OVIDIUS UNIVERSITY OF CONSTANTA
DOCTORAL SCHOOL OF MEDICINE
MEDICINE DOMAIN

DOCTORAL THESIS

THE VALUE OF LIGHT-BASED TISSUE IMAGING TECHNIQUES IN ORAL CANCER SCREENING

SUMMARY

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GENERAL PART

CURRENT STATE OF KNOWLEDGE

I. ANATOMY, PHYSIOLOGY AND IMMUNOLOGY OF THE ORAL CAVITY

I.1. Oral mucosa – definition and limits.

Three main types of mucosa can be recognized, identified in relation to their main function: masticatory mucosa, lining mucosa and specialized mucosa. [1,2]

I.2. Oral mucosa – composition.

Histologically, the oral mucosa is divided into three layers. The orientation of these layers from the outside to the inside is as follows: a squamous stratified epithelium; basement membrane; connective tissue, formed by lamina propria and submucosa. [3]

I.3. Oral mucosa – functions.

The oral mucosa has several functions: the protective function, the sensory function and the secretion. By performing these functions, oral soft tissues are exposed to mechanical forces and surface abrasions, which is why the oral mucosa exhibits a series of epithelial and connective tissue adaptations to withstand these insults. The epithelium of the oral mucosa acts as the major barrier to the threats posed by the presence of microorganisms in the oral cavity. [1,11]

I.4. Oral mucosa – vascularization and innervations.

Capillary loops have been used as clinical indicators for diseases such as high-grade dysplasia, carcinoma in situ, systemic sclerosis, and invasive carcinoma in the diagnosis of oral mucosal pathology. [1,14] The nerve structures are dominated by fibers of the trigeminal nerve, and the afferent fibers of the facial (VII), glossopharyngeal (IX) and vagus (X) nerves, Meissner, Golgi and Rufini sensory corpuscles are also involved; they provide pain, tactile and thermal sensitivity. [15]

I.5. Immune defense of the oral mucosa.

The oral mucosa is densely populated with cells of hematopoietic origin that include macrophages, monocytes, dendritic cells and significant numbers of B and T lymphocytes. The immune system of the oral mucosa strikes a delicate balance by performing effective immune surveillance without triggering inflammatory responses exaggerated, tolerating harmless bacteria and antigens. [18,19]

I.5.1. Immunological defects associated with oral cancer. Patients with oral neoplastic pathology, had showed the damage of delayed hypersensitivity to dinitrochlorobenzene in 36-70% of the cases, compared to the control group which showed only 5%. [43-45]

II. ORAL CANCER DIAGNOSIS

II.1. Oral cancer Epidemiology.

Oral cancer is among the most common types of cancer in the world. In Romania, GLOBOCAN reported for 2020, 98,886 new cancer cases, of which 1,351 were of oral cavity and 747 deaths were due to this pathology. [49,50]

II.2. Carcinogenesis.

The "carcinization field" can also be defined by the expression of mutations in exons of tumor suppressor genes. One such tumor suppressor gene is P53, which undergoes mutations or deletions in most carcinomas, processes also identified in approximately 80% of oral cancers. [37,54-56] Mutations of the P53 gene lead to the disappearance of suppressive and regulatory properties, with the consequent loss of control over cell growth and finally to the formation of cancer cells. [57,58]

II.3. Biomarkers.

It reveals genetic and molecular changes related to early, intermediate and late endpoints in the process of carcinogenesis. [62]

II.4. Risk factors.

The most important risk factors for the development of oral cancer are tobacco and alcohol consumption. Although alcohol consumption and smoking are independent risk factors, they have a synergistic effect and together significantly increase the risk of developing oral cancer. [66,67]

II.5. Lesions with malignancy potential.

II.5.1. Oral submucosal fibrosis is a chronic and potentially malignant condition characterized by juxtaepithelial fibrosis of the oral mucosa. In this patology, the reported rate of malignant transformation was 7.6%. [80-82]

II.5.2. Chronic hyperplastic candidosis. Candida can produce carcinogenic compounds such as nitrosamines or N-nitrosobenzylmethylamine. [83-85]

II.5.3. Sideropenic dysphagia (Plummer Vinson Syndrome) is a premalignant condition, in which the patient presents with the classic triad: iron deficiency anemia, dysphagia, and possibly a post-cricoid esophageal web that may predispose to malignant changes [86-88]

II.5.4. Oral lichen planus. The prevalence of oral lichen planus varies from 0.5% to 2% [89,90] Clinically, oral lichen planus can be classified into six types: papular, reticular, plaque, atrophic, erosive, and bullous. [91] The rate of malignant transformation has been reported as 0% to 10%, and the increased risk of malignant transformation occurs in erosive forms and in cases of localized lesions on the tongue. [94]

II.6. Premalignant lesions.

II.6.1. Leukoplakia. It is defined as "a white plaque that cannot be removed by wiping and that cannot be classified into any other well-defined type of lesion." It is a relatively rare disease with an estimated prevalence of about 2.6%. [95] Oral leukoplakia can be divided into two subtypes: homogeneous and non-homogeneous. Verrucous leukoplakia is another type of non-homogeneous leukoplakia, with an unpredictable evolution, which can quickly transform into verrucous carcinoma. [96,97]

II.7. Oral cancer symptoms.

Carcinomas in the early stages pass, usually unnoticed, because they are asymptomatic. Pain is a common symptom of patients with oral cancer, representing 30-40% of the main complaints. [99] Other symptoms include ear pain, bleeding, tooth mobility, breathing problems, difficulty speaking, dysphagia or problems with wearing prostheses, onset of trismus, and paresthesia. [100,101]

II.8. Anatomo-clinical early types of oral cancer.

