SP, diagnosed at our institute during 2009-2015, were retrieved from pathology archives. Only those cases were included in the study which showed at least focal area of residual SP along with carcinoma or SP in prior biopsy. Histopathological parameters reviewed include: Tumor type, tumor grade, type of SP and dysplasia in SP. Clinical details and radiological findings were obtained from electronic medical records.

Results: 27 cases of sinonasal Ca-ex-SP were identified with male to female ratio being 1.7:1.0 and age ranging from 35 to 70 years (Mean: 51). Ten cases showed tumor involving multiple anatomic sites. The commonest site involved was maxillary sinus (21 cases) with extension to nasal cavity, followed by ethmoid sinus (6 cases) extending to frontal sinus in 2 cases and sphenoid sinus in 1 case. Majority of them were squamous cell carcinoma (25 cases, including: 14 poorly differentiated, 8 moderately differentiated, 2 well differentiated, 1 transitional type), others being undifferentiated carcinoma (1 case) and adenosquamous carcinoma (1 case). Synchronous tumors were common (24 cases), while three were metachronous with prior history of SP. Invasive focus was differentiated from papilloma by presence of one or more of following features: loss of basement membrane, cellular pleomorphism, paradoxical maturation, atypical mitoses, stromal response. The commonest morphology of residual papilloma was inverted type (in 25 cases), followed by oncocytic type (1 case, associated with adenosquamous carcinoma) and mixed inverted-oncocytic type (1 case). Dysplasia ranging from mild to severe was seen in residual SP with three cases showing carcinoma-in-situ. Two cases showed scanty focus of invasive carcinoma associated with SP showing severe dysplasia in one case and carcinoma in situ in the other.

Conclusions: This is largest series of sinonasal Ca-ex-SP, an uncommon tumor. These tumors are known to have better clinical outcome. Presence of dysplasia in SP associated with carcinoma is described in literature and is also seen in our series. A thorough examination of specimen of SP with dysplasia is needed to look for presence of invasive carcinoma.

1301 HPV Prevalence in HIV Patients with Head and Neck Squamous Cell Carcinoma

Annabelle Picard, Cecile Badoual, Muriel Hourseau, Caroline Halimi, Helene Pere, Beatrix Barry, Sebastien Albert. Bichat Hospital, APHP, Paris, France; European G Pompidou Hospital, APHP, Paris, France; Bichat Hospital, Paris, France.

Background: The implication of HPV in head and neck squamous cell carcinoma (HNSCC) is well established, especially in oropharyngeal SCC. HIV patients have a higher risk of persistent HPV infection. We investigated the role of HPV in HNSCC carcinogenesis in HIV population.

Design: We conducted a retrospective monocentric study. We studied HIV patients who presented with HNSCC between 1994 and 2014. For each patient, tumor characteristics, HIV disease and survival information were collected. Tumor HPV testing was performed using p16 immunohistochemistry, *in situ* hybridation and PCR. We assessed the percentage of HPV in this population of HIV patients with HNSCC and compared HIV disease characteristics based on HPV status.

Results: Forty seven patients were included : 11 women/36 men, the median age was 50 years. Tumor HPV testing was performed in 40 patients. Tumors were located in oropharynx (32%), oral cavity (32%), larynx (21%) and hypopharynx (11%). At the time of diagnosis, median CD4 level was 385/mm^3, 31% of the patients were stage CDC C. The percentage of HPV linked to HNSCC for all locations in HIV patients was 30% (n=12). HPV16 accounted for 50% of all HPV genotypes. HPV positive status was associated with a stage CDC 3 (p=0,026), but not with CD4 level at time of diagnosis (p=0,414). HPV negative tumor was associated with poorer 5-year overall survival (HR=15,2 ; IC95% 2,5-92,5 ; p=0,0031).

Conclusions: HPV plays a critical role in HNSCC development in HIV population. HIV immunodeficiency may increase HPV persistence and progression of HNSCC.

1302 MYC and MYB Are Coexpressed in Adenoid Cystic Carcinoma

Marc Pusztaszeri, Patrizia Bordignon, Thomas McKee, William C Faquin. Geneva University Hospitals, Geneva, Switzerland; Massachusetts General Hospital, Boston, MA.

Background: A specific translocation t(6;9) involving *MYB* and *NFIB* genes has been identified in adenoid cystic carcinoma (AdCC) where it contributes to MYB overexpression. MYB targets many genes, including c-*KIT, BCL2* and *MYC,* involved in cell cycle control, transcriptional regulation, and apoptosis. C-KIT, BCL2, and MYC have been shown to be overexpressed in AdCC, and recently a potential role of MYC in AdCC dedifferentiation has been suggested. This is the first systematic study to investigate the combined expression of MYB and MYC protein expression in a series of AdCC.

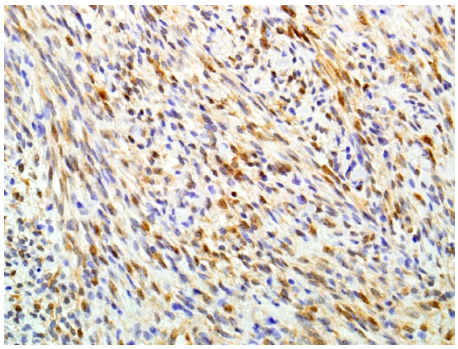
Design: We assessed the expression of MYB and MYC in AdCC (n=20) and in a control group of pleomorphic adenomas (PAs; n=20) using immunohistochemistry on formalin-fixed paraffin embedded tissue from surgical resection specimens. The nuclear expression of MYB and MYC was assessed semi-quantitatively using the Allred scoring system (0 to 8).
Results: MYB and MYC were both variably and heterogeneously expressed in AdCC with a mean Allred score of 6.25 (range: 2-8) and 5.7 (range: 4-8), respectively. The expression levels of MYB and MYC were significantly higher in AdCC than in PAs where the mean Allred score was 2.45 (range: 0-4) for MYB (p=0.0001) and 2.75 (range: 0-6) for MYC (p=0.0001). Using a cut-off score ≥6, the sensitivity and specificity to distinguish AdCC from PA were 60% and 100% using MYB, and 50% and 95% using MYC. Focal cytoplasmic staining with MYC was also present in a minor subset of PAs but not in AdCC.
Conclusions: The expression of MYC correlates with the expression of MYB in AdCC, and is significantly higher than in PA. This suggests that MYC is activated in MYB positive AdCC. Large clinico-pathological studies should investigate the prognostic and predictive values of MYC and MYB in AdCC.

1303 Myb and Androgen Receptor Expression in Salivary Gland Basal Cell Adenoma and Basal Cell Adenocarcinoma

Sydney Rooney, Brennan Tesdahl, Robert Robinson. University of Iowa, Iowa City, IA.
Background: Molecular markers and hormone receptor expression have been suggested to be of value in the diagnosis as well as treatment of certain salivary gland neoplasms. Basal cell adenoma and basal cell adenocarcinoma represent uncommon basaloid salivary gland neoplasms, appearing morphologically very similar to one another. Besides basal cell adenoma and adenocarcinomas, other salivary gland neoplasms are also composed of basaloid cells, sometimes causing significant difficulty in the histologic separation from these other neoplasms. Recently, *myb* expression has been suggested as a means of supporting a diagnosis of adenoid cystic carcinoma, which can be a mimic of basal cell adenoma and basal cell adenocarcinoma, particularly in small or limited samples. Using tissue microarrays, we studied a group of basal cell adenomas and basal cell adenocarcinomas for expression of *myb* and androgen receptor.
Design: We have previously reviewed the pathologic features of 69 neoplasms diagnosed as basal cell adenoma or basal cell adenocarcinoma gathered from our institution. From these tumors we constructed tissue microarrays using 30 basal cell adenomas and 17 basal cell adenocarcinomas with each tumor replicated in triplicate. The arrays were then stained with antibodies to *myb* and androgen-receptor. Staining was assessed for presence or absence and intensity within the tumor. Nuclear staining was evaluated for both tumors and a minimum of 10% staining in the averaged tumor cores was considered positive. Intensity of staining was graded on a 1-3 (weak to strong) basis.
Results: For *myb*, staining was almost always 2 or 3+ intensity as was androgen receptor in both the basal cell adenomas and basal cell adenocarcinomas. Basal cell adenomas expressed *myb* in 17/30 (57%) of cases while basal cell adenocarcinomas expressed *myb* in 9/17 (53%) of cases. No correlation of *myb* expression to clinical outcome or tumor morphologic characteristics was found with either the basal cell adenomas or adenocarcinomas. Androgen receptor expression was seen in only 1/30 (3%) of basal cell adenomas and 3/17 (18%) of basal cell adenocarcinomas and no correlation to clinical outcome or morphology was noted.
Conclusions: The findings suggest that anti-androgen receptor agents would not be effective in treating basal cell adenocarcinomas. *Myb* expression does not help separate basal cell adenomas from basal cell adenocarcinomas nor does it appear likely that it could separate either of them from adenoid cystic carcinoma.

