BRAIN. Broad Research in Artificial Intelligence and Neuroscience
e-ISSN: 2067-3957 | p-ISSN: 2068-0473
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2025, Volume 16, Issue 1, pages: 205-215.
Submitted: November 14th, 2024 | *Accepted for publication:* January 16th, 2025

The Progressive Integration of AI Software in the Histopathological Diagnosis of Oral Cancers

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Abstract: *As in any other field, medicine is advancing and striving to adapt to increasingly complex demands, aiming to find rapid solutions in establishing certain diagnoses that can save or significantly improve the patient's quality of life. The integration of AI systems in the medical field is vital and requires openness, as well as a continuous desire for learning and improvement. Although the use of artificial intelligence in the medical field in Romania has not yet reached widespread development, there are still some AI software and applications that prove their effectiveness and ease the work of medical specialists. Oral cancer is one of the most common forms of malignant or premalignant lesions globally, with a high prevalence. Although developed countries are less affected compared to developing ones, they are also seeing an increasing incidence of cancers in the oro-maxillofacial region. The etiology of oral cancer is complex, influenced by both genetic and epigenetic factors. Currently, research is increasingly focused on epigenetic factors, including smoking, chronic alcoholism, diet, and improper use of mouthwash. These behaviours are associated with significant risks for the development of oral cancer, highlighting the importance of awareness and prevention within the global population. In Romania, factors such as low dental visit frequency, poor infrastructure, and lack of education contribute to disease prevalence. According to GLOBOCAN data, oral cancer in Romania ranks second in incidence, after leukemia, with a rate of 5.6 per 100,000 individuals. The purpose of our study is to highlight the importance of histopathological examination in establishing a definitive diagnosis, as well as the significance of AI software used in storing and processing the data obtained in the laboratory.*

Keywords: *oral cancer; GLOBOCAN; histopathology diagnosis; oral cancer screening; epigenetic factors.*

How to cite: Cumpătă, C.N., Liliac, I.M., Buşu, O.V., Predescu, A.M., Iacov, C.A., Popescu, A.D., Andrei, E.C., Busuioc, C.J., & Munteanu, C.M. (2025). The progressive integration of AI software in the histopathological diagnosis of oral cancers. *BRAIN. Broad Research in Artificial Intelligence and Neuroscience*, *16*(1), 205-215. https://doi.org/10.70594/brain/16.1/15

1. Introduction

Oral cancer tends to occupy a leading position in terms of the prevalence of malignant lesions or those with the potential to become malignant globally (Montero & Patel, 2015). Although the most affected countries are those that are underdeveloped or developing, it is notable that even developed nations are facing an increased incidence of cancers in the oro-maxillofacial region (Montero & Patel, 2015; Siegel, Naishadham, & Jemal, 2013).

The etiology of oral cancer is divided into genetic and epigenetic factors (Kumar et al., 2016). Current trends are increasingly focusing on epigenetic factors, which include: smoking (Kumar et al., 2016; Gupta et al., 1995; Rodríguez-Molinero et al., 2021; Gupta et al., 2022), chronic alcoholism (Barsouk et al., 2023), diet (Munteanu et al., 2024; Rodríguez-Molinero et al., 2021; Jané-Salas et al., 2003), and improper use of mouthwash (Kumar et al., 2016; Ustrell-Borràs, Traboulsi-Garet, & Gay-Escoda, 2020).

2. Epidemiology

We accessed the Global Cancer Observatory online platform to collect statistical data on the incidence, mortality, and morbidity associated with oral cancer globally and regionally. The most recent data provided by the *GLOBOCAN* platform pertains to 2022.