Initially, oral cancer manifests as well-defined erythroleukoplastic areas, the essential characteristic of these lesions being induration. Early lesions of oral cancer are usually non-ulcerated, although over time, one or more ulcerated areas with irregular, prominent, and gradually deepening margins appear in the erythroleukoplastic plaques. [49,102]

II.9. Anatomo-clinical types of oral cancer

II.9.1. Penetrant ulcer. The ulceration has an irregular floor and borders, prominent and induration. The bottom of the ulceration shows fleshy buds, the appearance being dirty, covered by fibrino-leukocyte deposits. [102,103]

II.9.2. Exophytic ulcer. The lesion develops on an ulcerative background, having a conopidiform appearance, with raised edges. [103]

II.9.3. Less frequent types. Oral cancer can manifest as paresthesia or numbness of the chin. In some cases, delayed post-extraction healing is noted, and sometimes, it manifests as dysphagia or weight loss. These advanced cases can be associated with metastases in the neck, detected as enlargement of the cervical lymph nodes, especially if the fixation or induration of the lymph node is perceived on palpation. [101]

II.10. Diagnosis of oral cancer.

To confirm the diagnosis of oral cancer, biopsy (incisional or excisional) and anatomopathological examination are mandatory. Imaging tests commonly used in the evaluation of oral cancer are: CT, MRI, ultrasound and positron emission tomography (PET-CT). [104]

II.12. Therapeutic management of oral cancer

Treatment approaches for oral squamous cell cancer include surgery, radiation therapy, and chemotherapy. These therapeutic options represent alternatives with major repercussions on the quality of life. [108,109] Unfortunately, most cases of oral cancer are

diagnosed in advanced stages (III or IV), with a 5-year survival rate of less than 50% and a cure rate of 30%. [110,111]

III. ORAL CANCER SCREENING

Screening has been defined as the application of a test or tests to persons who are apparently free of a disease in order to separate those who probably have the disease from those who probably do not. [112]

III.1. Conventional oral examination.

A number of publications have suggested that conventional oral examination may be of limited as a method for detecting precancerous or early cancerous lesions [113]; others have reported a relatively high degree of sensitivity, specificity, and positive predictive value of the conventional oral examination. A meta-analysis of these data showed a weighted cumulative sensitivity of 0.848 and a specificity of 0.965, indicating satisfactory performance of the conventional oral examination method. [116]

III.2. Oral brush cytology.

This test was specifically designed to investigate mucosal abnormalities that would otherwise not be biopsied due to low-risk clinical features. [119] The main advantages of the technique are attributed to the fact that it is a simple, well tolerated, minimally invasive and relatively painless diagnostic technique for harvesting representative cells of the oral mucosal layers. [121,122]

III.3. Vital staining.

Toluidine blue is a vital dye that stains nucleic acids. Vital toluidine blue staining is used successfully in combination with chemiluminescence or other tools in the process of diagnosing precancer and oral cancer. [124]

III.4. Lugol's solution, Lugol's iodine.

The diagnostic value of Lugol's iodine has been described as limited due to a high degree of non-specific staining. [125]

III.5. Confocal reflectance microscopy.

Confocal reflectance microscopy provides high-resolution in vivo imaging at the cellular level using focused laser illumination and detecting light reflected to vital structures with different refractive indices. [127] The indication for the use of this technique is related to the diagnosis of basal cell carcinoma when the suspicion is particularly high, this being performed instead of a biopsy. [128]

III.6. Chemiluminescence.

In chemiluminescence, energy is produced by a chemical reaction, usually between hydrogen peroxide (H2O2) and a high-energy compound. [130] ViziLite® (Zila

Pharmaceuticals, Phoenix, AZ) was approved as an adjuvant technology by the FDA in November 2002. Some studies suggest that the chemiluminescence-based technique may help identify occult lesions that cannot be detected under incandescent light. [140]

III.7. Imaging using porphyrins.

Administration of excess exogenous 5-ALA can increase PpIX production and its accumulation in highly proliferating tumor cells. 5-ALA/PpIX has been used for both photodynamic detection and tumor therapy. [141]

III.8. Delay in oral cancer diagnosis

Conceptually, the delay in oral cancer diagnosis represents the time interval from the first symptom or sign, to the the establishment of the definitive diagnosis. There are potential factors responsible for late diagnosis of oral cancer. [146]

IV. AUTOFLUORESCENCE IN ORAL CANCER SCREENING

IV.1. Brief history.

In the late 1970s, it was discovered that autofluorescence (also called natural or endogenous fluorescence), which until then had only been regarded as a disturbing background signal in the detection of exogenous fluorescence, could also be used for cancer detection. [154]

IV.2. Tissue autofluorescence – biological principles.

Hyperkeratosis, hyperchromatin, or increased concentration of adenine dinucleotide can alter the autofluorescence emitted by the tissue. [155] Lane [164] attributes the loss of autofluorescence signal in images of precancerous and cancerous oral lesions primarily to collagen matrix degradation and increased hemoglobin uptake and secondarily to epithelial factors such as increased epithelial scattering and thickness.

IV.3. Use of autofluorescence in oral cancer screening.

Autofluorescence can improve the ability to distinguish normal mucosa from neoplastic tissue due to the emission of the fluorescence signal in tissues at different wavelengths without additional fluorescent agents. [165] The endogenous fluorophores most relevant for optical screening and diagnosis of precancer and cancer are those that excite in the spectrum from visible violet/blue (400–450 nm) to UV-A (315–400 nm) and have properties that have been spectroscopically correlated with the rate of disease progression. [170]

THE SPECIAL PART
PERSONAL CONTRIBUTION

VI. OBJECTIVES OF THE STUDY

The personal research aims id to evaluate the value of light-based tissue imaging techniques in oral and maxillofacial cancer screening. Starting from this goal, during the progress of the study we pursued the fulfillment of the following main objectives:

VI.1. Main objectives of the study

- Establishing the correlation between risk factors and the occurrence of pathological lesions of the oral mucosa in a group of patients from the Dobrogea area.
- Evaluation of the prevalence of premalignant, malignant and malignant oral lesions in a group of patients from the Dobrogea area, using the screening method based on clinical examination by inspection under conventional light (white light from the dental unit) and palpation.
- Evaluating the effectiveness of fluorescence tissue using the OraIID™ visualization device in oral cancer screening, by determining the sensitivity and specificity of identifying premalignant and malignant lesions in dental practice.
- Quantification of the descriptive parameters of premalignant, malignant and malignant oral lesions identified by the two examination methods, as predictive factors in oral cancer screening.

