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Editorial

Oral Cancer and the Tragedy of Thinking Inside the Box

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Editorial

Cancer screening and its execution are sadly in a great dilemma due to inconclusive, contradictory research [1].

Analyzing The National Cancer Data Base, Fujiwara et al. (2016) concluded that oral cancer treatment delay significantly impacts overall survival [2]. On December 26th, 2022, the following statement could be identified on the website of the National Cancer Institute: "There is inadequate evidence to establish whether screening would result in a decrease in mortality from the oral cavity and nasopharyngeal cancers" [3]

One cannot ignore the contradiction created by other groups [4], concluding that "delays of 4-6 weeks seem acceptable" while praising the value of AI to reduce diagnostic delays [5]. Head and neck cancer is currently ranked by the World Health Organization as the eighth most spread tumor worldwide, affecting the oral cavity mainly. Questionable treatment success and inefficiency are associated with advanced disease estate, while early disease diagnosis leads to healing and favorable outcomes. Clinical practitioners, specialists, healthcare insurance companies, and in-charge authorities controversially reject oral cancer screening disqualifying its value due to controversial provided evidence, low valuation of available protocols, economic priorities, etc. Not using early cancer identification dramatically influences treatment outcomes and survival rates [6]. Multiple calls to action have been and continue to be launched regarding the developing and practical use of advanced technology with high sensitivity and specificity. The author intends to address the reasons behind this questionable approach and to offer a solution considering Bouaoud et al.'s call to action (2022) [7]. It is scientifically agreed that mucosal changes may lead to Oral Squamous Cell Carcinoma. Point of care diagnosis of oral potentially malignant disorders (OPMD) is the central goal of early oral cancer screening. Science documents the 5-year survival to be 75% for stage I, dropping to 30% at stage IV [8,9]. The value of early detection is, at this moment, misunderstood and misvalued by those in charge. The currently-in-use recommended

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protocol and the applied ones mirror available scientific controversies and dilemmas and involve "must" and "facultative, adjunct" steps. The recently celebrated success rates in tumor surgery are due to the implementation of visual diagnosis protocols enhancing precise margin identification and preventing excessive/insufficient tissue removal. The benefits can be summarized from additional surgical prevention to cost reduction, from the rise in patients' postoperative quality of life to a death rate reduction.

The conventional "scientific" way of comparing diagnostic devices with each other contributes to the rise of denied use. The complete incremental evaluation of different imaging modalities cannot be considered helpful and does not guarantee beneficial integration, as suggested by Mieog et al. 2022 [10]. A successful combination of different techniques harbors the opportunity of raising sensitivity and specificity and granting valuable data disease-related data.

The available procedures are:

A. conventional examination,
B. vital staining,
C. optical imaging,
D. oral cytology.

A. Conventional oral cancer diagnosis protocol

The detailed execution of cancer screening by dental clinicians is currently described by the protocol published by the National Institute for Dental and Craniofacial Research (NIDCR) via direct visual inspection complimented by palpation is the starting point. Adding adjunct procedures and technology potentially improves differential diagnosis and secures biopsy recommendations followed by histopathologic valuation. It must be mentioned that voices also ask for redefinition and re-standardization of essential histopathologic valuation criteria.

The sensitivity of conventional oral cancer examination has recently been scaled, ranging from 25-100% and specificity from 24-100% [11]. There are many reasons behind the described variations with disastrous consequences. The "clinical observer variation" has to be named first. It urgently requires a researcher's consensus agreement and, of course, implementation into current graduate education syllabi as the first step to generate the desired positive change. The data presented by the above-mentioned group of researchers [11], of course, justify the current rejective position of those in charge.

B. Adjunctive technologies

a. Vital staining

1. Vital staining using "toluidine blue" potentially identifies cells with an increased DNA level and dysplastic cells of the same kind. Calculated sensitivity reaches 92.6%, while specificity ranks at 67.9%. Different researchers concluded an accuracy of 80%. To identify glycogen presence in normal oral mucosa staining with Lugol's iodine finds its applicability. The combination of the two vital staining methods is acknowledged to be helpful for the identification of biopsy topography.
2. "Methylene blue staining" identifies nucleic acids, having a sensitivity of 90–91.4% and a specificity of 66.6 – 69%.

