Oral Potentially Malignant Disorders (OPMD): state of the art and a roadmap for research

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ABSTRACT BOOK

LECTURES

Risk classification

Differentiated features of oral dysplasia often lead to underestimation of diagnosis, and possibly to delay in prevention/ early detection of malignant transformation

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The WHO classification postulates that the more advanced the degree of dysplasia, the higher the likelihood of developing oral squamous cell carcinoma (OSCC). However, literature reports that OSCC may also arise from seemingly non-dysplastic epithelium. The histology of these lesions is subtle and shows great conformity with the well-known entity differentiated dysplasia of the vulva and penis. However, very little is known about this type of dysplasia in the oral cavity.

We determined reliable histological criteria for the diagnosis of differentiated oral dysplasia and assessed immunohistochemical markers as diagnostic aid. Consecutive OSCC cases were studied for the presence of dysplasia. The histopathological features of differentiated dysplasia were enumerated, and immunohistochemistry with cytokeratin 13 (CK13), cytokeratin 17 (CK17)/ Ki67was conducted. Differentiated dysplasia was present adjacent to 71% (147/207) of OSCC, with subtle atypia in 74%. Loss of CK13, expression of CK17 and an altered Ki67 were noted.

Through this study, we hope to improve the undervalued diagnosis of differentiated oral dysplasia, and to alert involved caregivers to the existence of this lesion with often subtle histology, and possibly distinct clinical appearance. Based on correct diagnosis further research to assess its malignant potential can be conducted. We hope that the WHO will include refined histological criteria for diagnosis of differentiated oral dysplasia.

Genomic classification - *Ruud Brakenhoff*

Head and neck squamous cell carcinomas (HNSCC) develop in the mucosal lining of the upper aerodigestive tract. The tumors are preceded by precancer changes in the mucosal lining. Some, typically in the oral cavity, are macroscopically visible as lesions and collectively named oral potentially malignant disorders or OPMD. Most frequent lesions are leukoplakias: white patches in the oral mucosa.

Accurate risk classification has been difficult. As tumors are caused by an accumulation of genetic changes, genomic markers have been studied since 1996. Loss of heterozygosity of chromosomes 3p and/or 9p by microsatellite PCR have been shown reliable markers for malignant transformation, but the applied assays have their limitations and became somewhat outdated.

Microscopic examination is applied routinely to exclude invasive growth of OPMDs. In addition, morphologic changes, graded as mild, moderate and severe dysplasia, were considered for risk assessment. Consequently dysplasia grading has remained the standard risk assessment tool, but was never very accurate. The recent introduction of differentiated dysplasia as additional class seems a game changer, and genomic markers should be incorporated in the classification dominated by dysplasia. Novel methods using next generation sequencing have been introduced, and this has revolutionized research.

In this presentation the basis of next generation sequencing will be presented to make it understandable for clinicians, the state of the art in genomic classification will be discussed, and promising approaches using next generation sequencing in the era of differentiated dysplasia.

Phenotypic classification – *Pierre Saintigny*

Phenotypic classification - Oral squamous cell carcinoma is a major cause of cancer-associated morbidity and mortality and may develop from oral erythroleukoplakia, the most common oral potentially malignant disorder. We will summarize our work aiming at understanding the phenotypic diversity of oral erythroleukoplakia using gene expression profiles. This work may provide a framework to the development of a biologically-driven and actionable classification needed to develop future efficient interventions strategies to prevent oral cancer development in patients with erythroleukoplakia.

Preclinical models:

Preclinical research: state of the art and models for research (cell cultures, organoids, animal models - *Moshe Elkabets*

Understanding the complex biological changes that lead to neoplastic transformation of pre-malignant disorders of the oral cavity will likely guide the development of methods for improved diagnosis, monitoring and treatment of oral squamous cell carcinoma (OSCC). The development and use of *in vitro* and *in vivo* models that closely simulate the histopathology and molecular pathogenesis of potentially pre-malignant oral epithelial lesions (PPOELs) in humans would greatly expand the research possibilities and provide a means of testing potential therapeutic agents. In order for investigators to select the appropriate model to answer scientific questions, it is important to understand the benefits and limitations of available models for the study of PPOEL. The purpose of this work is to give an overview of the most pertinent *in vitro* and *in vivo* pre-clinical models of PPOEL..

Role of microenvironment - *Leon Van Kempen*

Neoplastic progression is the result of a dynamic interplay between transformed cells and the microenvironment. The early stages of tumour growth can be regarded as wounds that fail to heal, with evidence of continued fibroblast activation, matrix remodelling, angiogenesis and recruitment of inflammatory cells. This eventually culminates into a protumourigenic microenvironment. Elucidating the contribution of stromal cells to early tumour development not only advance our understanding tumour biology but may also provide avenues for prevention strategies. With lessons learned from cutaneous squamous cell carcinoma, I will highlight the importance of mouse models of de novo oral squamous cell carcinomas to dissect the complex stromal interactions and to understand the contribution of the tumour microenvironment to neoplastic progression.