VII. MATERIAL AND METHOD

As part of my doctoral research, I conducted a prospective cross-sectional clinical-statistical study. The study was attended by 219 patients who presented themselves in the years 2016-2020 in the Oral Pathology clinic of the Faculty of Dental Medicine Constanța and in the Department of Oral and Maxillofacial Surgery in the "Sf. Ap. Andrei" from Constanța for control and specialized treatment. The study has the approval of the Bioethics Commission of the "Ovidius" University of Constanța, and all patients included in the batch signed an informed consent in this regard.

219 participants were enrolled in the study.

The inclusion criteria were related to:

→ patients over the age of 18,

→ patients who have expressed their consent to participate in the study,

→ patients patients who complained of symptoms / presence of lesions in the oral cavity.

The exclusion criteria were related to:

→ patients under the age of 18,

→ pregnant/breastfeeding patients,

→ patients with mental disorders, incapable of good cooperation,

→ patients previously diagnosed with oral cancer for which they also received specific therapy.

The 219 patients who met the inclusion criteria underwent clinical examination with the aim of performing preventive oncological examination using conventional light from the dental unit. The patients underwent local treatment with a mouthwash based on antiseptic and antibiotic substances for 14 days, after which they presented for re-examination. Of the 219 participants, 78 were found to have suspicious injuries. Of the 78 patients, 6 did not attend all study examination sessions and were excused. The 72 participants were examined under conventional light and using the Oral ID device based on the autoflorescence of the oral mucosa. Subsequently, the biopsy of suspicious lesions was performed in 65 cases, by the specialist in oral and maxillofacial surgery or dento-alveolar surgery.

OralID (Oral Cancer Screening) KIT – scanner for detecting cancerous lesions. The light emitted by the OralID device has a wavelength in the range of 425-460 nm. Under this light, the normal oral mucosa emits green autofluorescence, while the abnormal mucosa absorbs the fluorescent light, taking on a dark appearance.

In each patient, we performed the fluorescence map for the following locations: cheek, tongue - lateral border, dorsal and ventral side, oral floor, upper and lower vestibule, gum, inner mucosal part of the lips, red border of the lip, soft palate and hard palate. Each location was two times measured with an integration time of 1 second. Tissue fluorescence photographs, using Oral ID, were taken by a digital camera with a resolution of 48 mega pixels, with a single lens covered by a long-pass filter included in the device kit.

The experimental data were processed using the statistical processing program IBM SPSS Statistics 23 and Microsoft Office Excel 2007.

VIII. RESULTS

VIII.1 Results of analyzing the entire study group.
Study group characteristics

The study group included 72 patients, 62.50% male and 37.50% female, aged between 30 and 83 years, the average age being 58.39 years . The male : female ratio in this study is 1 : 0.66.

48% of the study participants come from urban areas. The results of this study are confirmed in the specialized literature. [190]

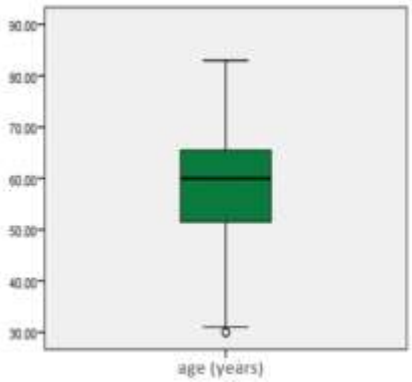

Figure 8. Histogram by age

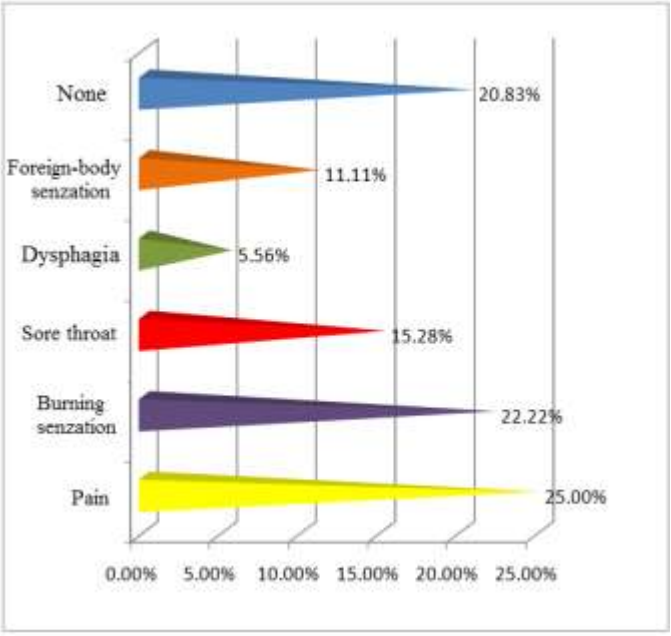

Figure 10. Symptoms distribution

To quantify and analyze the symptoms variable, the dominant symptom was considered for each subject in the study. The most frequent reported symptoms were represented by pain 25% and burning sensation in the oral cavity – 22.22%. Noteworthy is the fact that in 20.83% of cases, the study participants did not report any symptoms. In some of them, the oral lesions were detected by chance, as a result of the patient's presentation to the dental office for the therapy of other oro-dental conditions.

For each subject, were analyzed comorbidities, other than oncological ones, extracted from the anamnesis. For effective quantification, comorbidities were divided into 5 categories, whose distribution is shown in figure 13.