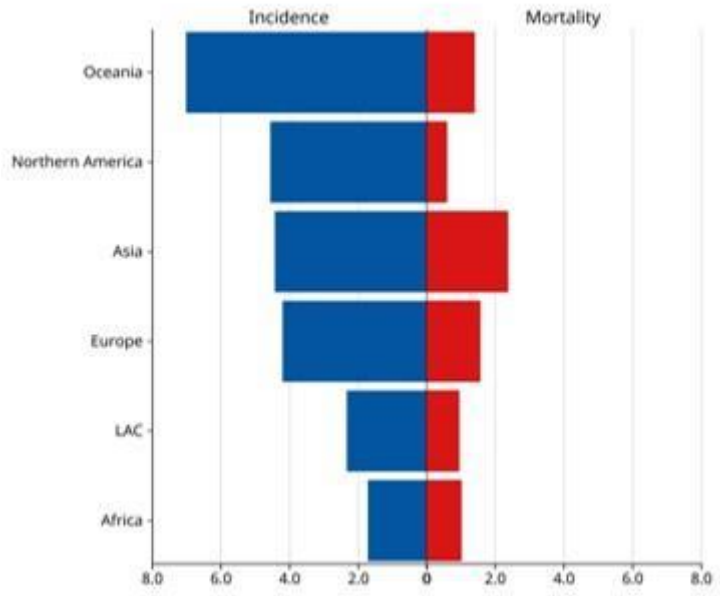

Figure 1. Statistical Data on the Incidence and Mortality Induced by Oral Cancer According to Global Population. Source: From GLOBOCAN 2022, International Agency for Research on Cancer (https://gco.iarc.fr/en).

Based on the data provided, it is observed that the European population ranks fourth in terms of oral cancer incidence, but faces a concerning mortality rate, which is higher than that of Oceania, which ranks first in terms of incidence. A possible factor contributing to this elevated mortality rate is the lack of medical consultation in the early stages, patients' inadequate attitudes towards their health, or, in some cases, the absence of infrastructure in underdeveloped countries that would allow patients access to healthcare services (Worsham, 2011).

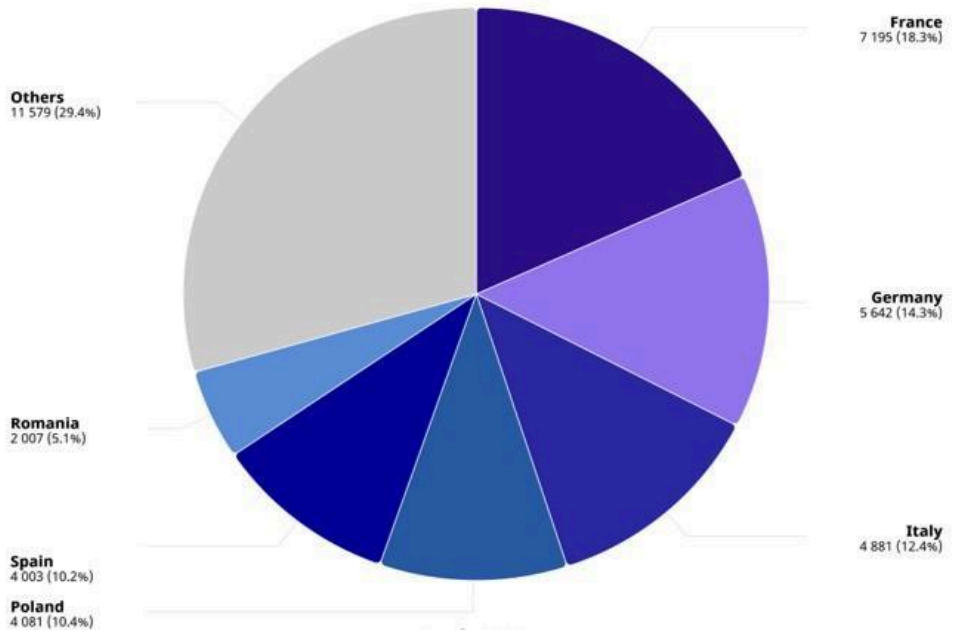

Figure 2. Incidence of Oral Cancer in Europe.
Source: From GLOBOCAN 2022, International Agency for Research on Cancer (https://gco.iarc.fr/en)

The data shows that Romania is among the most affected countries by oral cancer in Europe. However, Romania's incidence rate is much lower compared to other socioeconomically and healthcare-developed countries. A possible cause for the increased incidence in developed European countries is the financial power that allows the purchase of tobacco and alcohol products which significantly increase the risk of developing oral cancer (Montero & Patel, 2015; Siegel, Naishadham, & Jemal, 2013). In developing countries like Romania, the causes may include the low frequency of dental visits due to lack of infrastructure, social status, or inadequate education (Maier et al., 1993). Additionally, statistical data provided by GLOBOCAN shows that in Romania, oral cancer (with a rate of 5.6 per 100,000 individuals) follows leukemia (with a rate of 6.1 per 100,000 individuals) in terms of incidence, in both sexes.