The role of oral microbiota in cancer - *Jukka H. Meurman*

The manifold human microbiota contains 10 times more bacteria than human cells. Consequently, its impact on functions of the body is evident but the mechanisms involved still are mainly unknown (Meurman & Bascones-Martinez *Oral Dis* 2011, 17, 779-784). Furthermore, the huge diversity of microbiota makes it difficult to assess if certain microbial species might directly link to the development of cance. Infection and inflammation are nevertheless estimated to a play role in approximately 15 – 20% of all malignancies. As an example, we have found from our ongoing long-term cohort study from Stockholm, Sweden (with 1676 patients followed-up over 30 years), that gingival inflammation appeared to link to cancer in general with an OR 1.29 (1.00 – 1.65) (Virtanen et al. *J Cancer* 2014, 5, 79-85). High dental plaque index appeared to associate with 1.79 times the OR of death (CI 1.01 - 3.19; p<0.05) (Söder et al. *BMJ Open* 2012,2:e001083. doi: 10.1136/bmjopen-2012-001083). Incidence of breast cancer was 1.75% in subjects who had periodontal disease (Söder et al. *Breast Cancer Res Treat* 2011, 127, 497-502). When looking at certain oral microorganisms, *Aggregatibacter actinomycetemcomitans* showed strong association with malignancy while *Porphyromonas gingivalis* and *Prevotella intermedia* were suprisingly more prevalent among patients without malignancy. In principal component analyses, *A. actinomycetemcomitans* was in the strongest component while the second strongest component consisted of a combination of *Tannerella forsythia* and *Treponema denticola*, respectively (Söder et al. *Tumour Biol* 2021, 43, 1-9). As these examples show, oral infections may indeed have a role in carcinogenesis. The putative pathogenic mechanisms that explain the associations are the chronic and often subclinical inflammations caused by oral microbiota. These then lead to up-regulation of cytokines and inflammatory mediators and also affect DNA repair mechanisms. Systemic consequences like malignant transformation then results in the cellular level.

Clinical characteristics and management

Clinical classification and terminology - *Erik van der Mey*

Oral potentially malignant disorders (OPMDs) are associated with an increased risk of occurrence of malignancies of the oral cavity. In this presentation an update on the clinical classification and terminology of OPMDs will be given, based predominantly on their clinical features. A consensus report (2021) from an international seminar convened by the WHO Collaborating Centre for Oral Cancer will be used as a guideline. The focus in this presentation will be on oral leukoplakia and oral lichen planus/oral lichenoid lesions. Illustrated by a number of clinical cases it will be emphasized that not using the appropriate terminology and misclassification will lead to confusion, inaccurate reporting and under-, or sometimes over-, reporting of malignant transformation.

Biological endoscopy in detection of OPMD *Cesare Piazza - Alberto Paderno*

The 'biological endoscopy' is a concept in which endoscopic techniques aim to provide deeper insight into the behavior of a target lesion or to allow visualization of lesions that are not otherwise visible under conventional white light examination. Even though the gold standard for definition of the nature of a lesion remains the histopathologic examination of a formalin-fixed, paraffin-embedded tissue sample, biological endoscopy attempts to reduce the number of unnecessary biopsies and minimize the number of false negatives. This term encompasses various technical innovations in endoscopic tools for the evaluation of the upper aero-digestive tract (UADT) that have been reported in the literature. The concept is particularly relevant in the management of oral potentially malignant disorders (OPMD), where a clear-cut endoscopic diagnosis is even more challenging than in malignant disease.

In this field, Narrow Band Imaging is a particularly promising technology. In particular, NBI applies narrow-band spectrum filters to enhance the visualization of mucosal and submucosal microvascular patterns, based on the principle that light has different depths of penetration depending on its wavelength. NBI filters are focused on the blue and green lights (wavelengths of 415 and 540 nm, respectively), corresponding to the peaks of absorption of hemoglobin. These filtered wavelengths penetrate the superficial layers of mucosa, thus highlighting the capillary network, and deeper levels, enhancing the submucosal vessels. Interestingly, the main principle of NBI is not the evaluation of the neoplasm itself but its vascularization.

In the setting of OPMD, NBI patterns can provide essential hints on the benign, inflammatory, dysplastic, or malignant nature of a given lesion. However, the evaluation requires significant know-how and a relatively long learning curve, especially when evaluating early lesions of the oral cavity. The application of artificial intelligence algorithms, such as convoluted neural networks, is a recent development of this diagnostic approach. The aim of these attempts is to remove the main drawbacks of the technique; in particular, its operator-dependency and long learning curve. However, reports on this topic are still few and mostly preliminary.