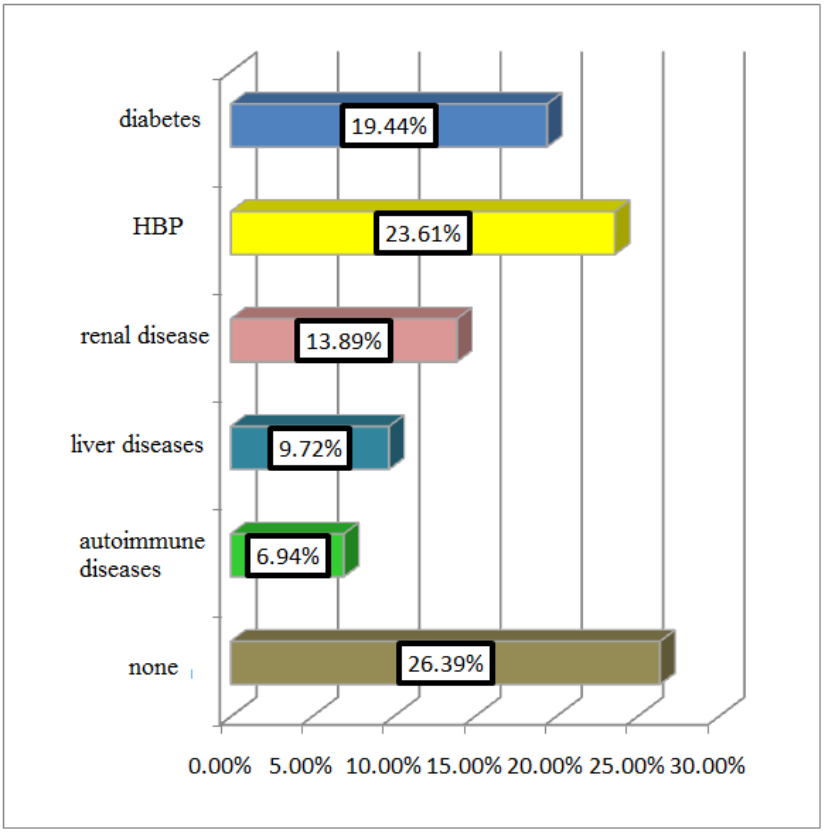

Figure 13. Comorbidities distribution

Autoimmune diseases were represented by: chronic autoimmune thyroiditis – 3 cases and dermatological lichen planus – 2 cases. All patients included in the study were monitored by the specialist, depending on the associated systemic condition. 61.11% of study participants were receiving therapy for associated conditions at the time of examination.

		Frequency	Percent
Valid	Indented tooth edges	21	29.17
	Microirritations secondary to dental fillings	10	13.89
	Incorrectly fitted dentures	16	22.22
	None	25	34.72
	Total	72	100.00

Table VIII.4. Frequency table of dental irritants

Regarding the exposure to the main risk factors of oral cancer, excluding smoking, the following results were obtained: 69.44% (50 cases) of the subjects denied prolonged exposure to the considered risk factors; 18.06% (13 cases) were exposed to UV radiation; 12.50% (9 cases) constantly consume alcohol.

Following the intraoral clinical examination, the presence of dental irritant factors was detected in 65.28% of the patients.

Most of the patients - 34.72% reported functional disorders related, in particular, to the disturbance of mastication and swallowing. At a significant percentage - 29.17%, no associated signs were recorded.

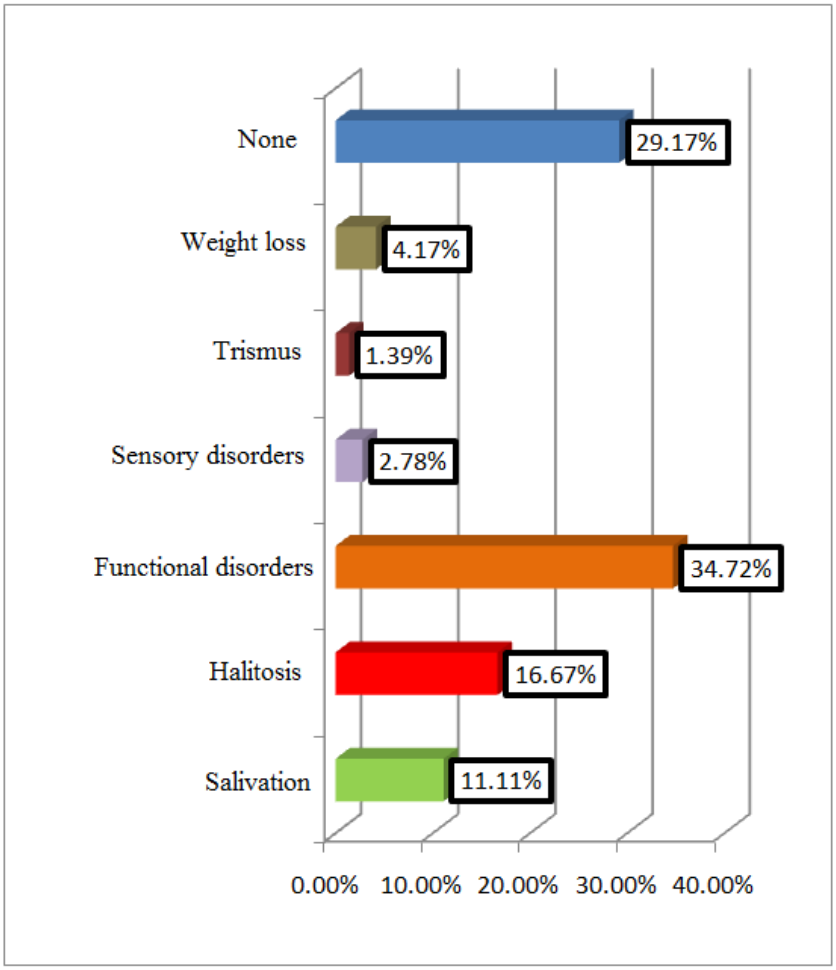

Figure 17. Associated signs distribution

Regarding the oral lesion type identified by the clinical examination, the percentage distribution revealed the following: the highest percentage - 16.67% was represented by the lesions having the clinical appearance of a tumor with associated signs of malignancy, followed in 15, 28% of cases of lesions with the appearance of leukoplakia and the same percentage of

those with the appearance of exophytic ulcer tumors. 13.89% are represented by ulcers, 12.50% are penetrant ulcer tumors, 11.11% are represented by papillomatous tumors, in 6.94% oral lichen planus was detected, and in the same proportion of 4.17% chronic hyperplastic candidiasis and oral submucosal fibrosis were clinically detected.