1304 Nuclear B-catenin Expression Provides a Consistent Immunohistochemical Correlate for PAX3 Rearrangements in Biphenotypic Sinonasal Sarcoma

Lisa M Rooper, Shih-Chiang Huang, Cristina Antonescu, William H Westra, Justin A Bishop. Johns Hopkins Hospital, Baltimore, MD; Memorial Sloan Kettering Cancer Center, New York, NY.
Background: Biphenotypic sinonasal sarcoma (BSNS) is a recently recognized low-grade sarcoma exhibiting both neural and myogenic differentiation. This unique dual phenotype stems from recurrent rearrangements in PAX3, a transcription factor that promotes commitment to either lineage. Among other mechanisms, PAX3 functions through activation of the Wnt-B-catenin pathway. While identification of PAX3 rearrangements by FISH can confirm a BSNS diagnosis, this assay is not widely available. This study evaluates whether an expanded immunohistochemical panel can facilitate differentiation of BSNS from mimickers including cellular schwannoma, malignant peripheral nerve sheath tumor (MPNST), and leiomyosarcoma.
Design: Nine cases of BSNS were identified from the surgical pathology archives of two academic medical centers. In 6 cases, the diagnosis was confirmed by FISH using custom probes for PAX3; in 3 cases FISH failed but histologic and immunophenotypic findings were diagnostic for BSNS. Immunohistochemistry (IHC) for S100, calponin, SMA, B-catenin, SOX10, myogenin, desmin and factor XIIIa was performed on whole slide sections.
Results: All 9 BSNS (100%) were at least focally positive for S100 as well as calponin and/or SMA. In addition, 8/9 BSNS (89%) expressed nuclear B-catenin, 6/8 (75%) were positive for factor XIIIa, 4/9 (44%) expressed desmin, and 3/8 (37.5%) were positive for myogenin. All 9 tumors were negative for SOX10.



Conclusions: Most cases of BSNS exhibit nuclear B-catenin immunoreactivity, consistent with Wnt-B-catenin activation resulting from their characteristic PAX3 rearrangements. In light of previous studies showing that cellular schwannomas, MPNSTs and leimoysarcomas do not express B-catenin in a nuclear distribution, an immunohistochemical profile that includes B-catenin could help separate BSNS from these mimickers and establish the diagnosis without the need for gene rearrangement studies.

1305 A Second-Generation Probe for HPV DNA In-Situ Hybridization Lacks Sensitivity for HPV Detection in Oropharyngeal Squamous Cell Carcinoma

Lisa M Rooper, Justin A Bishop, William H Westra. Johns Hopkins Hospital, Baltimore, MD.
Background: The need to establish the HPV status of oropharyngeal squamous cell carcinomas (OPSCCs) is important, but the ability to perform accurate HPV testing has been jeopardized by the recent withdrawal from the market of a popular first-generation DNA in-situ hybridization (DISH) probe. A second-generation HPV DISH platform has since been introduced but has not been rigorously evaluated against other highly sensitive and specific assays such as RNA-in situ hybridization (RISH).
Design: The second-generation Patho-Gene HPV Type 16/18/31/33/51 DISH (Enzo Life Sciences, Lausen, Switzerland) was performed on 83 whole-slide sections of OPSCCs that had previously been evaluated with p16 immunochemistry (MTM Laboratories, Heidelberg, Germany) and RNAscope HPV-HR18 RISH (Advanced Cell Diagnostics, Hayward, CA). All slides were independently scored by 3 reviewers.
Results: Patho-Gene HPV DISH was positive in only 17 out of 59 (28.8%) cases that were positive for p16 and HPV RISH. It was negative in all 5 cases (0%) that were p16 positive but HPV RISH negative. It also was negative in all 19 cases (0%) that that were p16 negative and HPV RISH negative. Reviewers achieved only moderate inter-observer agreement when evaluating Patho-Gene DISH (kappa = 0.704), while HPV RISH facilitated almost perfect agreement (kappa = 0.939).
Conclusions: This study demonstrates that a second-generation HPV DISH probe has inferior performance for HPV detection compared to HPV RISH. The sensitivity of Patho-Gene HPV was just 28.8% compared to a gold standard of RISH positivity. Moreover, Patho-Gene HPV showed considerably poorer inter-observer agreement than RISH. HPV RISH remains a preferable alternative to second-generation HPV DISH for HPV testing in OPSCC.

1306 Expression of an Androgen Receptor Splice Variant in Salivary Duct Carcinoma: An Instrument of Resistance?

Dipti Sajed, Chin-Lee Wu, Vania Nose, Vikram Deshpande. Massachusetts General Hospital, Boston, MA.
Background: Salivary duct carcinoma (SDC) is an aggressive salivary gland tumor which presents at an advanced stage, often with nodal metastases, and has a high recurrence rate. Despite aggressive management with resection, lymph node dissection, and chemoradiation, SDC carries a poor prognosis. Alternative therapeutic efforts exploiting androgen receptor (AR) expression in these tumors in the form of androgen deprivation therapy (ADT) have not demonstrated unequivocal clinical benefit. Recent revelations in the field of prostate cancer have highlighted a strong association of the expression of a ligand-independent, constitutively active AR splice variant - ARV7 - with resistance to ADT. Similarly, we hypothesize that the expression of ARV7 in SDC may in part account for resistance to ADT observed in preliminary studies.
Design: In situ hybridization (ISH; QuantiGene® ViewRNA, Affymetrix) using AR and ARV7 RNA probes was performed on 12 FFPE tissue samples from patients with SDC. Scoring as follows: 3 - diffuse signal at 4x; 2 - diffuse signal at 10x; 1 - diffuse or focal signal at 20x; 0 - equivalent to background signal. AR and Her2 IHC were reviewed.
Results: Age range was 50-83 (mean = 65) years, with 9 male and 3 female pts. All cases were of conventional apocrine histology with the parotid as the 1° site (two exceptions: 1 buccal, 1 unknown). All but 3 had nodal metastases and 3 arose in the setting of carcinoma ex pleomorphic adenoma. All SDCs were diffusely positive for AR via IHC. IHC and ISH scoring as follows:

Score	ISH AR	ISH ARV7	IHC Her2
3+	8/12 (67%)	0	5/12 (41%)
2+	4/12 (33%)	3/12 (25%)	3/12 (25%)
1+	0	4/12 (33%)	2/12 (17%)
0	0	5/12 (42%)	2/12 (17%)

A strong ISH score (3+/2+) correlated with AR positivity by IHC. There was no association between AR ISH and ARV7 ISH nor between ARV7 ISH and Her2 IHC.
Conclusions: Our results indicate that AR ISH correlates with AR IHC in SDC, matching previous reports of high AR expression in the vast majority of SDC cases. Importantly, this is the first demonstration of mRNA expression of an AR splice variant that is associated with resistance to ADT in a large subset of SDCs (58%). The significance of the expression of a ligand-independent, constitutively active AR splice variant in SDC is at least twofold. One, clinical trials evaluating the efficacy of ADT in SDC should take into account ARV7 expression status to avoid masking any benefit of ADT. Two, a low expression of ARV7 might contribute to resistance, a consequence of the expansion of ARV7-positive clones.

1307 BRAF, KIT, NRAS and TERT Mutation Analysis in Head and Neck Mucosal Melanomas

Sule Sari, Ismail Yilmaz, Orhun C Taskin, Yasemin Ozluk, Nesimi Buyukbabani. IU Istanbul Faculty of Medicine, Istanbul, Turkey; GATA Military Hospital, Istanbul, Turkey.
Background: Head and neck mucosal melanomas (HNMM) are rare tumors consisting less than 1% of all malignant melanomas (MM) known to be more aggressive than their dermal counterparts. Mortality rates are high as they are resistant to conventional therapies. Various genetic alterations have been discovered in MM throughout the last decade. Given the rarity of HNMMs the frequency of BRAF, KIT, NRAS mutations have not been well characterized in these tumors. Mutation of TERT promoter region has been recently introduced in cutaneous melanoma. Frequency of this mutation in HNMMs is yet to be determined as it has been investigated only in few series. This study aims to analyze BRAF, KIT, NRAS, TERT gene mutations in HNMMs, better define their frequency and provide data for their potential application in targeted therapy.
Design: We collected 32 cases of HNMMs (21 sinonasal, 9 oral mucosa, 2 nasopharynx) diagnosed at our institution between 2001 and 2015. DNAs were isolated from manually microdissected unstained sections. BRAF (exon (ex.) 15) , KIT (ex. 9,11,13,14,17,18), NRAS (ex. 2,3), and TERT promoter region (including the position of C228T and C250T mutations) were amplified by PCR. The amplicons were submitted to direct sequencing in both directions by using Big Dye Terminator kit and analyzed in the ABI 3730 automatic sequencer.
Results: The Female/male ratio of patients was 18/14 with a mean age of 62.1 (28-87). Follow-up period ranged from 5 to 142 months, with a median of 16.5. Twenty four (75%) patients died from melanoma related reasons. Overall 18.75% (6/32) of cases harbored one of BRAF (1/6), KIT (1/6), NRAS (1/6) and TERT (3/6) mutations. Aforementioned mutations were observed to be mutually exclusive.