3. The role of AI systems in the diagnosis of oral cancers

The role of the physician in traditional pathology should not be altered or minimised with the implementation of artificial intelligence systems but rather should be enhanced and leveraged to achieve the most accurate diagnoses and treatment plans, in a timely, rapid, and minimally invasive manner for the patient (Baxi et al., 2022). One of the most important roles of AI software in pathology is its ability to process tissue images obtained and processed after biopsy sampling. Some of the systems, the high-performance ones, offer the pathologists the opportunity to visualise colour or luminous signals that guide them in identifying pathogenic elements/structures (Lu et al., 2019; Baxi et al., 2022). Another major advantage is the pathologist’s possibility to analyse and interpret tissue and cellular data remotely (Baxi et al., 2022; Mroz, Parwani, & Kulesza, 2013). AI software used in the field of pathology is rigorous, and the quality of the expressed results depends greatly on how the tissue processing and slide mounting were performed. The biopsy must be cleaned of impurities, with no artifacts or air bubbles resulting from improper slide preparation (Pantanowitz et al., 2013; Baxi et al., 2022). Additionally, the pathologist's experience significantly influences the AI software's performance. The pathologist's role is to select samples with properly performed histological stains or immunohistochemical reactions, in accordance with protocols, to choose the appropriate microscope objective when capturing the image, and to select regions of interest (Baxi et al., 2022).

4. Types of AI Software Used in Oral Pathology

Image Pro AI for Life Science - it is a software frequently used in histopathology, featuring a simplistic approach with clear and easily accessible commands, but with limited options. It can analyse and visualise three-dimensional images with good resolution. It works on all types of cells and tissues, both on general and specific histological stains, as well as on immunohistochemical reactions. With this system, we can segment histological images to highlight regions of pathological interest, perform morphometric analysis of cellular/tissue structures, obtain accurate measurements, and improve the contrast, clarity, and brightness of captured histological images (Francisco, Pinto, & Dias, 2004; Pre-trained solutions make analysis easy Angiogenesis (Tube Formation) Cell Count (Label-Free) Cell Morphology Overlapping Nuclei (Florescence) Stained Tissues & Colonies, n.d.)

QuPath – an AI software for histology and pathology available in a free version, which comes with a wide range of tools to help researchers obtain clear, high-resolution microscopic images and perform cell identification through specific annotations (inflammatory cells, positive cells, negative cells), as well as tissue areas (stroma, necrosis area, tumor regions) (Humphries, Maxwell, & Salto-Tellez, 2021).

ImageJ – an AI software dedicated to microscopic images resulting from immunohistochemical reactions with various biological markers. It is also free and easily accessible, with numerous tools that can even perform multiple and complex statistical analyses (Schindelin et al., 2015).

5. Oral Cancer Screening

Screening is a non-invasive detection method for a potential pathology that may significantly impact the individual's quality of life, with the subject potentially being asymptomatic (Warnakulasuriya & Kerr, 2021). The criteria underlying screening were first outlined and detailed in 2003 by the UK National Screening Committee, with updates scheduled in 2015 and 2022 (UK National Screening Committee, 2003). The screening programmes in each country require a thorough understanding of the population at risk (in the case of oral cancer, this includes individuals in their third decade of life, smokers (Kumar et al., 2016), even e-cigarette users (Gallagher, Vargas, & Santos-Silva, 2024), chronic alcohol consumers (Kumar et al., 2016), immunosuppressed individuals (Kumar et al., 2016; Patini et al., 2023), those working in toxic environments or constantly exposed to radiation (Kumar et al., 2016; Cruz et al., 2000; Swanson & Belle, 1982), as well as the economic impact it will generate. Screening tests must also meet certain conditions: they must be easy to use, provide concrete and accurate results with a low rate of false positives or negatives, and be safe for the subject (UK National Screening Committee, 2003). Currently, the focus is not only on the clinical identification of oral lesions with malignant potential but also on the detection of HPV infection. The HPV virus, specifically HPV-16 and HPV-18, is largely responsible for the onset of head and neck cancer (Warnakulasuriya & Kerr, 2021; Andrei et al., 2022).