Practical insights from oral medicine - *Noam Yarom*

The management of patients with oral potentially malignant disorders (OPMD) is challenging. In the lack of robust evidence concerning effective treatment of OPMD and predictive biomarkers for malignant transformation, decision making is based on the oral care provider's clinical judgment. Although, only a small proportion of patients with OPMD will eventually develop cancer, all patients are kept under close follow-up routine. The purpose of the presentation is to review the current knowledge regarding the management of patients with OPMD.

Ongoing clinical research in OPMD – *Paolo Bossi*

Oral Potentially Malignant Disorders (OPMD) represent a challenge from different points of view. At diagnosis, the identification of clinical and pathological characteristics predicting an increased risk of malignant transformation is an outstanding issue. Till now, loss of heterozygosity (LOH) is the most solid available molecular determinant; however, research is still in its infancy in this field, as we need more accurate determinants of malignant transformation, to better select patients for clinical trials. For what concerns chemoprevention, several compounds have been studied (retinoids, COX-2 inhibitors, antiEGFR antibodies or tyrosine kinase inhibitors, agents against p53 and others), but no one turned out to be effective. Ongoing clinical trials are studying different pathways to

promote cancer interception and to limit the risk of precursor stages to evolve into cancer. One of the most exciting fields is represented by the possibility to modulate the immune microenvironment of OPMD, considering that they represent an equilibrium phase in the immunoediting concept. Therefore, pushing the immune system could allow to restore competence and to stop the process of carcinogenesis. There are a few trials in this regard that are exploring the activity and safety of immune checkpoint inhibitors in OPMD. Drugs used to treat hyperglycemia, such as metformin, rosiglitazone and pioglitazone, have been also repurposed in order to modify the microenvironment of OPMD. Also, targeting epigenetic is another field of interest in chemoprevention, and sodium valproate represents an example of a compound currently being studied. Selecting the populations most at risk and the subjects who could derive the highest benefit is critical in designing a new trial to prevent OPMD transformation. It is also crucial defining correct surrogate and final endpoints for a well designed and informative clinical trial.

ABSTRACT PRESENTATION

Analysis of infrared absorbance spectra identifies the transformation potential of oral epithelial dysplasia

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Background: Oral epithelial dysplasia (OED) is a histopathologically-defined, potentially premalignant condition of the oral cavity. The rate of transformation to frank carcinoma is relatively low (12% within 2 years) and prediction based on histopathological grade is not unambiguous, leading to over treatment with its associated morbidity. Alternative approaches include infrared (IR) spectroscopy, which is able to classify cancerous and non-cancerous tissue in a number of cancers, including oral. The aim of this study was to explore the capability of FTIR (Fourier-transform IR) microscopy and machine learning as a means of predicting malignant transformation of OED.

Materials and methods: Supervised, retrospective analysis of longitudinally-collected OED biopsy samples from 17 patients with high risk OED lesions: 10 lesions transformed and 7 did not over a follow-up period of more than 3 years. FTIR spectra were collected from routine, unstained histopathological sections and machine learning used to predict malignant transformation, irrespective of OED classification.

Results: PCA-LDA (principal component analysis followed by linear discriminant analysis) provided evidence that the subsequent transforming status of these 17 lesions could be predicted from FTIR data with a sensitivity of 79 ±5% and a specificity of 76 ±5%. Six key wavenumbers were identified as most important in this classification.

Conclusion: Although this pilot study used a small cohort, the strict inclusion criteria and classification based on known outcome, rather than OED grade, make this a novel study in the field of FTIR in oral cancer and support the clinical potential of this technology in the surveillance of OED.

Effectiveness of a non-invasive salivary diagnostic test for early identification of potentially malignant lesions and squamocellular carcinoma of the oral cavity: quantitative and qualitative evaluation of salivary markers CD44 and total proteins

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Background Human salivary markers, as diagnostic tools, can offer an easy, inexpensive, safe and non-invasive approach for early disease detection. The aim of this study is to evaluate the diagnostic value of two salivary tests to detect the presence of CD44 and total salivary proteins, in order to early identify oral and oropharyngeal cancer.
Materials and Methods All consecutive patients with a suspicious diagnosis of oral squamous cell carcinoma (OSCC) or dysplasia, were asked to participate to the study before biopsy was performed. For each candidate, an oral salivary sample was collected and immediately tested for qualitative markers (OncAlert RAPID), such as human CD44 and total proteins. The quantitative examination was then performed in laboratory with the ELISA technique. The data was subsequently entered into an algorithm to define the oral cancer risk profile of the patient (OncAlert LAB). The histopathological analysis was then acquired. Specificity and sensitivity, positive and negative predictive values and likelihood ratio of the two tests were calculated.
Results 46 patients were enrolled for a total of 23 cases of carcinoma, 11 dysplasia and 12 non-neoplastic lesions. The RAPID test discriminated OSCC from non-neoplastic lesions and low-grade dysplasia from lesions with severe dysplasia or OSCC (Se=89%, Sp=70%). The LAB test and the algorithm led to the definition of risk profiles that did not correspond to the histopathological diagnosis.
Conclusion The RAPID test seems to be a useful clinical aid for the oral cancer screening and follow-up. The LAB test and algorithm need to be improved.