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3. "Lugol's iodine staining" identifies the glycogen present within the cytoplasm, which malignant cells fail to support due to advanced glycolysis and loss of cellular differentiation. The healthy mucosa will stain brown-mahogany, while the dysplastic and cancerous one will appear pale. Sensitivity is rated with 87.5 –94.7% and specificity 83.8–84.2%.

b. Light based optical imaging serves as a further adjunct examination approach

1. "Autofluorescence" of human tissue is generated by light emission through preexisting fluorophores (collagen, tryptophan, elastin, keratin, hemoglobin, NADH) and changes in mucosa architecture occur once excitation by specific wavelengths happen. The quantitative changes of mentioned fluorophores can be identified using bio photonics. Diagnostic accuracy of exclusive autofluorescence using technologies has scientifically proven a sensitivity of 33%–100% and a specificity between 12%–88.6%.

2. "Multiple wavelength" diagnosis combining three wavelengths: white/405/green- amber. The white light, as used in the conventional approach, will enhance the detection of any surface changes in the mucosa; the violet wavelengths will let dysplastic and malignant tissues appear darker than healthy mucosa because of their loss of fluorescence; while the green-amber wavelength will help contrast between vasculature and surrounding tissue facilitating visual differentiation between normal and abnormal because abnormal tissue has a diffuse vasculature. The green-amber light enhances optical contrast between vasculature and surrounding tissue facilitating visual differentiation between normal and abnormal vasculature.

3. Most recent "chemiluminescence technologies" advocate a combination of 1% acetic acid and toluidine blue excited by multiple wavelengths, demonstrating a sensitivity of 71–100% and a specificity of 0–84.6%. AF (Autofluorescence) and CL (Chemilumiscence) present a high sensitivity in the diagnosis of dysplastic and malignant oral cavity lesions, demonstrating that diagnostic biopsies may be avoided in case of a negative test result" [12]. Fluorescence Guided Surgery (FGS) emerged immensely, being in several surgical disciplines well-established, leading to tumor-free margins. Systemically or locally applied fluorescence imaging agents are excited at a specific wavelength using external light sources. Photodynamic Diagnosis, the concept successfully used in FGS, has the potential to provide accurate point-of care diagnosis support. Lima et al. (2021) analyzed scientific evidence and identified 5-Aminolevulinic acid (5-ALA) as the most used fluorescent probe celebrating a sensitivity of 90%–100% accompanied by a specificity of 51.3%–96% [13]. The same researchers concluded that combining light technologies with fluorescent probes "can provide an accurate diagnosis of oral cancer, assisting the dentist during (a) daily clinical activity." For "Fluorescence Guided Surgery" (FGS) purposes, the fluorescent probe is delivered systemically, followed by incubation time. Point of care diagnosis allows topical application of the photosensitizer.

4. "Photodynamic diagnosis" is the composition of locally applied photosensitizers and luminescence. Three different approaches can be successfully bored from Fluorescence Guided Surgery:

a) topical application of 5-aminolevulinic acid (at this stage applied via a prolonged rinse) followed by light excitation of 405nm wavelength. The emission of malignant cells will shine blue.

b) topical application of sodium fluorescein followed by light excitation of 405nm wavelength or a combination of 520 and 620nm;
c) the combination of the two above mentioned photo sensitizers.

5. ALA and sodium fluorescein and a multiple wavelength excitation.

The author's conclusion suggests a “thinking outside the box” approach by combining different, at this stage defined “adjunctive” technologies with the conventional approach into one protocol consisting of:

I. Conventional diagnosis.

II. Vital staining using toluidine blue.

III. Photodynamic diagnosis choosing version “4c” as described above.

The author hereby sends out an urgent call to action, to combine the immediate implementation of the above-suggested protocol, a change of guidelines by professional committees, financial sponsorship of early cancer screening by healthcare insurers and governmental authorities, and last but least, a change in professional grad and post-graduate education.

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