4. Materials and methods

Oral mucosa biopsies were collected from subjects who presented to the Oro-Maxillofacial Surgery Clinic of the Craiova Emergency Hospital between July 2024 and December 2024. Informed consent was obtained from each subject for the biopsy collection and for photographing the oral lesion. A medical history was recorded for each subject, and they were included in a database that included the following parameters: sex, age, place of origin, location of the oral lesion, duration of the lesion, and presumptive diagnosis.

The oral mucosa biopsies were washed with physiological saline to remove impurities and blood clots, and then placed in 10% formalin for 48 hours. Afterward, they were sent to the Histology and Immunohistochemistry Laboratory of the University of Medicine and Pharmacy in

Craiova for processing. In the laboratory, the biopsies were introduced into an automated tissue processor, embedded in paraffin, sectioned at 4 microns using a microtome, and standard hematoxylin-eosin histological staining was performed with kit 011802 - Bio-Optica, Italy.

The sections were analysed and photographed using a Nikon Eclipse 55i microscope equipped with a Digital Sight DS-L1 digital camera, and image processing was carried out using the Image ProPlus 7 Nikon software (Media Cybernetics Inc., Buckinghamshire, UK). The AI software we used for storing and processing histological images were Image Pro AI for Life Science (contrast enhancement, brightness adjustment, quality improvement by 25%) and QuPath (for cellular differentiation).

5. Results

5.1. Clinical aspect: oral squamous cell carcinoma

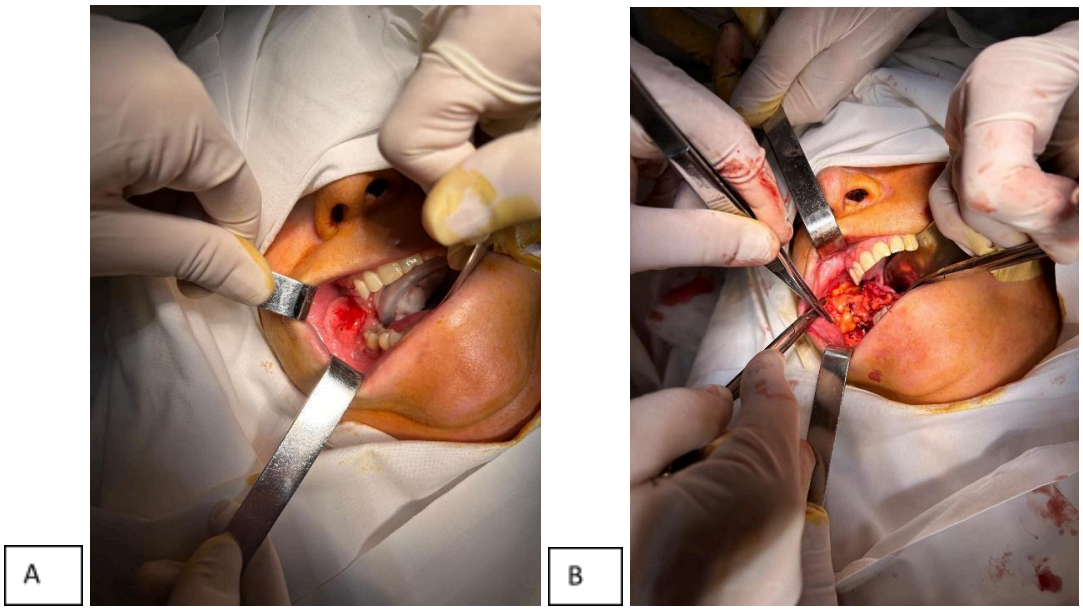

Figure 3. A – Clinical aspect of the lesion, located on the buccal mucosa, irregular shape, red color, highly vascularised epithelium, irregular borders, size 5cm; B – Intraoperative appearance of the tumoral lesion.