OPMD Issue CLINICAL MANAGEMENT

SAVER: Sodium Valproate for the Epigenetic Reprogramming of High-Risk Oral Epithelial Dysplasia. A Phase II randomised controlled clinical trial

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Background There is a paucity of evidence for chemopreventative interventions in the management of Oral Epithelial Dysplasia (OED). Surgery and close surveillance are the most commonly utilised management strategies but both have limitations due to the risk of over- and under-treatment and there is a lack of robust evidence for either approach. Sodium Valproate has been associated with a reduced risk of Head and Neck Cancer.
Materials and methods The SAVER trial (Sodium Valproate for the Epigenetic Reprogramming of high-risk oral epithelial dysplasia) is a phase IIb, open-label, randomised controlled, window-of-opportunity trial of Sodium Valproate vs observation in the management of high-risk OED lesions and is currently recruiting. Patients (n=110) will be recruited from up to ten sites in the UK and Ireland and randomised to treatment or observation arms, with 4 months of active treatment for those in the intervention arm. The composite, surrogate endpoint of change in lesion size, histological grade and LOH markers at 8 key microsatellite regions will be utilised. Feasibility outcomes are also included: recruitment targets, adverse events and compliance with study protocol. An embedded mechanistic study will explore mechanism of action of Sodium Valproate and an embedded qualitative study will explore patient experience of the trial.
Conclusion This trial represents an opportunity to explore an inexpensive, well-tolerated drug as a repurposed agent in the management of OED. The challenges and opportunities of early phase trials in oral epithelial dysplasia will be discussed, particularly in relation to the authors' experience of the SAVER trial.

Optical Coherence Tomography (OCT) and Oral Potentially Malignant Disorders: critical review on potential diagnostic patterns.

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Background: OPMDs comprise heterogeneous clinical manifestations including Oral Leukoplakia (OL) and Oral Lichen Planus (OLP). OCT has been proposed as valuable diagnostic support, although, to date, there are no standardized OCT-diagnostic patterns applicable. In this context, the aim of our study was to conduct a potential identification of specific OCT patterns for OL and OLP from a critical review of the literature.
Materials and methods: Research was performed considering original articles on in vivo OCT diagnostic patterns of histologically confirmed OL and OLP.
Results: 5 papers resulted eligible for a total of 114 OL and 53 OLP cases. Comparing with healthy mucosa (Fig.1 A), we detected the following potentially discriminatory OCT patterns.

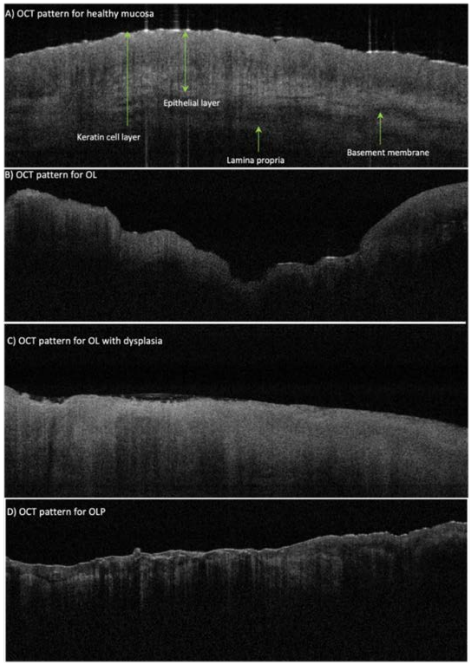

Figure 1

For OL, OCT showed a keratin layer with increased reflectiveness, basal hyperplasia and less clear visualization of lamina propria; in presence of dysplasia, it was reported a loss of epithelial layers stratification (Fig. 1, B-C). For OLP, OCT showed a reduction of epithelial thickness and keratin cell layer with a hyper-reflective sub-epithelial area of inflammatory infiltrate and poor visualization of basement membrane and lamina propria (Figure 1, D).

Conclusion: The discriminatory criteria should be oriented towards the evaluation of epithelial thickness as potential OL and OLP discriminant diagnostic using OCT. Further studies should be used to validate these preliminary reports.

Identification of an epigenetic profile associated with malignant transformation of oral lichen planus: preliminary study.