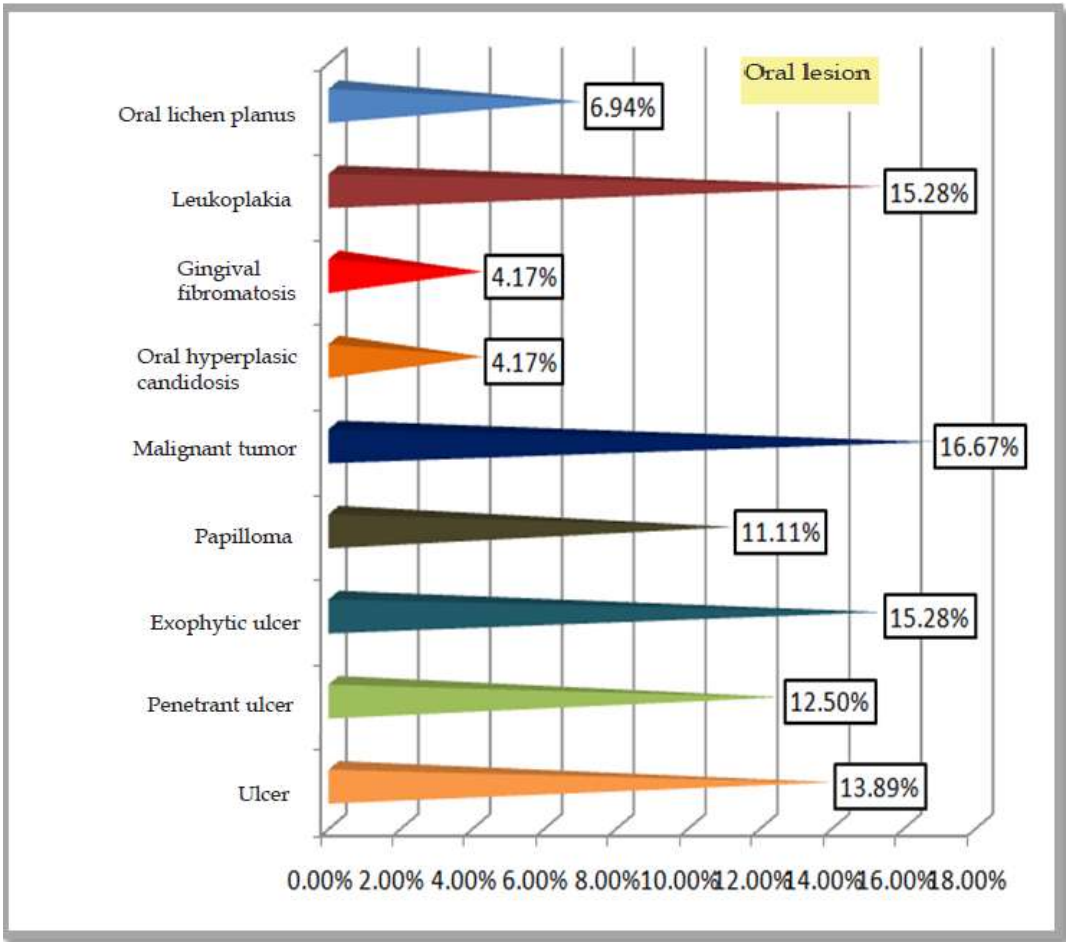

Figure 18. Clinical type of oral lesion distribution

The association between the lesion variable and the location variable revealed the following:

- on the tongue and cheek, the most frequent lesion reported is the clinical form of ulceration - 5.6%, respectively 8.3%.
- on the oral floor, the most frequent lesion reported is the clinical form of tumor with associated signs of malignancy - 5.6%,
- on the alveolar ridge, the most frequent lesion reported is the clinical form of exophytic ulcer - 4.2%,
- more than half of the cases of oral lichen planus have multiple locations.

			Localisation								Total
			Tongue	Cheek	Oral floor	Palate	Alveolar ridge	Lower lip	Upper lip	Multi-ple	
Lesion	Ulcer	Count	4	2	1	0	1	1	1	0	10
		% of Total	5.6%	2.8%	1.4%	0.0 %	1.4%	1.4%	1.4%	0.0 %	13.9 %
	Penetrant ulcer	Count	1	2	2	0	1	3	0	0	9
		% of Total	1.4%	2.8%	2.8%	0.0 %	1.4%	4.2%	0.0%	0.0 %	12.5 %
	Exophytic ulcer	Count	3	1	1	1	3	1	0	1	11
		% of Total	4.2%	1.4%	1.4%	1.4 %	4.2%	1.4%	0.0%	1.4 %	15.3 %
	Papilloma	Count	3	2	0	2	1	0	0	0	8
		% of Total	4.2%	2.8%	0.0%	2.8 %	1.4%	0.0%	0.0%	0.0 %	11.1 %
	Malignant tumor	Count	3	2	4	0	1	0	1	1	12
		% of Total	4.2%	2.8%	5.6%	0.0 %	1.4%	0.0%	1.4%	1.4 %	16.7 %
	Oral hyperplasic candidosis	Count	0	0	0	0	0	0	0	3	3
		% of Total	0.0%	0.0%	0.0%	0.0 %	0.0%	0.0%	0.0%	4.2 %	4.2 %
	Gingival fibromatosis	Count	0	0	0	1	1	0	0	1	3
		% of Total	0.0%	0.0%	0.0%	1.4 %	1.4%	0.0%	0.0%	1.4 %	4.2 %
	Leukoplakia	Count	1	6	0	0	0	1	0	3	11
		% of Total	1.4%	8.3%	0.0%	0.0 %	0.0%	1.4%	0.0%	4.2 %	15.3 %
	Oral lichen planus	Count	0	1	0	1	0	0	0	3	5
		% of Total	0.0%	1.4%	0.0%	1.4 %	0.0%	0.0%	0.0%	4.2 %	6.9 %
Total		Count	15	16	8	5	8	6	2	12	72
		% of Total	20.8 %	22.2 %	11.1 %	6.9 %	11.1 %	8.3%	2.8%	16.7 %	100. 0%

Table VIII.8. Crosstabulation test results to establish the association between the lesion and the location variable

The oral lesions detected following the examination by the two methods used in the study were classified, after the histopathological examination, into three categories, with the following distribution: premalignant lesions – 33.33%; malignant lesions – 48.61% (35 cases); other types of injuries – 18.06%.