5.2. Histopathological aspects

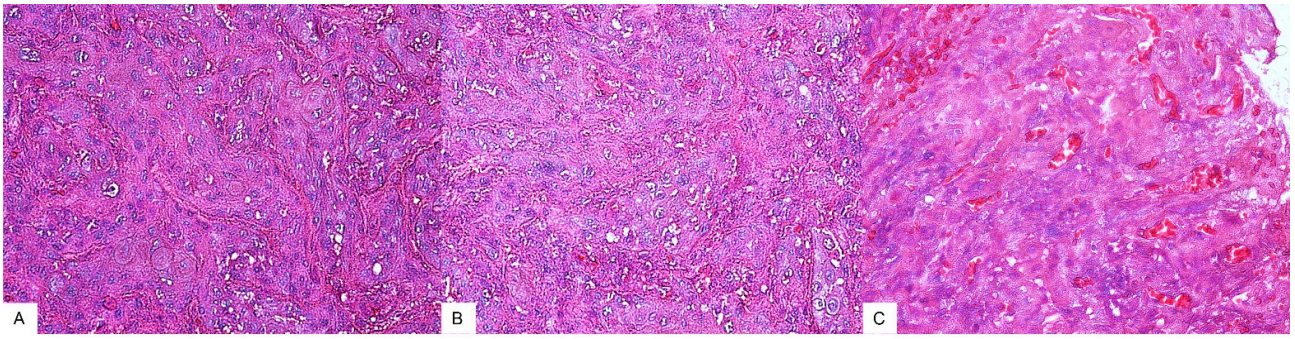

Figure 4. A - Presence of keratin pearls; B - Cellular islands; C - Presence of numerous neoformed vessels (hematoxylin-eosin stain).

5.3. Clinical aspect: peripheral gingival fibroma

Figure 5. Tumoral lesion located at the gingival level, hard, fibrous texture with occasional inflamed areas, highly vascularised, irregular shape, size 7cm, firmly attached to the alveolar ridge; the patient reported mastication difficulties, inability to eat, speech disturbances, and facial deformities.