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Background: Oral Lichen Planus (OLP) is a chronic inflammatory autoimmune disease included among risk conditions for oral Squamous Cell Carcinoma (OSCC) development. In the present study we assessed DNA methylation status in a group of 12 OLPs-associated OSCC and a second group of 25 OLPs who didn't develop an OSCC starting from oral brushing cell collection.
Material and Methods: Two brushing specimens were collected in the group of 12 consecutive OLPs-associated OSCC patients: one from the tumor mass area (GROUP 1a) and the other from distant mucosa with presence of lichenoid lesions (GROUP 1b). One oral brushing sample was collected in the group of 25 consecutive OLPs who didn't develop an OSCC in a mean follow up period of 60 months (GROUP 2). DNA methylation level of a series of 273 CpGs representatives of the 15 previously described methylated genes in OSCC (*ZAP70, KIF1A, LRRTM1, PARP15, FLI1, NTM, LINC0059, EPHX3, ITGA4, MIR193, GP1BB, MIR296, TERT, miR137 and PAX1*) were investigated by bisulfite-Target Next Generation Sequencing (NGS).
Results: most of CpGs of *NTM, miR296, miR137* and *ZAP70* genes showed similar methylation levels in OSCCs (GROUP 1a) and their respective OLPs (GROUP 1b), whereas a significantly distinct methylation level was found in the group of OLP who didn't develop an OSCC (GROUP 2).
Conclusion: Following preliminary data seem to reveal that our procedure based on DNA methylation analysis from oral brushing may be able to identify a specific OLP epigenetic profile associated with malignant transformation.

13-gene DNA methylation analysis from oral brushing for early detection of malignant and pre-malignant lesions of the oral cavity.

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Background: in the present study we evaluated the diagnostic performance of a minimally-invasive method based on 13-gene DNA methylation analysis for early detection of oral carcinomas and Oral Potentially Malignant Disorders (OPMDs) in an extensive collection of oral brushing samples.
Material and Methods: Oral brushing specimens were collected in a total of 644 patients with different types of lesions (237 Oral carcinomas, 29 OPMDs with various grades of dysplasia, 15 oral leukoplakias without presence of dysplasia, 30 Oral lichen planus, 15 benign inflammatory lesions, 9 benign reactive lesions, 5 infectous lesions, 3 patients in chemotherapy for breast cancer and 301 healthy donors). A set of 13 previously described methylated genes in OSCC (*ZAP70, KIF1A, LRRTM1, PARP15, FLI1, NTM, LINC0059, EPHX3, ITGA4, MIR193, GP1BB, MIR296, TERT*) were investigated by bisulfite-Target Next Generation Sequencing (NGS) using MiSEQ platform (Illumina, San Diego, CA). Each sample was determined in blindness as positive or negative based on a predefined cutoff value.
Results: 248/266 (93.2%) brushing specimens collected from patients with oral cancer or an OPMD with various grades of dysplasia were detected as positive. 321/378 (84.9%) brushing samples collected from healthy donors and patients with benign inflammatory, infectous and non-dysplastic potentially malignant disorders were detected as negative. 2 non-dysplastic OPMDs that during follow up period developed an oral carcinoma showed a positive score.
Conclusion: Following data confirmed the diagnostic performance of our novel procedure and suggested that this easy-to-perform method could be proposed as a reliable measure of oral cancer risk.

Oral cancer prediction by noninvasive genetic screening

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Background

Oral squamous cell carcinomas (OSCCs) develop in precancerous changes in the mucosal lining characterized by tumor-associated genetic changes, also coined fields, which are mostly not visible but occasionally present as oral leukoplakia (OL). The aim of this study is to evaluate a noninvasive genetic assay using next-generation sequencing (NGS) to detect the presence of genetically altered fields, and demonstrate clinical utility of oral precancer screening.

Materials and methods

Brushed cells and corresponding biopsies were obtained from 41 OLs. Brushed cells of 29 age-matched healthy individuals were included as controls. All samples were subjected to low-coverage whole genome NGS, followed by target-enrichment NGS of 12 genes that are commonly mutated in OSCC. We examined brushed cells from 42 Fanconi anemia patients, 17 of whom developed OSCC, to test clinical utility of noninvasive oral precancer screening.

Results

Genetic alterations were found in 31 of 41 OL biopsies. Analysis of brushed samples demonstrated a sensitivity of 84% and a specificity of 90% to detect genetic changes in the underlying lesion. Genetic alterations were absent in the 29 control samples. In Fanconi anemia patients detection of mutations in brush samples of normal-appearing oral mucosa was predictive for development of OSCC (hazard ratio 3.4, $P < 0.01$).

Conclusion

NGS analysis of noninvasively collected samples offers a highly accurate method to detect genetically altered fields in the oral cavity, and predicts development of OSCC in high-risk individuals. Noninvasive genetic screening can be employed to screen high-risk populations for oral cancer, monitor interventions, and follow carcinogenesis.

