Bioimpedance: A Tool for Screening Oral Cancer – A Systematic Review

Abstract

Objective: The successful management of cancer depends on proper screening and treatment methods. Bioimpedance spectroscopy (BIS) is an established technique in detecting breast cancer, cervical cancer, and prostate cancer. This systematic review sought to investigate the current evidence regarding the clinical application of bioimpedance in the detection of oral squamous cell carcinoma and oral potentially malignant disorders. **Study Design:** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed to perform this review. Electronic databases such as PubMed, MEDLINE, Embase, EBSCOhost, and Google Scholar were searched till March 2022. Articles published in the English medical literature on human participants report on the application of BIS in the screening of precancerous and cancerous lesions. The primary endpoint was defined as the ability to differentiate between normal and cancerous tissue. **Results:** A total of 6754 articles were identified; of which 481 were eligible for inclusion. Only five articles met the eligibility criteria and were included in the study. Qualitative analysis for each study was done to assess the data provided. All the studies demonstrated a significant divergence in BIS metrics between cancerous and normal tissue at 20 Hz and 50 KHz. **Conclusion:** Bioimpedance appears to be a promising novel tool for the detection of various malignancies which can be used in community screening due to its noninvasiveness and portability.

Keywords: *Bioimpedance, bioimpedance spectroscopy, cancer screening, electrical impedance spectroscopy, malignancy, oral cancer, oral squamous cell carcinoma*

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Introduction

Impedance is an effective resistance of an electric circuit or constituent to alternating current (AC), occurring from the joint result of ohmic resistance and reactance, and it is measured as a ratio of voltage-to-current in an AC circuit. The impedance sourced by inductance and capacitance jointly represents reactance and presents the imaginary part of impedance, whereas the resistance presents the real part.[1]

Impedance spectroscopy (IS) is a common phrase that considers the small-signal assessment of the linear electrical reaction of a material of concern (including electrode effects) and the consequent examination of the response to give valuable data about the physicochemical characteristics of the method.[2]

Bioelectrical impedance or bioimpedance can be described as organic tissue's response to block an external electric current or how a living organism responds to the current. It is the measurement of the impedance signal, done by inserting electrical currents and assessing the voltage produced by the tissue impedance through the electrodes. The physiological and chemical status of the biological cells and/or tissues greatly influences the frequency response of bioimpedance and differs for each individual.[3,4]

Bioimpedance includes both resistance and capacitance and may be described as $Z = R + jX$, where X is reactance, R is resistance, and Z is impedance. Resistance measured is the opposite of the conductor of electricity, and reactance is created by the excess antagonism to the current from capacitance result of cell membranes. Capacitance can be defined as a parameter, which helps to store energy by resisting a change in voltage. In the simplest terms, the real part of impedance represents simple resistance, and the imaginary part of impedance represents reactance. The cells' condition and integrity with cell lipid status depict the phase angle. It is presented in degrees and alters as a reaction to alteration in the current

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frequency. There is a direct linear correlation between the phase angle and cellular health.[1]

The impedance of biological tissue can be easily measured with the help of the bio IS (BIS) technique over a wide frequency range. BIS is technically comparable to electrical IS (EIS), a general harmless and inexpensive method used to exemplify the electrical characteristics of different resources; however, in BIS, the method is exclusively practical for biological tissues.[5] BIS analyzes the nonbiological features of cells, which can tolerate the disease impact, and assesses for noninvasive detection. A cell shows resistance to an electric field when exposed to the current flow. Living cells showed varied insulating properties under diverse applied frequencies. To maintain the requisite possible variation, cells provide altering capacitance and resistance.[6]

The frequency of electric current changes the electric properties of cells described as alpha, beta, and gamma dispersion. The alpha dispersion is affected by the ionic environment surrounding the cells and is obtained at low frequency ranging from 10 Hz to 10 kHz. The beta dispersion shows structure relaxation at frequency ranging from 10 kHz to 10 MHz. The gamma dispersion obtained at higher frequencies is associated with water molecules. Most changes in the cell and tissue occur in the frequency range of alpha and beta dispersion and, thus, have more medical implications.[7]

