Identifying mitoses in tumors and metastatic deposits in lymph nodes can be laborious and time-consuming tasks. Advances in digital pathology and machine learning algorithms have demonstrated promising results by automating these assignments in breast tissue and sentinel lymph node sections. These breakthroughs have made automated histopathological diagnosis a possibility. All prior studies have used high-resolution images from expensive whole slide image (WSI) scanners for training and detection of cellular events. Our aim was to investigate the efficacy of deep learning algorithms for automated detection of mitotic events on low quality images of oral squamous cell carcinoma (OSCC) produced by cellphone cameras.

Methodology: A FAST region-based convoluted neural network was trained on WSI from breast cancer. The mitotic events were highlighted through provision of pixel locations to the training algorithm, each patch was approximately 301 × 301 in size. The non-mitosis regions were randomly selected on the images. The final training data set comprised of 4407 image patches. Transfer learning was applied to generate results. Similar algorithms were employed on a data set of comparable size acquired through a cellphone camera from 13 different OSCCs at high-power (40x).

Results: The WSI demonstrated true positive rates of 0.46 and a false positive of 0.76 with an overall F1 precision of 0.57. The results from cellphone camera showed true positive rates of 0.46, and false positive rates of 0.54. The overall F1 score was 0.49.

Conclusion: Although WSIs outperformed cellphone images in identifying mitoses, enhancing image quality through modified algorithms may improve efficacy. This will facilitate use of low-cost data sets for training future algorithms for automated detection of cellular events, and widen its impact by making it accessible to every pathologist with a cellphone camera.

STRATIFICATION OF HEAD AND NECK SQUAMOUS CELL CARCINOMA USING COMBINED ANALYSIS OF PROGRAMMED DEATH LIGAND 1 AND SEMAPHORIN 4D EXPRESSION BY THE INFLAMMATORY CELLS IN THE TUMOR MICROENVIRONMENT.

DR. RANIA YOUNIS[A], DR. SONIA SANADHYA[B], DR. IOANA GHITA[C], DR. INGY H. ELKOMARY[A], DR. HAIYAN CHEN[A]. [A] UNIVERSITY OF MARYLAND, SCHOOL OF DENTISTRY, [B] UNIVERSITY OF MARYLAND BALTIMORE, [C] UNIVERSITY OF MARYLAND

Objective: Inhibition of the immune check point PD-1/PD-L1 has shown unprecedented improvement in overall survival of platinum resistant head and neck squamous cell carcinoma (HNSCC) patients. PD-L1 immunohistochemical diagnostics showed to be more prognostic of the patient response. Yet, patients' response remains limited to 45% out of the PD-L1 positive cases, where PD-L1 can be expressed by the tumor cells or by the tumor associated inflammatory cells (TAIs). Semaphorin 4D (Sema4D) is an immune modulator molecule expressed by several inflammatory cells, as well as several tumor cell types including HNSCC. We have recently described a HNSCC stratification model based on combined analysis of PD-L1/ Sema4D IHC expression by the tumor cells. Here we would like to extend our analysis to further stratify HNSCC according to Sema4D/ PD-L1 expression by TAIs in the tumor micro-environment.

Findings: IHC analysis of Sema4D/PD-L1 in 136 HNSCC tissue cores showed: 61% (83 cases) to be Sema4D +ve in TAIs, and 29% (39 cases) to be PD-L1 +ve TAIs. Accordingly, we were able to stratify the examined HNSCC cores into 4 subtypes using the expression of Sema4D/PD-L1 by TAIs in the tumor micro-environment: (1) Sema4D only positive (37%) (50 cases), (2) PD-L1 only positive (4%) (6 cases), (3) Sema4D/PD-L1 (+ve/+ve) (24%) (33 cases), and (4) 35% (47 cases) to be (-ve/-ve). Sema4D only +ve TAIs were significantly higher than PD-L1 only +ve TAIs.

Conclusion: HNSCC stratification according to Sema4D/PD-L1 expression by TAIs in the tumor microenvironment can open new avenues for personalized targeted therapy and might interpret resistance or cytotoxic effects to PD-1/PD-L1 inhibition in HNSCC.

ADENOID CYSTIC CARCINOMA WITH HIGH-GRADE TRANSFORMATION: A RETROSPECTIVE STUDY FOCUSED ON CLINICOPATHOLOGICAL FEATURES AND PROGNOSTIC VALUE IN A SINGLE CENTER.