ORAL CAVITY CARCINOMA IN PATIENTS WITH AND WITHOUT A HISTORY OF LICHEN PLANUS: A COMPARATIVE ANALYSIS OF CLINICAL AND PATHOLOGICAL CHARACTERISTICS

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Background: Oral potentially malignant disorders (OPMD) are associated with the risk of malignant transformation (MT) into oral carcinoma (OC). Oral Lichen Planus (LP) is one of the most common OPMDs in western countries. Although there is a substantial amount of research on progression to cancer, a specific analysis of the clinical characteristics and prognosis of cancer developed in patients with a history of LP versus patients without a history of LP has not been investigated so far.

Materials and methods: Retrospective evaluation of 89 patients treated for OC at the University of Torino with a known history of LP compared to a representative sample of 100 patients treated for OC without a known history of LP. Comparative analyses were performed on age at presentation, sex, TNM staging, clinical characteristics, pathology characteristics, 3- and 5-years overall survival (OS) and disease-free survival (DFS).
Results: It was shown that patients with a history of LP were significantly younger at first presentation than patients without a history of LP (mean age difference 4 years, 95% CI 2.1-5.7, p <0.005). Also, patients with a history of LP were in higher proportion females (OR 1.4, 95% CI 1.1-19). The main pathological stage at presentation was significantly lower in the LP group (p<0.005). OS was significantly better in the LP group (HR 0.57 95% CI 0.54-0.60). DFS was also higher in the LP group (HR 0.46, 95% CI 0.54-0.60).
Conclusion: The study may have the potential to increase the understanding of clinical and prognostic characteristics of patients with a known history of LP that develop OC compared to patients without a known history of LP. The results of the study can help in developing specific indications regarding the therapeutic approaches, follow-up measures, and future lines of research for this subset of patients.

OPMD Issue CLINICAL MANAGEMENT

Identification of putative laryngeal and pharyngeal lichen planus lesions: an endoscopic preliminary evaluation in 16 patients

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Background
Oral Lichen Planus (OPL) is the most diffuse type of lichen planus (prevalence 1%-2%). Recent studies have investigated the presence of esophageal lichenoid lesions in OPL patients, with a focus on malignant transformation risk. Nowadays, this risk is still unknown, but it is considered equal to oral lesions one (about 1-3%). Our study investigates the presence of pharyngeal-laryngeal lesions, with the same characteristics of oral ones, equally with an unknown malignant potential.
Materials and methods
16 consecutive patients were enrolled, with an age range of 47-85 yo, all with confirmed OPL diagnosis, and afferent to our outpatient clinic specialized in otolaryngology and oral pathology, Oral Pathology Interdisciplinary Center (Centro Interdisciplinare di Patologia Orale - CIPO). An oral pathologist and an ENT surgeon examined all subjects simultaneously for oral and pharyngeal/laryngeal symptoms. All patients underwent a conventional oral examination, an oral endoscopy, and an optical fibre examination of the upper aerodigestive tract with both white light and narrow band imaging (NBI) technique.
Results
All patients were diagnosed with oral lesions at the time of examination. OPL-compatible lesions were found in 7 out of 16 patients at the endoscopic examination of the upper aerodigestive tract, particularly on the posterior wall of the hypopharynx. No lesions were found in the nasal cavities or rhinopharynx.
Conclusion
Our study is the first to focus on pharyngeal-laryngeal lichenoid lesions. Our data are preliminary, particularly towards neoplastic transformation risk. Nevertheless, they underline the importance of a multidisciplinary approach to OPL and other oral premalignant lesions.

Malignant transformation of oral leukoplakia in oral squamous cell carcinoma: a case report.

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Aim: Oral leukoplakia (OL) is defined as "a white mucosal patch that cannot be defined as any other disorder and carries an increased risk of malignant transformation". OL, the most observed oral potentially malignant disorder, possesses an annual risk for malignant transformation of 2-3%.
Methods: We report a case of a patient who was referred to our sector of Oral Medicine (AOUP "P. Giaccone" Palermo, Italy) for the presence of a white plaque on the tongue.
Results: A 62-year-old woman came to our attention in 2012, showing a hyperkeratotic plaque on the left lateral border of the tongue. The clinical examination revealed the presence of a uniformly white patch with regular margins, with a flat surface, measuring 2cm x 0,5cm. The biopsy confirmed the diagnosis of OL; subsequently, the patient was included in a follow-up program. However, the patient didn't show to any visit from the end of 2013 to April 2021. The clinical examination revealed the presence of a 1cm ulcerated roundish lesion on the left lingual margin with irregular surface and margin. The patient underwent a CT scan, then a biopsy was carried out. Based on the histological and radiological findings, the diagnosis of oral squamous cell carcinoma (OSCC) was confirmed. The patient was referred to Oncology Unit the staging and management.
Conclusion: Even if OL possesses a low risk of malignant transformation, since its transformation is scarcely predictable, it is essential to check the patient periodically and to increase the empowerment of the patient to follow-up compliance.