No	Mutation	Age	Sex	Localization	Survival	Follow-up (months)
1	BRAF (c.1799T>A, p.V600E)	56	F	Nasal cavity	DOD	13
2	KIT (c.1727T>C, p.L576P)	66	F	Nasal cavity	Alive	98
3	NRAS (c.34G>T, p.G12C)	35	M	Paranasal sinus	Alive	100
4	TERT (250C>T)	46	F	Nasal cavity	DOD	7
5	TERT (250C>T)	60	M	Nasal cavity	DOD	9
6	TERT (250C>T)	81	M	Maxillary sinus	DOD	12

Conclusions: Our results show that BRAF, KIT, NRAS and TERT mutations are rarely present in HNMMs and TERT mutation is the most frequently encountered. One other striking finding is the absence of any mutation in oral mucosa or nasopharynx. We think that our study will contribute to the literature that has limited data about molecular alterations in HNMMs.

1308 Programmed Cell Death-Ligand 1 (PD-L1) Expression in Oral Cavity Squamous Cell Carcinoma (OSCC)

Laveniya Satgunaseelan, Jason Madore, Noel Chia, Trina Lum, Carsten E Palme, Michael Boyer, Richard A Scolyer, Jonathan R Clark, Ruta Gupta. Royal Prince Alfred Hospital, Sydney, NSW, Australia; University of Sydney, Sydney, NSW, Australia; Melanoma Institute of Australia, Sydney, NSW, Australia; University of New South Wales, Sydney, NSW, Australia; Chris O'Brien Lifehouse, Sydney, NSW, Australia; Sydney Head and Neck Cancer Institute, Sydney, NSW, Australia.
Background: Interaction of PD-L1 with the PD-1 receptor on T-cells negatively regulates T-cell function thereby promoting tumour-mediated immune evasion. Clinical trials of monoclonal anti-PD-1 antibodies have reported high response rates and improved survival in patients with a variety of malignancies. The efficacy of these treatments in OSCC is unknown. PD-L1 expression correlates with response to anti-PD1 therapies in some tumour types. Data regarding immunohistochemical expression of PD-L1 in OSCC is limited. The aim of this study was to characterise the immunohistochemical expression of PD-L1 in OSCC and determine its associations with clinicopathological features and patient outcome.
Design: Histopathology review of 217 patients with OSCC in the Sydney Head and Neck Cancer Institute database was performed for various pathological features including tumour-infiltrating lymphocytes (TILs). Tissue microarrays were constructed and immunohistochemistry for PD-L1 (clone 22C3), CD4 and CD8 was performed.
Results: PD-L1 expression in >5% of tumor cells was present in 40 (18.3%) cases; it was significantly more frequent in females (p=0.013), in SCC of the tongue (p=0.05), and in tumors with dense TILs (p>0.001). The percentage of cells showing PD-L1 expression was significantly associated with disease-free survival (p=0.05), however this was not an independent predictor on multivariable analysis. There was no significant association with overall survival or improved outcome following adjuvant chemoradiotherapy.
Conclusions: PD-L1 expression is frequent in OSCC, particularly in women. An inflammatory phenotype may be a surrogate marker of PD-L1 expression, particularly in small biopsies, as PD-L1 expression can be heterogeneous.

1309 The Effects of Chemoradiotherapy on Patient Outcomes and Tumor Viability in Cervical Lymph Node Metastases in Head and Neck Squamous Cell Carcinoma

Kathryn Scherpelz, Mark Lingen, Nicole A Cipriani. University of Chicago, Chicago, IL.
Background: Head and neck squamous cell carcinoma (HNSCC) frequently metastasizes to cervical lymph nodes. Prior to surgical resection, patients are occasionally treated with chemoradiation (CRT) to decrease tumor burden. The effects of preoperative CRT (pCRT) on histologic evidence of tumor viability have not been well-studied or correlated to patient outcomes. This study investigates the features of HNSCC metastatic to lymph nodes and aims to correlate histologic and immunohistochemical features to patient outcomes.
Design: 92 HNSCC patients with lymph node metastasis who underwent neck dissection at the University of Chicago were identified. 63 received pCRT; 29 did not. Diagnostic slides from the neck dissections were reviewed for the presence of viable SCC or the presence of treatment effect (fibrosis, hemosiderin, foamy histiocytes, nucleate or anucleate keratin debris) without viable SCC. Immunomarkers of proliferation (Ki67, cyclin D1), apoptosis (caspase 3), and DNA damage (H2AX) were performed on lymph nodes with viable SCC or nucleate keratin debris. Staining was graded as high, intermediate, or low (cyclin D1, caspase 3, H2AX), or by percent of positive tumor cells (Ki67). pCRT status and tumor viability were correlated to disease recurrence.
Results: Of 63 patients receiving pCRT, 17 had viable SCC and 46 had treatment effect only (8 with nucleate keratin debris). All 29 patients without pCRT had viable SCC. Amongst patients who received pCRT, those without viable tumor had decreased risk of disease recurrence compared to those with viable tumor after pCRT (p=0.016). Patients with viable tumor who had received pCRT had a higher risk of disease recurrence than those with viable tumor who did not receive pCRT (p=0.026). Patients with viable tumor who received pCRT had significantly decreased expression of Ki67 compared to those with viable tumor who did not receive pCRT (p=0.034). Expression of cyclin D1, caspase 3, and H2AX was not significantly different. Nucleate keratin debris had negligible levels of staining for all markers.
Conclusions: HNSCC patients who receive pCRT and have no viable tumor remaining at resection have superior outcomes to patients with viable tumor after pCRT. Nucleate keratin debris should not be considered viable carcinoma. Patients who have viable lymph nodes on resection after pCRT have worse outcomes than patients with viable lymph nodes who did not receive pCRT. Despite a decreased proliferative index, viable tumor after CRT may be an indicator of tumor aggressivity, as these patients had worse outcomes.

1310 Cuniculatum, Papillary & Verrucous Carcinomas: A Comparative Assessment

Akeesha Shah, Simion I Chiosea, Christopher C Griffith, Seungwon Kim, Raja R Seethala. University of Pittsburgh, Pittsburgh, PA; Emory University, Atlanta, GA.
Background: Carcinoma cuniculatum (CC), papillary/exophytic squamous cell carcinoma (PEC) and verrucous carcinoma (VC) are rare, indolent variants of squamous cell carcinoma (SCC) with morphologic overlap. We perform a comparative analysis of these rare SCC variants in the oral cavity and larynx.
Design: 6 CC, 5 VCs and 6 PECs of the oral cavity and larynx were retrieved (2013 -2015). Clinicopathologic and morphologic features were compared.
Results: Patient and tumor demographics are reported in the table below.

	CC (N = 6)	VC (N = 5)	PEC (N = 6)
Age range, mean (yrs)	49-83, 67	60-83, 74	52-70, 58
Sex Distribution (M:F)	3:3	4:1	3:3
Tumor Location: Oral Cavity Larynx	 5 1	 4 1	 1 5
Tumor Size (cm)	1.1 to 7.5	0.7 to 2.5	1.5 to 3.8
Coexisting conventional SCC > 5%	2	4	4

CC and VC predominated in oral cavity, while PEC was more frequent in larynx (5/6). All tumors were grossly exophytic, but had distinctive growth patterns. CC were defined by an endophytic growth of complex arborizing keratinizing crypts and microcysts with a corrugated parakeratotic lining. VC showed a 'church-spire' pattern of parakeratosis and bulbous broad pushing rete; PEC were predominantly exophytic, but 4/6 showed invasive components with angulated nests similar to conventional SCC (median 35%). Both CC (2/6), and VC (4/5) also showed conventional components (median 35% & 25%, respectively). Pure CC and VC components were devoid of atypia, but PEC consistently showed mild to moderate atypia even in papillary/exophytic areas. Lymphoplasmacytic infiltrates were common in CC (4/6) and VC (3/5), but not PEC. All CC also showed intraepithelial neutrophils. All variants were locally aggressive, but only one PEC with a prominent conventional SCC component (40%) showed nodal metastasis.
Conclusions: CC, VC and PEC are rare locally aggressive variants of SCC delineated from one another by their growth patterns. CC and VC in pure form are truly well differentiated tumors with an inflammatory milieu, though coexisting conventional SCC is actually fairly common. PEC on the other hand have cytonuclear atypia that is similar to conventional well to moderately differentiated SCC; any perceived indolence is likely attributable to the architecture. A prominent conventional component abrogates any protective effect of this architecture as demonstrated by one case with nodal disease.