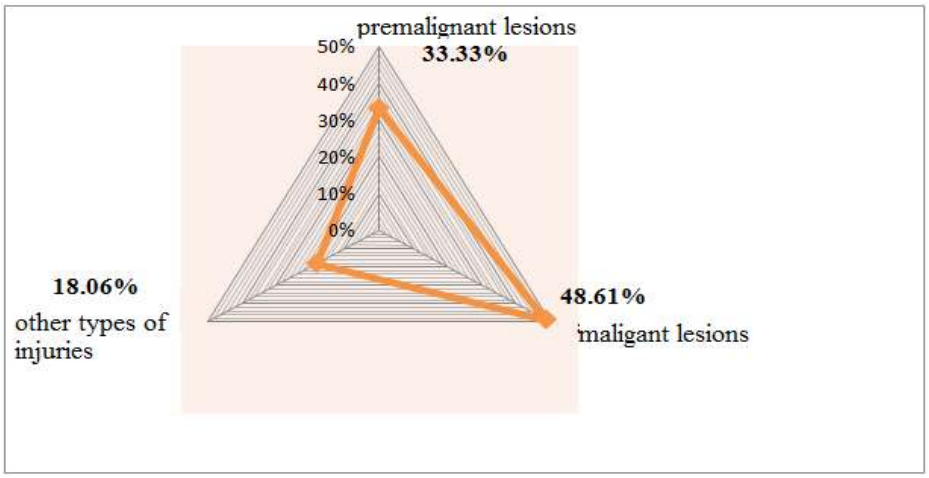

Figure 22. Type of oral lesion distribution

VIII.2 The results of the comparative analysis of oral lesions localization and characteristics in the male subgroup versus the female subgroup

The group of patients was divided into two subgroups (the male subgroup and the female subgroup), in order to identify the differences between the sexes regarding of the location and characteristics of the oral lesions detected by the two examination methods.

Male patients were: aged between 31-83 years, with a mean of 58.91 years and a standard deviation of 9.99 years. Female patients were: aged between 30-80 years, with a mean value of 57.52 years and a standard deviation of 14.25 years. The standard error of the mean was 1.49 points for the male subgroup and 2.74 points for the female subgroup. The results show that there are no significant differences between the two subgroups of patients regarding the maximum and minimum age distribution or the average age, the age of the patients in the two subgroups being similarly distributed.

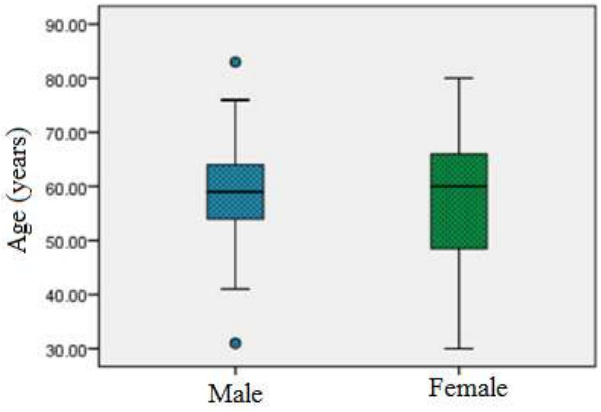

Figure 25. Age histogram of subgroups

I have analyzed the exposure to smoking, which is considered the main risk factor of oral cancer. Almost half of the patients – 47.22% are active smokers and 20.83% are former smokers. Most of the active smoking patients are male, they also represent the most cases of subjects consuming alcohol, but also the most cases of constant exposure to UV radiation, as a result of professional outdoors activities.

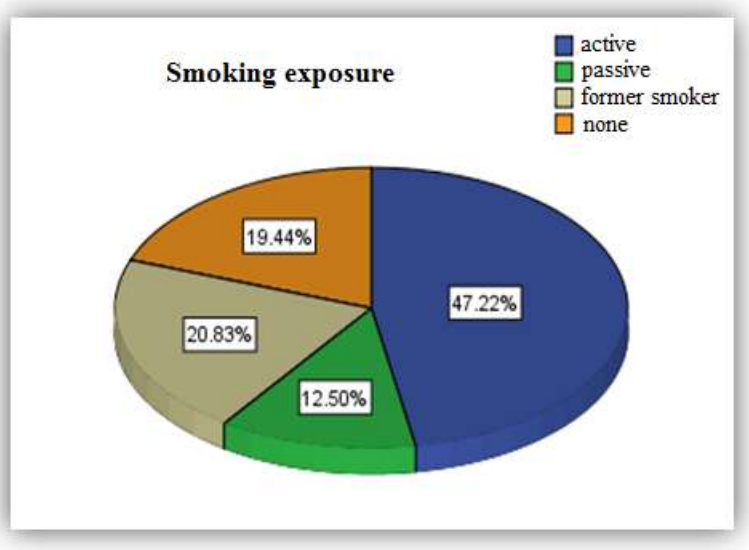

Figure 26. Smoking status distribution

The application of the Crosstabulation test, has determined the distribution of clinical types of the pathological oral lesions detected by clinical examination on subgroups. The results of the comparative analysis of the lesion types highlighted certain significant differences between the two subgroups, such as:

- → penetrant ulcer form and exophytic ulcer form are frequently reported in males (88.9% and 72.7%, respectively);
- → out of 11 cases of leukoplakia, 9 cases were reported in men;
- → chronic hyperplastic candidiasis was detected exclusively in men;
- → oral lichen planus was detected exclusively in women.

In the case of clinical type of tumor associated with malignancy signs, the male to female ratio is 1:0.5.

Regarding the location of the oral lesions detected in the oral cavity, from the comparative analysis on the subgroups we noted the following:

- → on the upper lip, oral lesions were detected exclusively in men;
- → on the oral floor and the lower lip, pathological oral lesions were more frequent in male patients;

→ on the tongue, cheek, palate or in the case of multiple localizations, no significant differences were recorded regarding the reported frequency, in the two subgroups, if the male : female ratio included in the study is taken into account.