The role for routine oral and upper aerodigestive tract endoscopy in premalignant oral cavity lesions evaluation

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Background

If we consider the ease with which an oral examination can be conducted, with the sole aid of an adequate light source and a mirror or tongue depressor, the use of complementary techniques such as endoscopy appears in the first instance redundant, despite their fundamental role in the diagnosis of non-oral head and neck squamous cell carcinoma.

Nonetheless, over time, endoscopy has carved out an increasingly important space for itself in the evaluation, treatment, and follow-up of oral cancer and premalignant oral cavity lesions, responding to the needs of holistic management of these patients.

Materials and methods

Over a 6-year period, we systematically employed oral and nasal endoscopy with narrow-band imaging in the follow-up of all premalignant oral cavity lesions and oral malignancies in a second-level multidisciplinary outpatient clinic.

Across roughly 2000 evaluations, we systematically reviewed the pearls and pitfalls of routine endoscopy use in malignant and premalignant oral cavity lesions.

Results

At the expenses of a negligible longer visit duration, routine endoscopy proved efficient in three major areas:

- It allowed a comprehensive upper aerodigestive tract evaluation during staging and follow up
- It allowed complete oral examination even in patients with reduced mouth opening
- It allowed earlier identification of malignant degeneration and recurrences and better margin definition both through magnification and enhanced visualization

Conclusion

Although it requires adequate training and a considerable monetary investment, oral endoscopy should become routine instrumentation for malignant and premalignant oral cavity lesions, as its positive outcomes far outweigh the negligible and mostly technical drawbacks.

OPMD Issue

CLINICAL MANAGEMENT

Effectiveness of Laser Photobiomodulation in a Case of Oral Dysplasia

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Background

The management of potentially malignant lesions of the oral cavity is often complex for the clinician.
Lesions with mild dysplasia can be followed-up, while lesions with severe dysplasia have to be treated surgically. As regards moderate dysplasia, the therapy is not univocal and needs to be evaluated case-by-case.
Smaller lesions that can be easily removed (notwithstanding adequate follow-up is always required due to the high recurrence rate) while the management of larger lesions can be instead more complex.
The aim of this report is to demonstrate a possible conservative therapy based on laser photobiomodulation in a complex case of oral dysplasia.

Materials and Methods
The patient a 57 years old, female, with a history of past demolition of a small squamous cell carcinoma of the hard palate (T1,N0,M0) went to our observation in 2018. She underwent a therapy based on oral acitretin and topical fluocinonide for a misdiagnosed Lichen Planus.
On physical examination, a red and white verrucous lesion affecting the hard palate and the buccal mucosa was observed. Multiple incisional biopsies were performed and the histological exam showed a high degree of lichen-like dysplasia.
With the patient's consent, a diode laser photobiomodulation (1W/cm^2 for one minute for each single spot with a flat top handpiece, fluence: 60 J/cm^2) was added to the medical therapy once a week with cycles of six sessions.
Results
Clinical improvement was observed, the laser treatment and biopsy were repeated in 2019, 2020 and 2021. The histologic examinations report a severe dysplasia, then moderate dysplasia, mild dysplasia and finally the absence of dysplasia.
Conclusion
There are a lot of conflicting data in the literature regarding the different laser therapies. Although this is an anecdotal case, experimentation with adequate criteria should be evaluated to verify its potential.

Routine otolaryngological endoscopic evaluation and management of oral manifestations of Graft-versus-Host Disease: a preliminary evaluation

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Background
Graft-versus-host disease (GvHD) is one of the most severe complications of hematopoietic stem cell transplantation (HSCT). The histocompatibility of the transplanted cells is a key point of the pathogenic of GvHD and it is related to the severity of the clinical manifestations. Patients with oral GvHD involvement (OGI) may suffer from recalcitrant mucositis, feeding impairment and relapsing infection. In literature, oral, salivary, and oropharyngeal involvement is widely acknowledged. Our study investigates the key role of the otolaryngological clinical examination (including oral and nasal endoscopy with narrow-band imaging) and the management of several phenotypical manifestations of the disease.

Materials and methods
We performed a preliminary longitudinal study on 6 consecutive OGI patients evaluated by our second-level multidisciplinary outpatient clinic (CIPO) from July 2021 undergoing systematical
periodical comprehensive otolaryngological evaluation with oral and nasal endoscopy.

Results
All the enrolled patients were transplanted with hematopoietic stem cells between 7 months and 22 years before enrollment. Endoscopy with NBI allowed to recognize different features of GvHD, early detection of any malignant and premalignant oral cavity lesions and to set a proper follow-up.

Conclusion
Routine otolaryngological evaluation could have a groundbreaking role in the management of transplanted patients with GvHD with oral involvement. Not just for the involvement of adequately skilled specialists, but also for the diagnostic role that endoscopy could have in the early management of malignant and premalignant lesions.