DR. RONG-HUI XIA, DR. CHUN-YE ZHANG, DR. LI-ZHEN WANG, DR. YU-HUA HU, DR. ZHEN TIAN, MR. TING GU, MRS. LEI LI, MRS. YING ZHANG, MR. JIA-JUN QIAN, PROF. JIANG LI. DEPARTMENT OF ORAL PATHOLOGY, NINTH PEOPLE'S HOSPITAL, SHANGHAI JIAO TONG UNIVERSITY SCHOOL OF MEDICINE; SHANGHAI KEY LABORATORY OF STOMATOLOGY

Objectives: High-grade transformation of adenoid cystic carcinoma(ACC-HGT) is an extremely rare phenomenon. We reported 18 cases of ACC-HGT and focused on the clinicopathological features and prognostic value in this study.

Findings: 202 cases of ACC were included in the current study. According to the criteria for ACC-HGT had been published by Seethala et al., 18 cases were diagnosed as ACC-HGT. Compared to conventional ACC, ACC-HGT showed a slight male predominance (61.1% vs. 49.5%), higher lymph node metastasis (27.8% vs. 8.2%, p=0.021), higher recurrence rate (44.4% vs. 13.6%, p=0.003), higher vascular invasion rate (77.8% vs. 40.2%, p=0.002) and detected at an advanced stage (55.6% vs. 26.1%, p=0.008). Log Rank test was used to evaluated the prognostic value of the ACC-HGT. Patients with ACC-HGT had a much worse overall survival (OS) compared with conventional ACC ($p<0.001$). More importantly, compared with solid ACC, a subtype which generally accepted showing stronger invasiveness and having worse prognosis, ACC-HGT had even much worse OS (p=0.015).

Conclusions: Compared to conventional ACC, ACC-HGT showed a slight male predominance, higher lymph node metastasis, higher recurrence rate, higher vascular invasion rate and detected at an advanced stage. ACC-HGT had a much worse OS compared with conventional and solid type ACC. Those results suggesting that ACC-HGT is a highly aggressive tumor and should be considered for neck dissection and closer follow-up. Pathological distinction of this tumor has great significance for treating and predicting patients prognosis properly.

ANTIOXIDANT RICH TROPICAL HERBS TO COMBAT ARECA-NUT INDUCED OPMDS.

DR. RASIKA ILLEPERUMA[A], MR. KASUN BANDARA[B], DR. DO KYEONG KIM[C], PROF.

SAMADARANI SIRIWARDENA[B], PROF. RUWAN JAYASINGHE[B], PROF. JIN KIM[C], PROF. WANNINAYAKE TILAKARATNE[B]. [A] DEPARTMENT OF MEDICAL LABORATORY SCIENCE, FACULTY OF ALLIED HEALTH SCIENCES, UNIVERSITY OF PERADENIYA, SRI LANKA, [B] CENTER FOR RESEARCH IN ORAL CANCER, DEPARTMENT OF ORAL PATHOLOGY, FACULTY OF DENTAL SCIENCES, UNIVERSITY OF PERADENIYA, SRI LANKA, [C] ORAL CANCER RESEARCH INSTITUTE, DEPARTMENT OF ORAL PATHOLOGY, YONSEI UNIVERSITY COLLEGE OF DENTISTRY, SEOUL, KOREA

Objectives: Areca-Nut (AN) induced Oral Premalignant Diseases (OPMDs) are a health burden in Asian countries which causes higher morbidity and mortality. Oral Submucous Fibrosis (OSMF) and Oral Leukoplakia (OL) are the most vulnerable AN induced OPMDs which have a considerable malignant transformation rate. The underline mechanism of the carcinogenesis in OPMDs is still obscure. It was found that the oxidative stress caused by the AN can induce the carcinogenesis in OPMDs. Based on our previous research, it was found that some of these OPMDs have DNA damage caused by oxidative stress. Tropical countries are rich of herbs with antioxidants. Our attempt was to test few herbs as a remedy to reverse the potential carcinogenesis in AN induced OPMDs by reducing the oxidative stress caused by the AN.

Findings: Expression of Phospho histone H2AX, DNA double-strand breaks (DNA DSBs) marker was tested immunohistochemically in OPMDs with the history of AN consumption and compared with normal oral mucosa (NOM) and oral squamous cell carcinoma (OSCC). Phospho histone H2AX was significantly increased in OL and OSMF compared to the NOM ($p<0.05$). In-vitro studies using immortalized human oral keratinocytes (IHOK) shown that AN induced reactive oxygen species (ROS) production can be significantly reduced by the ethanol extracts of the antioxidant rich herbs Shumacheria castaneifolia leaves (SC-extract) and Solanum nigrum linn leaves (SN-extract). Antioxidant properties of the herbs were analyzed by DPPH assay. Furthermore, the amount of Phospho histone H2AX in response to 24hr AN treatment was considerably reduced in pretreated IHOK cell with SC extract. Murine model experiment also revealed that the herbal extracts can reduce the AN induced DNA DSBs in oral mucosa.