1311 Comparison of p16 Antibody Clones for the Evaluation of Oropharyngeal Squamous Cell Carcinoma

Jeremy Shelton, Bibianna Purgina, Nicole A Cipriani, James Lewis. Vanderbilt University Medical Center, Nashville, TN; University of Ottawa, Ottawa, ON, Canada; University of Chicago, Chicago, IL.

Background: High-risk human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OSCC) has more favorable survival. p16 immunohistochemistry (IHC) is a prognostic marker and surrogate for high risk HPV. Several clones are commercially available, but no direct comparison has yet been performed. We evaluated 243 OSCCs using three commonly used p16 clones and correlated results with HPV RNA in-situ hybridization (ISH) and disease recurrence.

Design: p16 IHC using the E6H4, JC8, and G175-405 clones was performed on tissue microarrays and reviewed by a single head and neck pathologist. Positivity cutoffs of >75% and >50% nuclear and cytoplasmic staining were utilized, with intensity as weak, moderate, or strong. Results were correlated with HPV RNA ISH results as well as disease recurrence status. Background staining was also evaluated for p16 negative cases.

Results: At the 75% cutoff, correlated with HPV status, sensitivity, specificity, and positive predictive values were similar amongst p16 clones. However, the negative predictive value was significantly higher for E6H4 (31/36=86.1%) vs. JC8 (34/49=69.4%) and G175-405 (34/61=55.7%). This difference corrected somewhat with the 50% cutoff (E6H4, 88.6%; JC8, 86.8%; G175-405, 80.5%). Correlation with disease recurrence was similar for all at both the 75% and 50% cutoffs, although the E6H4 clone had the widest differential between p16 positive and negative tumors.

p16 IHC correlation with disease recurrence				
Clone	>75% = p16+		>50% = p16+	
	% p16+	% p16-	% p16+	% p16-
E6H4	21/170; 12.4%	12/39; 30.8%	21/171; 12.3%	12/38; 31.6%
JC8	22/152; 11.8%	16/53; 30.2%	21/163; 12.9%	13/42; 31%
G175-405	15/137; 10.9%	19/67; 28.4%	22/160; 13.7%	12/44; 27.3

Intensity for positive cases differed significantly with 85.9% of E6H4, 71.7% of JC8 and 66.4% of G175-405 showing strong intensity, respectively. In p16 negative cases, G175-405 displayed cytoplasmic or nuclear background staining in 25/35 cases compared with only 1/37 and 1/36 for E6H4 and JC8, respectively.

Conclusions: Only modest differences in results are found between p16 IHC clones. However, E6H4 showed slightly higher differential in disease recurrence rates between positive and negative cases, better correlation with HPV RNA status, and more intense staining (with low background) compared to the other clones.

1312 Diagnostic Pitfalls of Infarcted Warthin Tumor in Frozen Section Evaluation

Yaohong Tan, Oleksandr N Kryvenko, Christina Kovacs, Jennifer Chapman, David J Arnald, Andrew E Rosenberg, Carmen Gomez-Fernandez. Department of Pathology, Unversity of Miami Miller School of Medicine, Jackson Memorial Hospital, Miami, FL; Department of Surgery, Unversity of Miami Miller School of Medicine, Jackson Memorial Hospital, Miami, FL.

Background: Warthin tumor (WT) is the second most common benign salivary gland neoplasm with characteristic gross and microscopic features. Grossly, these tumors are soft, tan brown, and multicystic, often containing "motor oil" fluid. Microscopically, WTs have a unique morphology with papillae consisting of a bi-layer of oncocytic epithelial cells with underlying lymphoid-rich stroma. Fine needle aspiration (FNA) sampling may result in infarction. Infarcted WTs demonstrate variable gross and histologic alterations that may render the diagnosis challenging, particularly during intra-operative frozen section (FS) evaluation. We describe 6 cases with an emphasis on gross and histologic features that may present a diagnostic pitfall during FS evaluation.

Design: Six resection specimens with infarcted WT related to prior FNA were analyzed. For each case we reviewed the frozen sections and imprint slides performed during FS consultation.

Results: Four patients were males and 2 females, ranging from 49 to 85 years of age (mean, 65.3). All patients had FNA sampling prior to resection. FS diagnosis was WT in 2 cases, squamous cyst in 2 cases, chronic sialoadenitis in 1 case, and squamous cell carcinoma in 1 case. Macroscopically, the tumors were yellow-tan and partially cystic. Histologic findings were variable and included necrosis, ghost-like papillae, squamous metaplasia, cholesterol clefts, foamy macrophages, giant cell reaction, granulomatous inflammation and fibrosis. Each case had some, but not all, of these morphologic features. Most contained necrosis, inflammation, and fibrosis. One case had prominent granulomatous inflammation. Another was completely infarcted with ghost-like papillae. One case had extensive necrotizing sialoadenitis with squamous metaplasia and cytologic atypia, mimicking a squamous cell carcinoma on FS. Preservation of the salivary gland's lobular architecture confirmed the benign nature of the process on final review.

Conclusions: Infarcted WTs may present a diagnostic challenge during FS evaluation. Associated morphologic alterations may preclude a definitive diagnosis of WT. Awareness of the gross and microscopic features associated with infarcted WT is important, particularly for accurate FS evaluation of these salivary gland masses.

1313 Activating KRAS Mutations Are Characteristic of Oncocytic Sinonasal Papilloma and Associated Sinonasal Squamous Cell Carcinoma

Aaron Udager, Raja R Seethala, Evgeny Yakirevich, Jonathan McHugh, Bryan Betz, Megan S Lim, Kojo Elenitoba-Johnson, Noah Brown. University of Michigan Health System, Ann Arbor, MI; University of Pittsburgh Medical Center, Pittsburgh, PA; Rhode Island Hospital and Brown University, Providence, RI; Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA.

Background: Oncocytic sinonasal papillomas (OSP) are benign tumors of the sinonasal tract, a subset of which are associated with a synchronous or metachronous sinonasal squamous cell carcinoma (SNSCC). We recently identified activating *EGFR* mutations in nearly 90% of inverted sinonasal papillomas (ISP) – a related tumor with distinct morphology. *EGFR* mutations, however, were not found in OSP, suggesting that different molecular alterations drive oncogenesis in these unique tumors.

Design: 19 cases of OSP and 3 cases of OSP-associated SNSCC from 20 unique patients were identified retrospectively at four large academic institutions. Representative formalin-fixed, paraffin-embedded (FFPE) tissue from each case was selected for sequencing. In addition, representative FFPE tissue was obtained from 50 cases of ISP, 22 cases of ISP-associated SNSCC, 10 cases of exophytic sinonasal papilloma (ESP), and 20 cases of SNSCC with no known papilloma association. Sequencing techniques included next-generation sequencing (NGS) with the Ion AmpliSeq Cancer Hotspot Panel v2 (Life Technologies, Carlsbad, CA) and bidirectional Sanger sequencing with nested sequencing primers.

Results: NGS analysis of 2 OSP and 1 OSP-associated SNSCC revealed *KRAS* G12D mutations in all three tumors. Subsequent Sanger sequencing demonstrated *KRAS* exon 2 mutations in 19/19 (100%) of OSP and 3/3 (100%) of OSP-associated SNSCC, including: G12D (11); G12V (9); and G12C (2). The somatic nature of these mutations was confirmed in 5/5 cases with matched germline DNA. Both matched pairs of OSP and OSP-associated SNSCC had concordant *KRAS* genotypes. In contrast, *KRAS* exon 2 mutations were present in only 2 (10%) of SNSCC with no known papilloma association and none of the ISP, ISP-associated SNSCC, or ESP.

Conclusions: This is the first report of somatic *KRAS* mutations in OSP and OSP-associated SNSCC. The presence of identical mutations in OSP and associated SNSCC supports the putative role of OSP as a precursor to SNSCC, and the high frequency and specificity of *KRAS* mutations suggests that OSP and associated SNSCC are biologically distinct from other similar sinonasal tumors. Identification of *KRAS* mutations in these tumors represents an important development in our understanding of their pathogenesis and may have implications for diagnosis and therapy.

1314 Head and Neck Phosphaturic Mesenchymal Tumor: A Report of 5 Cases with FGFR1 Fluorescence In Situ Hybridization Analysis

Jason K Wasserman, Bibianna Purgina, Chi K Lai, Alyssa Mahaffey, Denis Gravel, Diana Bell, Simion I Chiosea. The Ottawa Hospital/University of Ottawa, Ottawa, Canada; University of Pittsburgh Medical Center, Pittsburgh, PA; MD Anderson Cancer Center, Houston, TX.