Characteristics of p27 protein diversity in oral leukoplakia and cancer

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Background. In last decades p27 protein has been proved in normal, dysplastic, and malignant cells of oral mucosa. Regulation of the cell cycle is an important factor in carcinogenesis. p27 has a tumor suppressor and oncogene function. It has been reported that the loss of nuclear p27 is associated with poor cancer prognosis. The aim of study was to characterize p27 expression in oral leukoplakia (OL) and oral squamous cell cancer (OSCC).
Materials and methods. Immunohistochemical visualization of p27 antigen was performed on the formalin-fixed paraffin-embedded control samples (n=10), OL (n=25) of different location and OSCC tissue (n=25). The sections were analyzed and assessed in 3 fields under x400 magnification, recalculated to full field of view. Results were evaluated by Excel program.
Results. In our study OL was diagnosed in buccal mucosa (52%), lingual mucosa (36%) and floor of mouth (12%). The average age of patients was 59 years. In control group in one field of vision the mean number of p27 positive nuclei was 21.2 but in OL it was 130.6. Labeled nuclei were in spinous and granular layers. In OSCC expression of p27 antigen was of mosaic pattern and its value was 22.2. In OSCC was proved patchy expression of p27 not only in nuclei but in cytoplasm, too. Lack of p27 was both in apoptotic cells and in epithelium with saved nuclei.
Conclusion. If amount of p27 labeled cells of OL decrease under the value of smallest number, it is prognostic marker for possible malignant transformation.

OPMD Issue PATHOLOGICAL/MOLECULAR CLASSIFICATION

Role of EBV and HHV-7 in the etiopathology of oral lichen planus

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BACKGROUND:
Oral lichen planus (OLP) is the most common non-infectious, chronic inflammatory oral disease affecting 1-2% of the general adult population with chronic potential of transforming into squamous cell carcinoma and therefore it considered to be a precancerous condition. The aetiology of OLP is unclear however

viruses have been in spot of investigation. The aim of the study is to provide currently available information on the association of different viruses mainly EBV and HHV-7 in the development OLP.

MATERIALS AND METHODS:

Online databases (PubMed, ProQuest, Scopus, Research gate, Science direct and Google Scholar) were searched from date of inception till November 2021. Studies were included if they met the following criteria: 1) observational studies, 2) the study comprised OLP patients and control subjects, 3) diagnosis of OLP was confirmed histopathologically, and 4) articles were in English.

RESULTS:

A total number of 10 studies (from 27) comprising 403 OLP cases and 216 controls were included for evaluating the role of EBV and HHV-7. The results of the pooled studies revealed a significant positive association between EBV and OLP prevalence being 25.5 % in 5 studies and between HHV-7 and OLP being 33.3% in just 1 study. Studies also showed significant role of other viruses (CMV, HPV, HSV and HCV) in the development of oral lichen planus.

CONCLUSION:

The results suggest that EBV and HHV-7 infection is significantly associated with increased risk of OLP. However, these results are preliminary, and high-quality, large-scale studies are required to further explore the potential role of viruses in the pathogenesis of OLP.

OPMD Issue CLINICAL MANAGEMENT

Development of a European-wide E-learning tool on the topic 'Oral Potentially Malignant Disorders for Healthcare Professionals'

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Background

Oral potentially malignant disorders (OPMDs) are a group of conditions that place affected individuals at an increased risk of developing cancer. To improve the outcomes for patients with OPMDs, it is imperative that healthcare professionals understand the core knowledge related to these conditions.

Aims

Through a European Union funded project via Erasmus+, and reflecting on the experiences of multiple European centres, we aim to produce an e-learning package and tool for healthcare professionals covering the detection, investigation, diagnosis and management of patients presenting with OPMDs. The online resource will be freely available and accessible to European Union healthcare professionals and translated into several languages.

Method

The online resource (www.OPMDcare.com) will run collaboratively between all institutions. A 5-phase development structure will be implemented to develop the e-learning package:

1. A consensus on the information to be included regarding OPMDs, histopathology, diagnosis, management will be reached.
2. The modules and content of the project will be circulated to the expert advisory panel for evaluation and then the information will be revised.
3. First draft of the international e-learning website will be presented to healthcare professionals to obtain pre-launch feedback.
4. The website content and eBook will be circulated to the advisory expert panel who will comment on the material.
5. A dissemination strategy will be presented, so that the number of participants, quality of poster/presentations, articles and number of visits to the website can be assessed.

Expected Outcomes and Impact

- Development of e-learning package and e-book summarising consensus findings
- Production of 6 posters for international presentations
- Educational impact – providing implementable advice regarding OPMDs
- Economic impact, reducing healthcare costs through improved diagnosis and treatment