Conclusions: This study is evident that blocking ROS generation by herbal extracts as a promising approach to reverse DNA DSBs caused by AN. Especially, to prevent malignant transformation in OPMDs

MICRORNA-222 AND MICRORNA-203 SIGNATURES IN ORAL SQUAMOUS CELL CARCINOMA: POTENTIAL ROLE IN PROGRESSION AND AS THERAPEUTIC TARGETS.

DR. MADHURA MG. DAPM R V DENTAL COLLEGE AND HOSPITAL, BENGALURU, KARNATAKA, INDIA

Objectives: To discuss the proposed role of microRNA-222 (miR-222) and microRNA-203 (miR-203) in oral squamous cell carcinoma in the progression and as possible therapeutic targets.

Findings: miR-222 is colocalized as a cluster in the short arm of chromosome X. Luciferase reporter gene assays in oral tongue squamous cell carcinoma (OTSCC) have shown that hsa-miR-222 regulates the MMP1 expression through both direct cis-regulatory mechanism (targeting MMP1 mRNA) and indirect trans-regulatory mechanism (indirect controlling of MMP1 gene expression by targeting SOD2). Hence, hsa-miR-222 might serve as a novel therapeutic target for OTSCC patients at risk of metastatic disease.
miR-222 has been shown to regulate TRAIL resistance and enhancement of tumorigenicity through PTEN and TIMP3(Tissue inhibitor of metalloproteinase 3) downregulation.
miR-222 has been implicated to target PUMA(p53 up-regulated modulator of apoptosis) to improve sensitization of UM1 cells to Cisplatin.
miR-203 acts as a molecular switch between keratinocyte proliferation and differentiation in adult epidermis by targeting ΔNp63 mRNA. Following DNA damage, ΔNp63 downregulates and a possible activation of the apoptotic program in head and neck squamous cell carcinoma has been thought of.
miR-203 has been shown to target EIF5A2 in colorectal cancer cells. Serving as a tumor suppressor gene, miR-203 has been thought to be a useful potential therapeutic target in colorectal cancer. miR-203 as a therapeutic target in oral squamous cell carcinoma needs further validation.

Conclusion: In tumour progression, several cellular pathways may be affected by a single microRNA since it can target multiple mRNAs. Much more light is to be shed by developing as well as by tracking the identified microRNA signatures in oral squamous cell carcinoma, to pave the way for their future clinical use in the diagnosis, management, and prognosis.

LADININ-1 IS INVOLVED IN CELL MOTILITY AND PROLIFERATION OF ORAL SQUAMOUS CELL CARCINOMA CELLS.

DR. TATSUYA ABE[A], DR. MANABU YAMAZAKI[B], DR. SATOSHI MARUYAMA[C], PROF. YOICHI AJIOKA[A]. [A] DIVISION OF MOLECULAR AND DIAGNOSTIC PATHOLOGY, NIIGATA UNIVERSITY GRADUATE SCHOOL OF MEDICAL AND DENTAL SCIENCES, [B] DIVISIONS OF ORAL PATHOLOGY, DEPARTMENT OF TISSUE REGENERATION AND RECONSTRUCTION, NIIGATA UNIVERSITY GRADUATE SCHOOL OF MEDICAL AND DENTAL SCIENCES, [C] ORAL PATHOLOGY SECTION, DEPARTMENT OF SURGICAL PATHOLOGY, NIIGATA UNIVERSITY HOSPITAL

Objectives: Oral squamous cell carcinomas (SCCs) and carcinoma in-situ frequently form the interface between cancer and non-cancerous epithelium. Previously, we identified the altered expression of 7 specific proteins around the interface between cancer and non-cancerous epithelium using proteome analysis of oral SCC tissue sections. Among identified proteins, ladinin-1 (LAD1) expression was significantly increased in the cancer tissue adjacent to non-cancerous epithelium. However, the function of LAD1 in oral SCCs is totally unknown. Thus, the aim of this study was to examine the function of LAD1 in the oral SCCs by in-vitro analysis.

Findings: The gene and protein expressions of LAD1 were confirmed by quantitative PCR and western blotting in three oral SCC cell lines, HSC-2, -3, and -4. Using immunofluorescence, LAD1 was localized in the peripheral area of the cytoplasm of cancer cells. High resolution morphological analysis using structured illumination microscopy revealed that LAD1 was co-localized with actin filament forming “actin arc” in the