Background: A subset of phosphaturic mesenchymal tumors (PMT) at non-head and neck sites were reported to harbor an FN1-FGFR1 fusion. We describe a series of head and neck PMTs and examine the diagnostic utility of FGFR1 fluorescence in situ hybridization (FISH).

Design: Multi-institutional, retrospective. Cases of head and neck PMTs were retrieved (n=5; 1990 to 2015). Clinical, biochemical, and pathological variables were reviewed. FGFR1 FISH was performed on paraffin sections using a commercially available FGFR1 dual-color break-apart probe (Cytocell, Cambridge, UK). Sixty to 120 cells were examined for each case of PMT.

Results: The clinicopathologic information is summarized in the table. Two patients were diagnosed with benign PMT and their symptoms resolved shortly after resection of the primary tumor. There was no recurrence. Three patients were diagnosed with malignant PMT based on cytologic atypia and high mitotic count. Two of these patients developed lung metastases and one had a local recurrence. FGFR1 translocation was detected in 80% of interface nuclei in one benign PMT and in 42% of nuclei in one malignant PMT.

Case #	Sex/ Age, years	Signs/ Symptoms	Tumor Induced Osteomalacia/ Hypophosphaturic Syndrome	Site	Original diagnosis	Benign or Malignant PMT	FGFR1 Status, FISH
1	Female/ 45	Vision loss	No	Frontal sinus	Cementifying fibroma	Benign	Translocated
2	Male/ 50	Pathologic fracture	Yes	C3 vertebra	Myxoid neoplasm	Benign	Intact
3	Male/ 58	Pathologic fracture	Yes	Floor of mouth	Benign phosphaturic mesenchymal tumor	Malignant (pulmonary metastasis)	Failed
4	Female/ 33	Rickets-like deformities	Yes	Nasal cavity, lip, tongue	Benign chondromesenchymal tumor	Malignant (pulmonary metastasis)	Translocated
5	Female/ 24	Airway obstruction	No	Larynx	Giant cell tumor	Malignant (cytologic atypia and 25 mitoses per 10 HPF)	Intact

Conclusions: We demonstrate the presence of FGFR1 translocation in a subset of head and neck PMTs. The diagnostic work-up of a suspected head and neck PMT with or without TIO/HPS may be facilitated by FGFR1 FISH.

1315 Parapharyngeal Nerve Sheath Tumors: A Clinicopathological Study of 34 Cases Including Four Malignant Peripheral Nerve Sheath Tumors

Jason K Wasserman, Akeesha Shah, Raja R Seethala, Bibianna Purgina. University of Ottawa, Ottawa, ON, Canada; University of Pittsburgh Medical Centre, Pittsburgh, PA.

Background: Tumors arising in the parapharyngeal space are rare. Although half are of nerve sheath origin, descriptions to date are limited to single cases or small series.

Design: Thirty-four parapharyngeal nerve sheath tumors (PPNST) including 27 schwannomas, 3 neurofibromas (NF), and 4 malignant peripheral nerve sheath tumours (MPNSTs) diagnosed at two academic hospitals between 1986 and 2015 were reviewed. Immunohistochemical analysis was performed in cases with available tissue.

Results: The median age at diagnosis was 47 years (range 18-73 years) with equal gender incidence. The median tumor size was 3.5 cm (range 1.2 – 11 cm). All but one of the schwannomas demonstrated classic histological features including verocay bodies, alternating Antoni A and B architecture, and degenerative change. Three out of four NFs were solitary and demonstrated classic histology; the fourth was plexiform in a patient in which the neurofibromatosis status was unknown. All four MPNSTs demonstrated cytologic atypia; tumor necrosis and infiltrative features were present in two. The tumor cells in two MPNSTs had an epithelioid morphology and prominent nucleoli; one of the two was associated with a benign cellular epithelioid schwannoma. All four MPNST were mitotically active and three had more than 8 mitotic figures per 10 HPF. None of the MPNSTs were associated with neurofibromatosis type 1. All three NFs were focally positive for S100 and CD34, negative for p53, and had a Ki-67 labelling index (LI) < 1%. All schwannomas were strong and diffusely positive for S100 and had a Ki-67 LI between 1-5%; 20 were focally/weakly positive for p53. Three of the four MPNSTs were focally positive for S100 and negative for CD34. Immunohistochemistry for p53 was only available for two MPNSTs: one was focally positive while the other was strong and diffusely positive. Tumors recurred in 4 patients (3 schwannomas, 1 MPNST) and one patient with MPNST developed metastatic disease. The median time to recurrence was 12 months (range 1-54 months).

Conclusions: This is the largest report of PPNST tumors to date. Most PPNST are expected to be benign however; 4 in our series were MPNST. Although MPNSTs typically arise either de novo or from malignant degeneration of a NF in a patient with neurofibromatosis type 1, rare malignant transformation of a schwannoma may be a possibility in this anatomic site.

1316 Molecular Analysis of Low-Grade Cribriform Cystadenocarcinoma & Related In-Situ and Invasive Carcinomas

Ilan Weinreb, Raja R Seethala, Simion I Chiosea, Bayardo Perez-Ordonez, Martin Hyrcza, Lei Zhang, Chun-Liang Chen, Yun-Shao Sung, Adel Assaad, Lester DR Thompson, Cristina Antonescu. University Health Network, Toronto, ON, Canada; University of Pittsburgh Medical Center, Pittsburgh, PA; Memorial Sloan-Kettering Cancer Center, New York, NY; Virginia Mason Medical Center, Seattle, WA; Kaiser Permanente Medical Center, Woodland Hills, CA.

Background: Low-grade cribriform cystadenocarcinoma (LGCC) is an intraductal neoplasm resembling atypical ductal hyperplasia of the breast. Occasional cases with widspread invasion have been described. The relationship of LGCC to salivary duct carcinoma (SDC) is controversial, but currently these are considered distinct entities. There are no molecular studies of SDC associated with low-grade intraductal lesions. In addition, LGCCs resemble mammary analogue secretory carcinoma (MASC) and only rare cases have been tested for ETV6 gene rearrangement typical of MASC.

Design: 19 intraductal salivary lesions were identified: 10 pure LGCC and 9 with an invasive carcinoma. 5 carcinomas with frozen tissue were subjected to next-generation paired-end RNA sequencing (NGS). Data analysis was performed using FusionSeq for fusion discovery and Mutation detection algorithms (MuTect & VarScan) for variant callers. Gene fusion candidates were validated by FISH and RT-PCR, and mutations by Sanger sequencing. In addition, ETV6 FISH was performed on pure intraductal LGCCs.

Results: The patients ranged from 25-80 yo with a M:F ratio of 14:3. There were 9 intraductal lesions with an invasive carcinoma. One showed a typical intercalated duct type LGCC progressing to cystadenocarcinoma. The remaining 8 cases were apocrine type LGCC with widespread invasion. The 10 pure LGCC had typical intercalated duct features with 1 showing focal apocrine change.

NGS predicted a NCOA4-RET fusion which was confirmed by RT-PCR in the intercalated duct type LGCC with invasion. Two additional cases of pure LGCC showed RET rearrangement by FISH (3/11=27%). No apocrine type LGCC with invasion showed RET rearrangement. All 9 LGCCs tested by ETV6 FISH were negative. NGS and subsequent Sanger sequencing identified PIK3CA (p.E545K, p.H1047R) and/or HRAS (p.Q61R) hotspot mutations in 6/8 (75%) apocrine type LGCC with invasive carcinoma.

Conclusions: Two distinct and unrelated intraductal lesions resembling LGCC are emerging based on molecular analysis. Classical intercalated type LGCCs show rare widespread invasion and occasional fusions involving RET. They show no resemblance to SDC. Apocrine intraductal lesions are typically associated with widespread invasion with no pure examples. These carcinomas vary in morphology and show similar PIK3CA and HRAS mutations to conventional SDC.

1317 Identification of a Novel Junctional Site in the Oropharynx, Permissive for Human Papillomavirus Infection

Robbie Woods, Helen Keegan, Christine White, Prerna Tewari, Danielle Costigan, Jacqueline Barry-O'Crowley, Mary Toner, Susan Kennedy, Esther M O'Regan, Cara M Martin, Conrad Timon, John O'Leary. Royal Victoria Eye and Ear Hospital, Dublin, Ireland; Dublin University, Trinity College, Dublin, Ireland; St. James's Hospital, Dublin, Ireland; The Coombe Women and Infants University Hospital, Dublin, Ireland; Cerviva Research Consortium, Dublin, Ireland.

Background: HPV-related oropharyngeal SCC represents a distinct clinico-pathological subgroup of head and neck tumours. We have identified a unique site in the oropharynx: a junctional site, permissive for HPV infection, similar to that recently described in the cervix. We have analysed HPV status, p16ink4A expression, expression of four novel junctional biomarkers in the head and neck, and two biomarkers of immune regulation, PD-1 and PD-L1.