At low frequency, cell membranes encompass high bioimpedance, and the transmitted current is confined to narrow extracellular passageways of the tissue, which leads to an elevated bioimpedance. However, these passageways are broader in oral cancer tissue and offer less bioimpedance. In addition, decreased cell volume permits electric current to take a straight passageway as shown in Figure 1. This leads to a low intensity of bioimpedance in oral cancer lesions.[8] Although EIS is extensively used in engineering over the past 30 years, BIS application and use have increased in the medical field. And now, BIS is part of a routine clinical exercise in the intensive care unit and nutritional remedy in the assessment of fluid volumes, fluid status, and body composition for nutritional intervention. For a few years, medical interest and research is exploring BIS changes in different malignancy subtypes.[9]

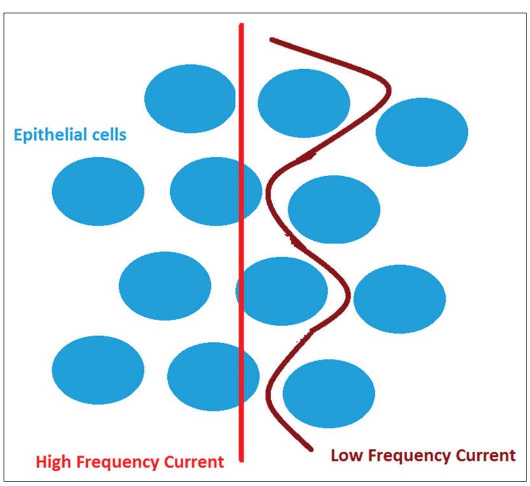

Figure 1: High- and low-frequency current pathway through the epithelium

The function of impedance in malignancy screening begins in 1926 with an initial article on breast malignancy. In 1990, Morimoto *et al*.[10] prepared a new impedance analytical structure, at a frequency range of 0–200 kHz by three-electrode technique. Subsequently, Emtestam *et al*.,[11] in 1998, assessed the bioimpedance technique for the preoperative evaluation of basal cell carcinoma (BCC). In 1999, Lee *et al*.[12] localized malignancy in intact prostate using bioimpedance. Soon after, in 2000, Brown *et al*.[13] with the help of a pencil probe analyzed electrical impedance among 124 women with cervical cancer. A thorough literature search shows the scarcity of studies on bioimpedance in oral cancer.[7]

Therefore, this systematic review was planned with an aim to assess the bioimpedance application in the detection of oral potentially malignant disorders (OPMDs) and oral squamous cell carcinoma (OSCC).

Methodology

Search strategy

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance, the qualitative systematic review was accomplished using the electronic database (PubMed, Scopus, MEDLINE, Embase, and EBSCOhost) and Gray literature (Google Scholar and ProQuest). Articles published till March 2022 were searched using the key phrases with Boolean operators OR: "impedance," "BIS," "bioimpedance spectroscopy," "bioimpedance," "electrical impedance spectroscopy," and "EIS." Obtained articles were further screened for "oral potentially malignant disorders," "oral cancer," and "oral precancerous lesion," and in total, 6754 articles were obtained. The search strategy in detail is shown in Table 1. There were 2169 duplicate studies, which were removed after screening using Microsoft Excel.

Selection criteria

Studies written in English with full text, conducted on human tissue either *in vivo* or *in vitro* or both, were included. Exclusion criteria were studies using diagnostic tools other than bioimpedance, animal studies, and case studies or case series. Around 56 studies were not in the English language, and 3040 articles were not on humans; hence, excluded. For 1008 studies, the full text was not retrievable. All the authors independently analyzed the abstracts of the 481 studies and found 385 studies were not on oral cancer. The remaining 96 articles entered phase 2 (full-text screening); from which 87 were not on bioimpedance, and four studies showed no data on the comparison of oral cancer against normal tissue.