5.4. Histopathological aspects

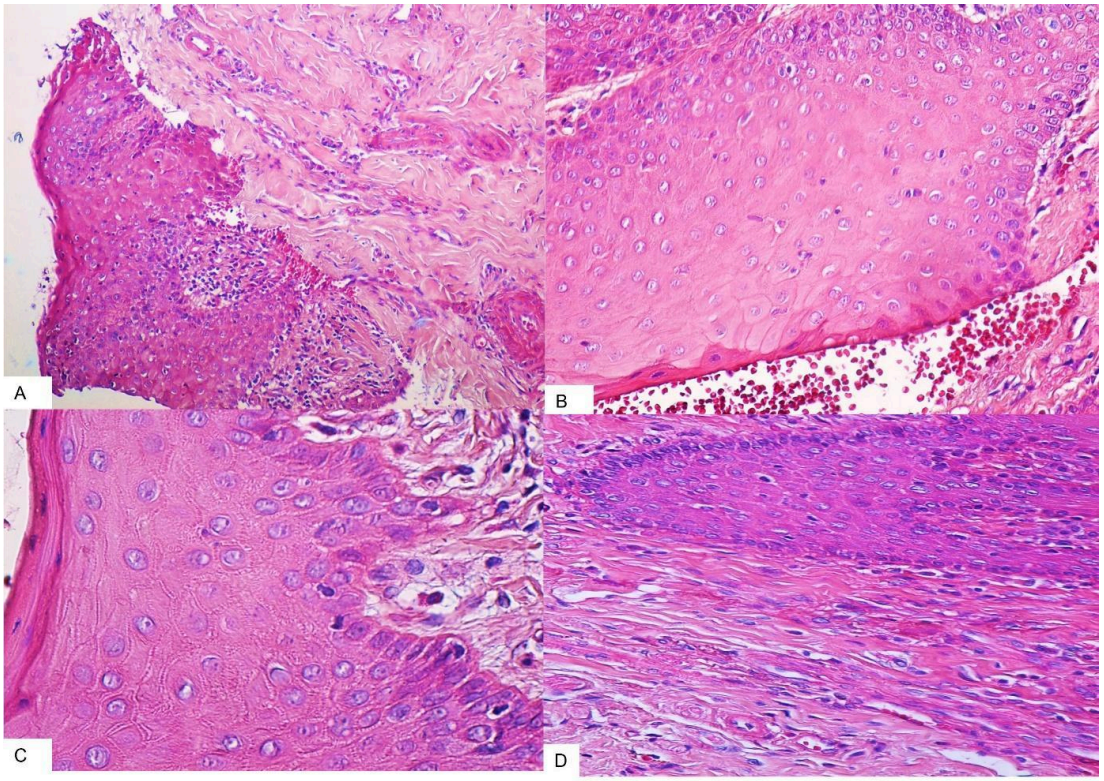

*Figure 6. Microscopic appearance of peripheral gingival fibroma. Stain: Hematoxylin-eosin (HE). **A** – epithelium with parakeratosis, reduced number of proinflammatory cells, increased number of collagen fibers in the gingival chorion; **B** – numerous mitotic cells in the basal layer of the gingival epithelium; **C** – epithelium with parakeratosis and dysplastic cells; **D** – proliferation of spindle cells, background of collagen fibers.*

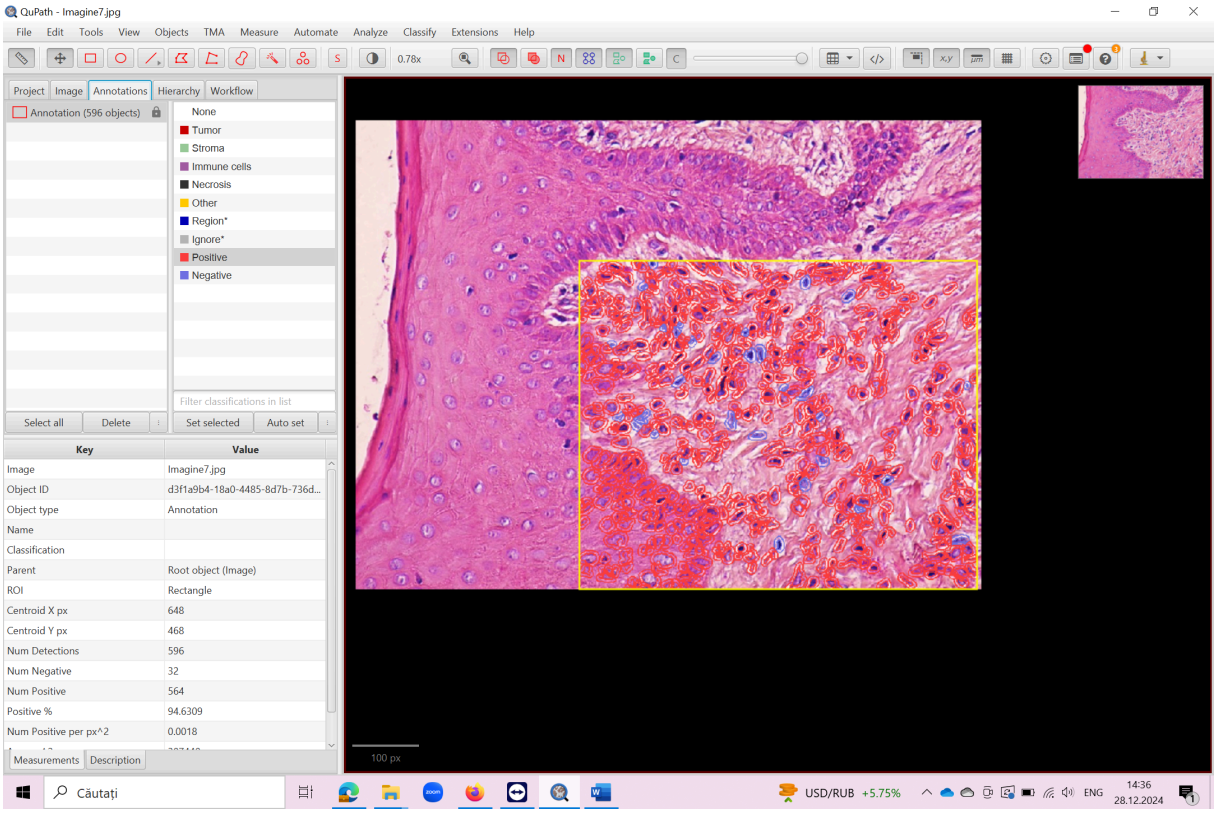

Figure 7. The QuPath software marked the positive inflammatory cells in red, distributed among the collagen fibers, while the cells marked in blue were negative.