Design: HPV-positive tumour specimens and epidemiological data were collected from patients presenting with primary oropharyngeal SCC at two centres in Ireland. DNA was extracted from tissue blocks and HPV testing performed using SPF10 PCR and INNO-LiPA HPV Genotyping test. Immunohistochemical staining for CK7, GDA, MMP-7, AGR-2, PD-1 and PD-L1 was performed. Slides were analysed and scored using the H scoring system. Expression was correlated with tumour, clinical and epidemiological data. Statistical analysis was performed using SPSS.

Results: HPV-related oropharyngeal SCC (n=16) and HPV-negative oropharyngeal SCC (n=5) were examined. 15/16 demonstrated p16ink4a positivity. Junctional biomarkers were expressed in tonsil crypt epithelium and to varying degrees in the tumours. Expression of PD-1 (n=13) and its ligand (n=14) were interpreted qualitatively, based on expression pattern.

CK7 expression was analysed in 220 cases of oropharyngeal SCC. 41% demonstrated p16ink4a positivity and 44% were HPV-positive. 56% of cases were positive for CK7 in tonsillar crypt epithelium, with 38% of cases demonstrating H score of >60. CK7 expression in the tumours was significantly linked to HPV and p16ink4a-positivity ($p<0.01$).

Conclusions: We have identified markers that selectively identify tonsillar crypt cells associated with HPV infection, which correlate with recently discovered 'junctional' cells in the cervix, where 'top-down' infection of HPV occurs. Markers of the PD-1:PD-L1 immune checkpoint pathway suggest a role for this immune complex in immune evasion in this subgroup. Our results also suggest that expression of CK7 in normal tonsillar crypt epithelial cells provides a selective advantage to HPV-related carcinogenesis at this site, possibly due to the unique propensity of CK7 to bind HPV-16 E7 transcripts.

1318 The Utility of p16 Immunostaining in Fine Needle Aspiration (FNA) Material in Human Papilloma Virus (HPV)-Related Head and Neck Squamous Cell Carcinoma (HNSCC)

Bin Xu, Ronald Ghossein, Jason Lane, Oscar Lin, Nora Katabi. Memorial Sloan-Kettering Cancer Center, New York, NY.

Background: Many patients with HPV related HNSCC present initially with cervical nodal metastasis. Fine needle aspiration (FNA) of the nodal disease may be the only available diagnostic material for p16 immunohistochemical analysis (IHC), which is used as a surrogate for HPV status. In this setting, the results of p16 IHC on FNA can be used to guide therapy. The current study aims to evaluate p16 IHC in FNA, establish guidelines for its interpretation and compare with the results obtained in surgical specimens.

Design: Sixty matched FNA cases evaluated for p16 with corresponding surgical cases were retrieved from the pathology file. The percentage and intensity (weak to strong) of nuclear and cytoplasmic p16 IHC staining were examined. HPV in situ hybridization (ISH) was performed and reviewed on 30 FNA cases. P16 IHC staining was correlated with the p16 results seen in the surgical specimens and with HPV-ISH. Cytomorphologic features including cellularity and necrosis were also analyzed.

Results: Analysis of different thresholds demonstrated that the threshold of 10% p16 positivity had the best overall concordance rate with surgical p16 IHC (kappa = 0.650) and with FNA HPV-ISH (kappa = 0.714). Using surgical p16 IHC as the gold standard test, FNA p16 IHC had a sensitivity of 84%, specificity of 100%, positive predictive value of 100% and negative predictive value (NPV) of 57%.

Applying the recommended p16 positivity threshold for surgical specimens (70%) on FNA materials generated low sensitivity (39%) and low NPV (26%).

Out of 46 cases with cytomorphologic features reviewed, 6 cases (13%) were negative for p16 in the FNA while positive for p16 in surgical specimens. All 6 cases were associated with necrotic background, 2 (33%) lacked large tumor clusters, and one (17%) had low cellularity.

Conclusions: The recommended threshold for p16 IHC used in surgical specimens should not be applied on cytology materials.

The best cutoff to determine if a FNA specimen is positive for p16 immunostain appears to be 10%.

When p16 IHC is negative on FNA material, a repeat p16 stain on corresponding surgical specimen is recommended to avoid a false negative result due to necrosis or inadequate cellularity.

1319 Prognostic Histological Features in the Phenotypic Spectrum of Polymorphous Low Grade Adenocarcinoma (PLGA) and Cribriform Adenocarcinoma of Minor Salivary Gland (CAMSG): A Unicenter Retrospective Study of 69 Patients

Bin Xu, Ronald Ghossein, Nora Katabi. Memorial Sloan-Kettering Cancer Center, New York, NY.

Background: PLGA shows histologic diversity with fascicular and targetoid features while CAMSG demonstrates predominant cribriform and solid patterns with glomeruloid appearance and optical clear nuclei. There is histologic overlapping between the two entities. Moreover, papillary architecture can be seen in both tumors. The current study is designed to identify pathological features that may predict clinical outcome in these tumors.

Design: 69 cases of PLGA/CAMSG were retrieved from the pathology file. The cases were subjected to detailed histopathological analysis and the latter correlated with outcome.

Results: 23 (33%) tumors had a high mitotic rate (≥4 mitosis/10 HPFs), while 8 (12%) displayed tumor necrosis. Large tumor size (≥2 cm), bone invasion, perineural invasion, lymphovascular invasion (LVI), positive lymph nodes (at initial surgery), and positive margins were found in 33 (48%), 16 (23%), 41 (59%), 4 (7%), 10/18 (56%), and 16 (25%) of cases respectively. 23 (33%) displayed prominent papillary pattern (≥10% of the tumor), and 8 (13%) had a significant cribriform pattern (>=30% of the tumor). Further histologic classification of the 69 tumors (based on the prior reported definition) showed 21 CASG (30%), 23 PLGA (33%), and 22 (32%) with mixed features of PLGA and CAMSG. Additionally, 3 (4%) tumors demonstrated predominant papillary pattern (≥ 50%).

FU was available on 61 cases (median, 45.2 months). Among the 61 patients, 7 had recurrences or distant metastasis (DM): 3 local (5%), 2 nodal metastases (3%), and 2 DM (3%). The following histological factors predicted disease free survival (DFS) on univariate analysis: tumor size ($p = 0.001$), bone invasion ($p < 0.001$), LVI ($p = 0.013$), ≥10% papillary pattern ($p = 0.048$), and ≥30% cribriform pattern ($p < 0.001$). On multivariate analysis, cribriform pattern was an independent prognostic factor of DFS (hazard ratio = 15.7, $p = 0.044$). Furthermore, the patient who died from his disease had a tumor showing >30% cribriform pattern.

Conclusions: Tumor size, bone invasion, and LVI are significant parameters that can predict adverse clinical behaviors in PLGA/CAMSG.

Using the prior reported dentition, an overlapping histology between PLGA and CAMSG was noted in over third of the cases, and it is not entirely clear whether these tumors represent two separate entities.

The percentage of cribriform and papillary patterns seems to be prognostically relevant and should be documented.

1320 Prognostic Significance of Perineural Invasion (PNI) in Oral Tongue Squamous Cell Carcinoma (OTSCC): A Clinicopathologic Study of 381 Patients

Bin Xu, Jennifer Cracchiolo, Jocelyn C Migliacci, Snehal Patel, Nora Katabi, Richard Wong, Ronald Ghossein. Memorial Sloan-Kettering Cancer Center, New York, NY.

Background: PNI is an established adverse risk feature in head and neck squamous cell carcinoma, and an indication for adjuvant therapies based on the National Comprehensive Cancer Network guideline. The study aims to clarify the prognostic significance of PNI in OTSCC, as it may potentially influence decision for adjuvant therapy.

Design: A meticulous clinico-pathologic analysis was performed in a cohort of 381 patients with oral tongue SCC operated and followed at a tertiary cancer center between 2000 and 2012 with a median follow-up of 40 months.

Results: PNI was identified in 105 patients (27.6%). The median number of PNI foci was 3 (range 1 – 52). The presence of PNI had a significant association with larger tumor size, increased tumor thickness, higher tumor grade, invasion of skeletal muscle and bone, pattern of invasion, lymphovascular invasion, margin status, and lymph node positivity (Chi square test, $p < 0.05$), but not with lymphoid interface host response ($p = 0.49$). Number of PNI foci, circumference of the perineural invasion and the form of invasion (perineural or intraneural) were significantly associated with presence of cervical lymph node metastasis (Fisher's Exact Test, $p < 0.05$).

PNI is an independent predictor for adverse clinical outcome with shortened overall survival (OS, hazard ratio HR= 2.82, $p < 0.001$), and disease specific survival (DSS, HR = 2.50, $p = 0.003$). PNI correlated with shorter locoregional/distant recurrence free survival (RFS) on univariate analysis only. Patients with extensive PNI, defined as 5 foci or more per tumor, had significantly shortened OS, DSS and distant RFS than those with focal PNI on univariate analysis. Additionally, PNI density, defined as number of PNI foci per tumor section, greater than 1.167 was an independent adverse pathological feature for predicting reduced DSS (HR = 2.61, $p = 0.015$) when adjusting for tumor size.