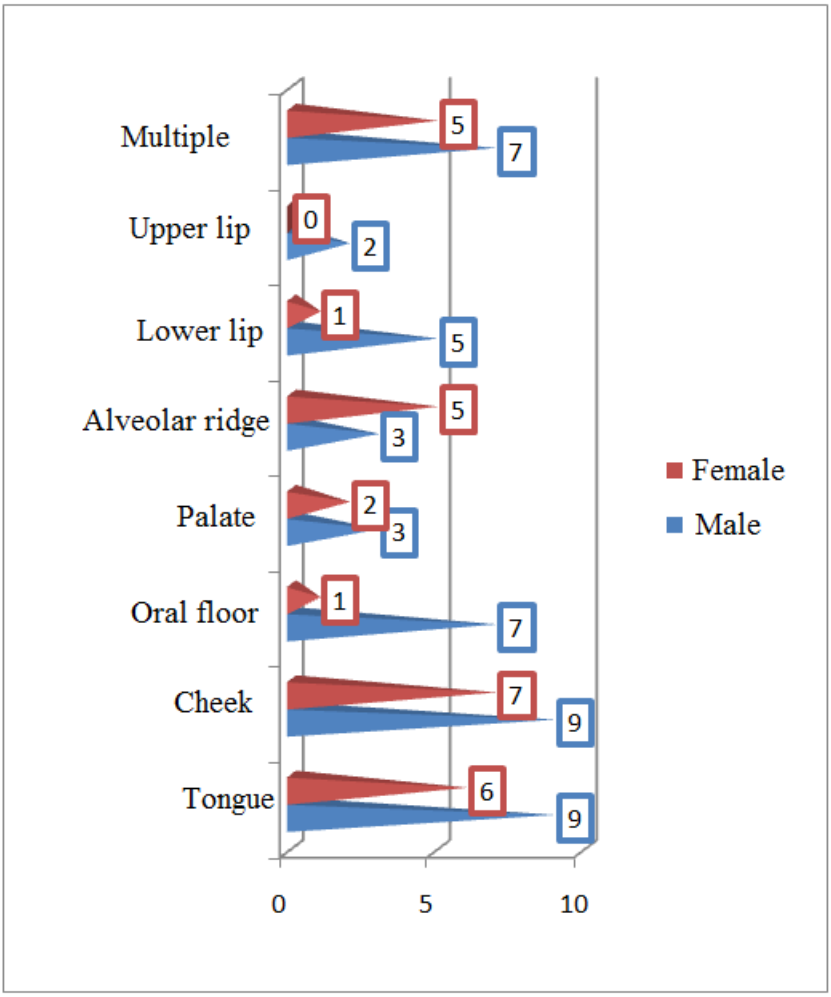

Figure 27. Oral lesion localization frequency by gender

I have analyzed the size of pathological oral lesions identified by inspection under conventional light. Male patients had: lesions ranging in size from 5-38 mm; the average value of the size of the lesions of 18.11 mm; standard deviation of lesion size 8.45 mm. Female patients had: lesions with dimensions between 4-46 mm; mean value of lesion size of 17.37 mm; standard deviation of 10.05 mm.

The median value is 15 mm for both sublots. The results show that there are no significant differences between the two subgroups of patients regarding the size distribution of pathological oral lesions. When examination of oral lesions was performed using the device based on oral mucosal autofluorescence, the size of oral lesions in male patients was between 0-40 mm, recording the same values in the subgroup represented by female patients.

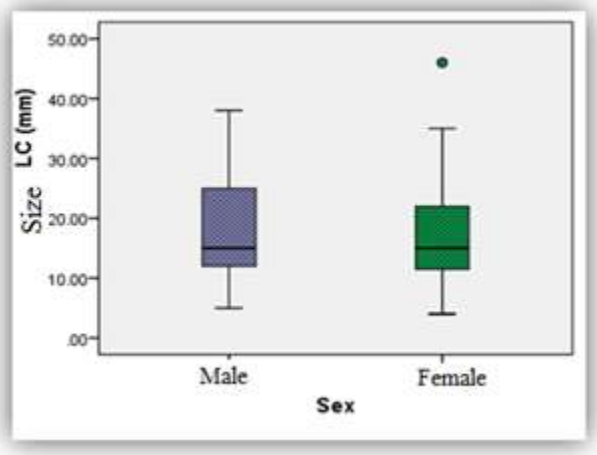

Figure 28. Size distribution histogram of oral lesion detected by inspection under conventional light by sex

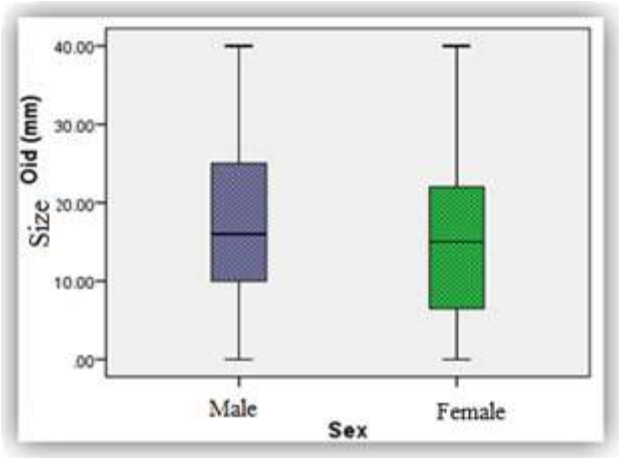

Figure 29. Size distribution histogram of oral lesion detected using the visualization technique based on the auofluorescence of the oral mucosa by sex

VIII.3 Results of the concordance testing between the method of examining the oral mucosa by inspection under conventional light and the examination method using the device based on the autofluorescence of the oral mucosa

The concordance between the two examination methods was studied for the following sites: tongue, cheek, oral floor, palate, alveolar ridge, lower lip and upper lip.

The concordance between the two examination methods regarding the outline and size of the examined lesions was also tested using specific statistical tests.

Of the 26 lesions identified by conventional light inspection on the tongue, 5 lesions were not detected by using the OralId device, however, the use of this device allowed the identification of 3 lesions that were not visible at conventional light inspection.