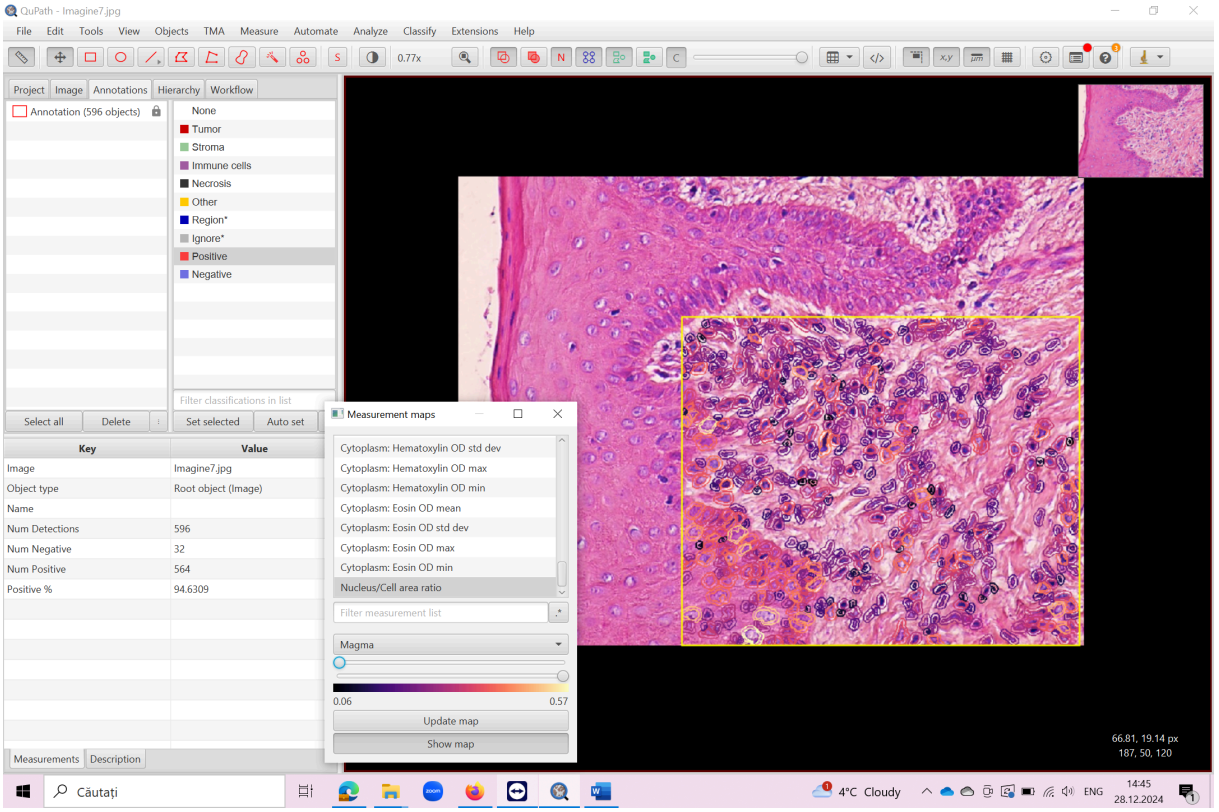

Figure 8. The QuPath software – through the nucleus/cell area ratio – marked the nuclei of cells with tumor potential.