Conclusions: PNI is an independent pathological predictor for adverse clinical outcome in OTSCC. In addition, stratification of the extent of PNI into foci per section seems to provide additional prognostic values.

1321 High Risk Human Papillomavirus in Primary Squamous Cell Carcinoma of the Parotid Gland

Bin Xu, Lu Wang, Laetitia Borsu, Nora Katabi, Ian Ganly, Snjezana Dogan. Memorial Sloan-Kettering Cancer Center, New York, NY.

Background: High-risk human papillomavirus (HR-HPV) has been identified as a putative oncogenic driver in a significant proportion of head and neck squamous cell carcinoma (HNSCC), primarily in those arising in oropharynx. The frequency of HR-HPV in primary squamous cell carcinomas of the parotid gland (ParSCC) is unknown. In the current study, we aimed to examine ParSCC for the presence of HR-HPV and associated molecular alterations.

Design: Eight cases of ParSCC were retrieved from our pathology archives and were diagnosed over the period of 13 years. A diagnosis of ParSCC is rendered after a detailed clinicopathologic review to exclude a possibility of metastasis and/or extension from another primary site, such as skin and oropharynx. HR-HPV status was determined based on immunohistochemistry (IHC) for p16 protein expression and by chromogenic *in situ* hybridization (CISH) for HR-HPV. Presence of a diffuse and strong nuclear and cytoplasmic p16 immunostain in at least 70% of the tumor cells and presence of nuclear dot-like signal indicative of integrated HR-HPV were both required to consider a case HR-HPV-positive. In addition, all cases were genotyped by multiplexed mass spectrometry assay interrogating 91 hotspot mutations in 8 cancer-related genes (*EGFR, KRAS, NRAS, BRAF, PIK3CA, AKT1, MEK1 and ERBB2*), and studied by IHC for PTEN protein expression. All except 2 cases (which showed retained PTEN protein by IHC) were examined for *PTEN* gene copy number alteration (CNA) by fluorescence *in situ* hybridization (FISH).

Results: Three of 8 cases (3/8; 37.5%) were positive for presence of HR-HPV by CISH and p16 IHC.

One of three (1/3; 33%) HR-HPV-positive cases harbored *PTEN* hemizygous deletion, and one (1/3; 33%) HR-HPV-positive case harbored *PIK3CA* E545K somatic mutation. No alteration of *PTEN-PI3K* pathway was detected in HR-HPV-negative tumors. Over a median follow-up period of 66.2 months, only the patient with HR-HPV-positive *PIK3CA*-mutated tumor died of his disease, while the remaining 7 patients were disease free.

Conclusions: Given the established etiologic role of HR-HPV in other HNSCC, it is likely that HR-HPV represents an oncogenic driver in the pathogenesis of more than one third of ParSCC. Presence of HR-HPV in ParSCC may be coupled with alterations in *PTEN-PI3K* pathway. HR-HPV and molecular characterization of a larger number of ParSCC is needed to determine the clinical significance of these findings.

1322 MUC4 Protects Aniokios in Head and Neck Squamous Cell Carcinoma

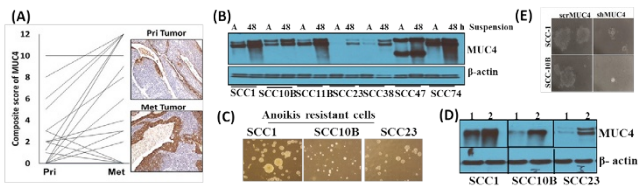
Xiu Yang, Sham S Kakar, Muzafar A Macha, Surinder K Batra. University of Louisville, Louisville, KY; University of Nebraska, Omaha, NE.

Background: Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer in America. Lymph node (LN) metastasis is one of the main prognosticators of survival. Resistance to anoikis, a type of apoptosis induced by loss of cell-matrix contact, is a prerequisite for their metastatic spread. MUC4 is a membrane-bound mucin expressed in several normal tissues, and its expression is elevated in malignancies. However, the role of MUC4 in metastasis of HNSCC is still unknown.

Design: Sixteen cases of HNSCC with positive LN metastasis are retrieved from 2012 to 2015. Immunohistochemistry and Western blot were performed using mouse monoclonal antibody, clone 8G7, which recognizes human MUC4. HNSCC cell lines SCC1, SCC10B and SCC23 were used for in vitro study. The *shMUC4* or a scrambled *shRNA* was transfected into cell lines to generate a stable knockdown of MUC4 (shMUC4) or a control (scrMUC4) using Lipofectamine 2000 (Invitrogen, CA).

Results: Among the sixteen cases, 9 are originated from oral cavity, 3 from oropharynx, and 4 from larynx. The mean age is 62.2 years old (from 50 to 76) with female to male ratio 1:1. The Immunohistochemical analysis showed significant upregulation of MUC4 in LN metastasis as compared to matched primary tumor (**Fig. A**). In addition, MUC4 was highly upregulated in HNSCC cells under suspended condition (anoikis inducing condition), compared to attached cells suggesting that MUC4 plays an important role in protecting cells under anoikis condition (**Fig. B**). Further, we developed anoikis resistant (AR) cells SCC1AR, SCC10BAR and SCC23AR from parental cells and observed upregulation of MUC4 in AR cells compared to the parental cells. The capacity of tumorigenesis, indicated by the size of colonies, correlates with the amount of MUC4 protein in different cell lines (**Figs. C** & **D**). Stable knockdown of MUC4 in SCC1 and SCC10B cells resulted in sensitization to anoikis as evidenced by small colonies (**Fig. E**).

Conclusions: Our study revealed a novel function of MUC4 in protecting anoikis in HNSCC and suggested that MUC4 could be a promising candidate in therapy, especially in the inhibition of cancer metastasis.



1323 Nonkeratinizing Carcinoma In Situ of the Upper Aerodigestive Tract: An HPV-Related Entity

Lingxin Zhang, James Lewis, Samir K El-Mofty, Manoj Gandhi, Rebecca Chernock. Washington University School of Medicine, St. Louis, MO; Vanderbilt University Medical Center, Nashville, TN; Affymetrix, Inc., Santa Clara, CA.

Background: The role of HPV in the etiology of premalignant lesions in the upper aerodigestive tract (UAT) is poorly understood. There are a few reports of oral cavity HPV+ severe dysplasia (SD) with unique morphology (prominent apoptosis/karyorrhexis imparting a 'bowenoid' appearance) and a single case report of HPV+

carcinoma in situ (CIS) with nonkeratinizing (NK) histology distinct from the 'bowenoid' pattern that extensively involved the UAT. Here, we characterize the clinicopathologic features of HPV+ CIS/SD of the UAT.

Design: All cases of UAT CIS/SD from July 2012 to March 2015 were categorized into histologic types: keratinizing (K), NK, mixed or 'bowenoid'. Exclusion criteria were: A) superficial biopsies where the base was not seen and B) CIS/SD within 1 mm of an invasive carcinoma, in continuity with a tonsil or base of tongue invasive carcinoma, or arising in another characterized lesion (Schneiderian papilloma, verrucous or papillary proliferation). P16 immunohistochemistry (positive if > 70%) and high-risk HPV RNA in situ hybridization (ISH) were performed on all NK/mixed and p16 on a subset of K cases.

Results: Of 99 patients with CIS/SD, 84 were K, 3 NK, 12 mixed, and 0 'bowenoid'. All 3 (100%) NK and 6 (50%) mixed cases were p16 and HPV RNA ISH+ (9% of all CIS/SD HPV+) with 100% concordance between p16 and HPV status. All representative (14) K cases were p16- and thus were not HPV tested. Among the HPV+ cases, the floor of mouth (FOM) was the most commonly involved site and large (≥ 4 cm) or extensive/unresectable disease was common [see Table of HPV+ cases].

Case	CIS/SD Type	Age	Sex	Site	Clinically Extensive
1	NK	63	M	Oral/larynx	Y
2	NK	60	M	Subglottis/trachea	Y
3	NK	69	M	Buccal/FOM/oral tongue/palate	Y
4	Mixed	65	F	Soft palate	N
5	Mixed	71	M	FOM	Y
6	Mixed	67	F	Nasal cavity	Y
7	Mixed	45	F	Vocal cords	N
8	Mixed	71	M	FOM/ventral tongue	Y
9	Mixed	60	M	FOM	Y

All patients had a history of tobacco use, all but 1 had invasive carcinoma (prior, concurrent or subsequent) and all but 1 (who was undergoing chemotherapy for recurrent invasive carcinoma) were free of disease at last follow up.

Conclusions: NK histology is a strong predictor of HPV+ CIS/SD. HPV+ CIS/SD is common in the FOM and often extensive/unresectable.