		Value	Asymptotic Standardized Error	Approximate T	Approximate Significance
Measure of Agreement	Kappa	(K) 0.755	.081	6.419	(p) 0.000
N of Valid Cases		72			

Tabelul VIII.43. Kappa concordance test results between the two examination methods in the identification of tongue lesions

For the tongue localization of the lesions, the observed concordance is 89.9%, and the concordance coefficient is K = 0.755.

The concordance testing between the two examination methods for the cheek localization had a value of 84.7%, and the concordance coefficient was K = 0.627.

The concordance between the two examination methods calculated for oral floor localization is 97.3%, and the concordance coefficient is K = 0.911. For palate localization, concordance tested between the two examination methods by which the lesions were detected had a value of 100%, and the value of the concordance coefficient was K = 1.000, which signifies the existence of a total concordance between the two evaluated methods.

		Value	Asymptotic Standardized Error	Approximate T	Approximate Significance
Measure of Agreement	Kappa	1.000	.000	8.485	.000
N of Valid Cases		72			

Tabelul VIII.49. Kappa concordance test results between the two examination methods in the identification of palate lesions

Testing the concordance between the two examination methods by which the alveolar ridge lesions were detected had a value of 100%, and the concordance coefficient was K = 1.000, which signifies the existence of a total concordance between the two evaluated methods.

The concordance value between the two examination methods for the lower lip localization was 97.2%, and the concordance coefficient was K = 0.819.

		Value	Asymptotic Standardized Error	Approximate T	Approximate Significance
Measure of Agreement	Kappa	.819	.124	7.064	.000
N of Valid Cases		72			

Tabelul VIII.53. Kappa concordance test results between the two examination methods in the identification of lower lip lesions

		Value	Asymptotic Standardized Error	Approximate T	Approximate Significance
Measure of Agreement	Kappa	.793	.201	6.879	.000
N of Valid Cases		72			

Tabelul VIII.55. Kappa concordance test results between the two examination methods in the identification of upper lip lesions

Testing the concordance between the two examination methods in assessing the outline of the lesions has a value of 98.6%, and the concordance coefficient is K = 0.970. The value $p < \alpha = 0.05$, the calculated value of K is considered to be statistically significant, and the intensity of agreement between the two evaluated methods is considered very good.

		Value	Asymptotic Standardized Error	Approximate T	Approximate Significance
Measure of Agreement	Kappa	.970	.030	8.232	.000
N of Valid Cases		72			

Tabelul VIII.57. Kappa concordance test results between the two examination methods in assessing the outline of the lesions

XI. CONCLUSIONS

- Pathological oral lesions at risk of malignancy are more common in males than in females, the ratio being 1:0.66.
- The average age of the study participants represented by the value of 58.39 years and the standard deviation with the value of 11.69, falls within what is reported in the specialized literature as the age category at risk for the development of oral cancer.
- The main symptom that the patients described at the time of the examination is oral pain (25%) and burning sensation of the oral cavity (22.22%).
- Although there is a strong positive association between alcohol consumption and the risk of developing oral cancer, we did not find a correlation between them.
- More than half of the patients diagnosed with oral lesions have poor oral hygiene, with plaque deposits present over half of the coronal surface.
- There is a statistically significant dependent relationship between the clinical form of the premalignant or malignant lesion and preexisting oral infections.
- Most of the patients - 34.72% reported functional disorders related, in particular, to the disturbance of mastication and swallowing. No signs were recorded at a significant percentage - 29.17%.
- Regarding the type of oral lesion identified by the clinical examination, the percentage distribution revealed the following: the highest percentage - 16.67% was represented by the lesions having the clinical appearance of a tumor with associated signs of malignancy.
- 33.33% of the subjects could not specify the onset of the oral lesion, and 30.56% reported a period greater than 2 weeks. The obtained results are confirmed by the specialized literature.
- The most frequent localization of detected oral lesions was recorded on the cheek (22.22%), followed by the tongue (20.83%). The rarest localization was recorded on the upper lip - 2.78%.
- Almost half of the patients – 47.22% are active smokers and 20.83% are ex-smokers. Most of the active smoking patients are male, they also represent the most cases of subjects consuming alcohol, but also the most cases of constant exposure to UV radiation, as a result of professional activities carried outdoors.
- The penetrant ulcer form and the exophytic ulcerform are frequently reported in males (88.9%, respectively 72.7% of the total number of cases registered for each individual clinical lesion).

- Most cases of leukoplakia have been reported in men. Chronic hyperplasic candidosis was detected exclusively in men. Oral lichen planus was detected exclusively in women.
- There is no statistically significant difference between the sexes regarding the tongue location of the pathological lesions. Regarding the cheek location, the most numerous lesions were reported, using both examination methods, in the females.
- On the oral floor localization, 4 times more pathological oral lesions were recorded in men than in women. On palate localization, the frequency ratio of oral lesions in males: oral lesions in females is 2:1, regardless of the examination method used. The lesions detected on the alveolar ridge are more numerous in the females.
- Regarding the size of detected oral lesions, when using the conventional light examination method from the dental unit, the average was 18.11 mm for males and 17.37 mm for females. When the examination method was represented by the visualization technique based on autofuorescence of the oral mucosa, the average was 16.76 mm for the male sex and 16 mm for the female sex. There is no statistically significant difference between the two sexes in terms of the size of the reported lesions.
- The use of the visualization method based on the autoflorescence of the oral mucosa improved the detection of the contour of the examined lesion, so using this technique, 25 lesions with regular contour and 47 oral lesions with irregular contour were reported.
- The concordance between the conventional light examination method and the examination method using the device based on the fluorescence of the oral mucosa was 88.9% with a Kappa coefficient of 0.755 for the tongue localization, 84.7% with a Kappa coefficient with the value 0.627 for the cheek localization, 97.3% with a Kappa coefficient with the value 0.911 for the oral floor localization, 100% with a Kappa coefficient with the value 1 for the palate and alveolar ridge localization, 97.2% with a coefficient Kappa with a value of 0.819 for the lower lip location, 98.6% with a Kappa coefficient with the value of 0.793 for the upper lip location.
- The average concordance between the two examination techniques is 95.24% with a Kappa coefficient with an average value equal to 0.84.

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