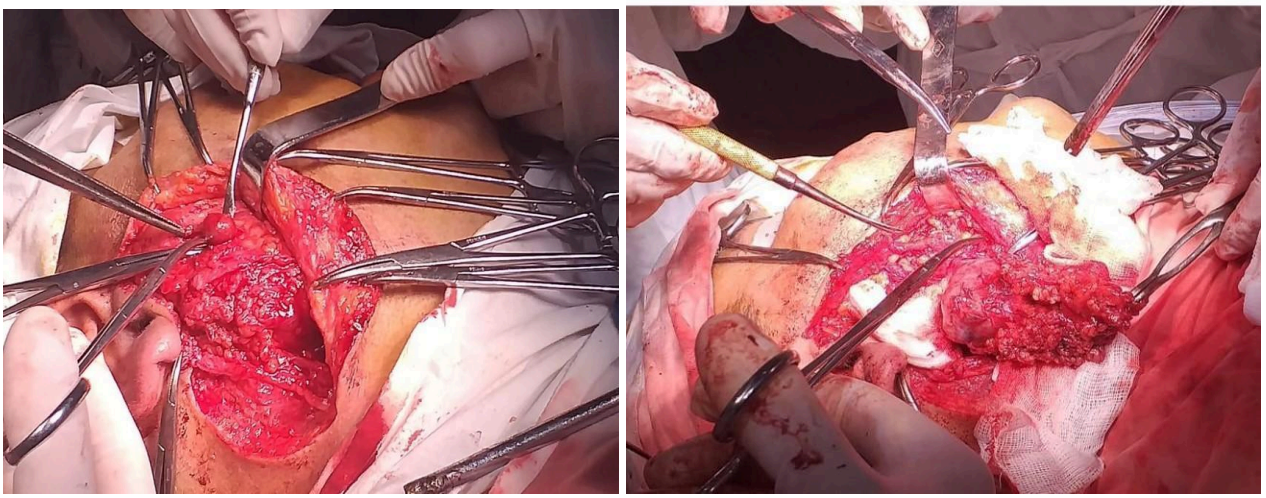

Figure 7. Intraoperative appearance of the parotid tumor.

6. Discussions

Epidemiologically, oral cavity cancer ranks 16th among the 26 most common types of cancer worldwide (Ilie et al., 2024; Kijowska et al., 2024). Oral cancer represents a major global public health issue (Kijowska et al., 2024), with continuous efforts to improve preventive measures and implement effective and rapid screening programs (Kijowska et al., 2024). According to the GLOBOCAN 2022 online platform, the geographic regions with the highest incidence rates of oral cavity cancer are (Table 1):

Table 1. The geographic regions with the highest incidence rates of oral cavity cancer.

Geographic area	**ASR (age-standardised rate)**
Melanesia	19.8
South Central Asia	13.5
Central and Eastern Europe	10.3
Western Europe	10
Australia and New Zealand	10

In Asian regions, a higher incidence of this type of cancer is noted, with betel chewing being the main risk factor (Kijowska et al., 2024), while in European regions, the primary risk factor is an unhealthy lifestyle, which includes heavy tobacco and alcohol consumption (Kijowska, 2024). In the Australian region, the main etiological factor for oral cancer is exposure to UV radiation from the sun (Kijowska et al., 2024; Huang et al., 2023).

Regarding the topography of cancerous lesions in the oral cavity, the WHO proposed a classification in 2022 that groups oral lesions with potential for malignant transformation or malignant lesions as follows: A. lesions of the oral cavity and lesions located at the lingual organ level (mobile part); B. oropharyngeal cancers (these include lesions in hard-to-reach areas such as the tonsils, base of the tongue, and adenoids) (Kijowska et al., 2024). Our study demonstrates the presence of cancerous lesions in various topographical areas of the oral cavity.

The clinical examination of the tumor lesion is not sufficient for establishing a definitive diagnosis (Neville & Day, 2002). The clinical examination can only generate a presumptive diagnosis, as the macroscopic appearance of the lesion may cause confusion and uncertainty. Similarly, in the case of our patient with peripheral gingival fibroma (a benign tumor), the clinical appearance, due to its significant volume and adherence, could have been mistaken for a malignant tumor. Only the histopathological examination of the biopsy can provide clarity and a definitive diagnosis (Neville & Day, 2002; Bugshan & Farooq, 2020).

7. Conclusions

The diagnosis of early-stage oral cancer is vital for maintaining the individual's quality of life. In Romania, oral cancer screening programmes are extremely rare or even nonexistent in many geographic regions of the country. Oral cavity cancer represents a public health issue, and we believe that large-scale implementation, covering a significant percentage of the population, could help in identifying lesions with the potential for malignant transformation or cancer in its early stages.

A definitive diagnosis of benignity or malignancy of a lesion cannot be established through clinical examination of the oral cavity alone; a biopsy of the oral mucosa must be obtained and sent to the laboratory for further analysis.

AI software for histopathological diagnosis proves to be vitally useful in establishing an accurate diagnosis. These tools aim to shorten the time required for diagnosis, reduce errors, decrease pathologist fatigue, and provide the possibility of working remotely and interdisciplinarily.

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