1324 The Utility of GATA3, GCDFP-15, Mammaglobin, SOX10, and ER in Differential Diagnosis of Salivary Tumors

Chaohui L Zhao, Evgeny Yakirevich, Kara A Lombardo, Douglas R Gnepp, Yihong Wang. Brown University, Providence, RI; University Pathologists, Fall River, MA.

Background: Since mammary and salivary glands are tubuloacinar exocrine glands and sharing similar histologic features, we investigated GATA3, GCDFP, mammaglobin, ER and SOX10 expression in a wide-spectrum of salivary tumors.

Design: 89 salivary tumors were retrieved between 2001 and 2015 including 23 pleomorphic adenomas (PA), 13 Warthin tumors, 13 mucoepidermoid carcinomas (MECa), 9 adenoid cystic carcinomas (AdCC), 8 basal cell adenomas (BCA), 7 acinic cell carcinomas, 5 salivary duct carcinomas (SDC), 4 carcinomas ex pleomorphic adenoma (CaexPA), 3 mammary analogue secretory carcinomas (MASC), 2 myoepitheliomas and 1 epithelial-myoepithelial carcinoma (EPCa). Immunoreactivity was assessed using the Allred scoring system; a combined score ≥ 3 was considered positive.

Results: GATA3 was expressed in 35.5% of salivary tumors across a variety of types (table1). Diffuse strong nuclear staining was observed in MASC (3/3) and SDC (4/5); the one GATA3 negative SDC was poorly differentiated and was also negative for other markers. No GATA3 expression was found in AdCC, myoepitheliomas and EPCa.Compared to GCDFP and mammaglobin, GATA3 had similar expression rates in the salivary tumors (P>0.05). SOX10 was expressed in all cases of AdCC, CaexPA, myoepitheliomas and EPCa. ER was negative in almost all tumors, except for focal weak staining in 2 PAs and 1 CaexPA. Compared with other markers, ER was the most useful marker in differential diagnosis of tumors of breast vs salivary origin (P<0.05).

Conclusions: GATA3 was expressed across many different types of salivary tumors. It appears to have the best utility in the differential diagnosis of SDC and MASC. A salivary tumor should be in the list of differential diagnosis of a GATA3-positive carcinoma. Combining GATA3 and SOX10 staining may help in subtyping salivary tumors, especially AdCC (all 9 cases were GATA3 negative/SOX10 positive).

	Cases	GATA3	GCDFP	Mammaglobin	ER	SOX10
PA	23	4/18	7/21	6/19	2/21	15/23
CaexPA	4	2/4	3/4	3/4	1/4	4/4
Warthin tumors	13	5/11	2/8	0/9	0/10	2/13
MECa	13	4/12	1/5	1/5	0/6	4/13
AdCC	9	0/8	1/3	0/3	0/3	9/9
BCA	8	2/8	0/3	0/3	0/3	6/8
Acinic cell carcinoma	7	3/7	3/5	1/5	0/5	4/7
SDC	5	4/5	3/4	1/3	0/5	1/5
MASC	3	3/3	2/2	2/2	0/2	2/3
Myoepithelioma	2	0/2	0/2	0/2	0/2	2/2
EPCa	1	0/1	0/1	0/1	0/1	1/1

Hematopathology

1325 Plasmablastic Lymphoma: Characterization of Tumor Microenvironment by CD163 and PD1 Immunohistochemistry

Janice Ahn, Flavia G Rosado, Aliyah R Sohani, Jeffrey Vos. West Virginia University, Morgantown, WV; Massachusetts General Hospital, Boston, MA.

Background: Plasmablastic lymphoma is an aggressive neoplasm commonly associated with EBV infection. Tumor microenvironment characterized by quantitation of tumor associated-macrophages (TAM) and tumor-infiltrating lymphocytes (TIL) appears to play a crucial role in the clinical outcome of neoplasms such as classical Hodgkin lymphoma. However, studies characterizing tumor microenvironment in PBL are limited.

Design: In an attempt to characterize tumor microevnironment of PBL, electronic medical records from 3 institutions were searched to obtain clinically and morphologically well-characterized cases of PBL. All archival material was reviewed and immunohistochemical (IHC) studies for CD163 and PD1 were performed on cases with available tissue blocks. Cases were evaluated for CD163 and PD1 expression independently by 2 pathologists. At least 10 medium power fields of tumor were scored and the average percentage of immunoreactive cells was determined for each case. Based on previously published methods, a cut off of >20% staining with CD163 and PD1 was established as high level of TAM and TIL, respectively. Survival data was obtained.

Results: Of the 14 cases that met criteria for PBL, 9 cases have been studied to date. The study included 7 male and 2 female patients with age ranging from 24 to 74 years (median 35). Six patients were HIV positive. Of the HIV negative, one was EBER positive. Biopsy sites along with IHC results are summarized in the table. Morphologically, 4 showed pure plasmablastic morphology, while 5 were a mix of plasmablastic and plasmacytic cells. TAM was considered high in 6/9 cases (67%) and TIL high in 2/9 cases (22%). A negative correlation between TAM and TIL was identified (p= 0.08), although the sample size was too small to reach statistical significance (see table).

Characterization of Tumor Microenvironment in Plasmablastic Lymphoma

Case #	Age	Gender	Site	HIV Status	EBER	CD163 (%)	PD1 (%)
PB04	35	M	Buccal mucosa	+	+	H (50)	L (5)
PB07	74	M	Inguinal lymph node	-	-	L (20)	H (40)
PB08	49	F	Mediastinum	+	+	L (20)	H (30)
PB11	58	F	Lymph node	-	-	H (30)	L (5)
PB26	26	M	Nasopharynx	+	+	H (30)	L (5)
PB27	27	M	Bone marrow	+	+	H (30)	L (10)
PB29	29	M	Mediastinum	-	+	H (30)	L (5)
PB30	30	M	Lymph node	+	n/a	H (60)	L (0)
PB31	31	M	Nasopharynx	+	n/a	L (20)	L (5)
n/a=not available, H=high, L=low; EBER = Epstein Barr Encoded RNA							

Conclusions: This is an ongoing multi-institutional effort to characterize the microenvironment of PBL. Preliminary data shows a high level of CD163 positive TAM using a 20% cut-off in a subset of PBL. Using the same cut-off for PD1 positive TIL, few cases are classified as high expression, suggesting an inverse relationship. The prognostic significance and prediction of therapy response warrants further study.

1326 Multi-Color Flow Cytometric Analysis of c-MYC Protein in B-Cell Lymphomas, a Correlation Study with Immunohistochemistry and FISH

Khaled Alayed, Karen Schweitzer, Amad Awadallah, Samir Turakhia, Howard J Meyerson. University Hospitals/ Case Medical Center, Cleveland, OH; King Saud University, Riyadh, Saudi Arabia.

Background: Recent studies demonstrated increased c-MYC protein expression and *c-MYC* gene rearrangements are poor predictive factors in aggressive B-cell lymphoma. As such c-MYC is routinely evaluated by IHC and FISH in these cases. However, IHC evaluation is subjective and can be difficult to interpret when neoplastic cells represent a small component of the infiltrate. The aim of the study was to develop an objective assay to detect c-MYC protein expression using multi-parametric flow cytometry (FC) as an alternative to subjective analysis by IHC and validate the method by comparison with IHC and FISH.

Design: 44 patient samples were evaluated. Lymphoma cells were obtained after analysis in the clinical lab and c-MYC staining was performed in combination with CD45 and CD19 and, in some samples, CD10. Cells were acquired on a FC and gated CD19+/CD10+ or CD19+ B cells were evaluated for the percent expression of c-MYC over isotype control. The percentage c-MYC+ cells by FC was correlated with morphology, c-MYC FISH and IHC. The percent c-MYC+ cells by IHC was determined blindly by manual counts of 1000x fields performed independently by two pathologists (median cell count/case = 1962).

Results: c-MYC expression determined by FC and IHC had a correlation coefficient of 0.773 indicating a robust assay. A spectrum of lymphoid processes was evaluated. Reactive cases (n= 8) showed low c-MYC protein expression (median: 8.3%, range: 4-24% of the gated B-cells). Low grade lymphomas (n=13) (FL grade 1/2 (6), MCL (2), MZL (3), CLL/SLL (1), and a CD5+ lymphoproliferative neoplasm (1)) showed the lowest c-MYC protein expression (median: 5.7, range: 1.5-14.8%). Aggressive and high grade B-cell lymphomas (n= 23) (DLBCL (19), B-cell lymphoma, unclassifiable, intermediate between DLBCL and BL (2), BL (1) and FL grade 3 (1)) revealed high c-MYC protein expression (median: 24, range: 1.7-94.4%). 14 of these B-cell lymphomas were analyzed by FISH. 4 cases demonstrated ≥50% c-MYC expression