After the screening, five articles were included in the study and were cross-referenced to make certain that no articles were skipped. Statistics obtained from the included articles were entered in Microsoft Excel, and qualitative data analysis was done with the endpoint being the differentiation of premalignant and malignant tissue from normal tissue using bioimpedance. Other clinically relevant results were also identified and reported.

Data extraction and quality assessment

Using the Quality Assessment of Diagnostic Accuracy Studies II (QUADAS II) tool, all the authors VG, UA, and PG separately assessed all the included articles for the risk of bias and applicability concerns [Table 2]. All the authors separately assessed the quality of each article and extracted the information; discussions were held in case of any discrepancy. Information was collected regarding author, country, publication year, number of patients, type of lesion, impedance, phase angle, and real and imaginary part of impedance.

Results

After the screening, five articles met the inclusion criteria and constituted adequate data that can be assessed. Figure 2 depicts the flowchart as per the PRISMA 2020 guidelines, prepared for the current systematic review. The articles included analyzed the BIS on carcinoma of various oral cavity tissues. These covered 295 patients' specimens analyzed by EIS (compared with corresponding normal tissue). All five articles have been published after 2010, and from these, two were published in or after 2015 [Table 3]. Three studies were conducted in Asia (two

Table 1: Search strategy of the study

Database	Step	Strategy
PubMed	Number 1	Squamous Cell Carcinoma of Head and Neck[Mesh] OR oral cancer [All fields] OR oral malignancy [All fields] OR oral carcinoma[All fields]
	Number 2	Oral potentially malignant disorder[All fields] OR Oral potentially malignant lesion [All fields] OR precancerous disorders[All fields]
	Number 3	Leukoplakia, Oral[Mesh] OR Oral Submucous Fibrosis[Mesh] OR Lichen Planus, Oral[Mesh] OR oral erythroplakia[All fields]
	Number 4	#2 OR #3
	Number 5	#1 AND #4
	Number 6	Bioimpedance[All fields] OR BIS[All fields] OR bioimpedance spectroscopy[All fields] OR impedance[All fields] OR electrical impedance spectroscopy[All fields] OR EIS[All fields] OR bioimpedance analyzer[All fields] OR bioimpedance analyzer[All fields]
	Number 7	#5 AND #6
Scopus	Number 1	"Squamous Cell Carcinoma of Head and Neck" OR "oral cancer" OR "oral malignancy" OR "oral carcinoma"
MEDLINE	Number 2	"Oral potentially malignant disorder" OR "Oral potentially malignant lesion" OR "precancerous disorders"
Embase	Number 3	"Leukoplakia, Oral" OR "Oral Submucous Fibrosis" OR "Lichen Planus, Oral" OR "oral erythroplakia"
EBSCOhost	Number 4	#2 OR #3
	Number 5	#1 AND #4
	Number 6	"Bioimpedance" OR "BIS" OR "bioimpedance spectroscopy" OR "impedance "OR electrical impedance spectroscopy" OR "EIS OR bioimpedance analyzer" OR "bioimpedance analyzer"
	Number 7	#5 AND #6

Table 2: Quality assessment regarding bioimpedance diagnostic performance using the Quality Assessment of Diagnostic Accuracy Studies II tool

Study	Risk of bias			Applicability concern			Flow and timing
	Patient selection	Index test	Reference standard	Patient selection	Index test	Reference standard	
Ching *et al*., 2010	Unclear	High	Low	Low	Low	Low	Low
Sun *et al*., 2010	Low	High	Low	Low	Low	Low	Low
Sarode *et al*., 2015	Low	High	Low	Low	Low	Low	Low
Murdoch *et al*., 2014	Low	Low	Low	Low	Low	Low	Low
Tatullo *et al*., 2015	Low	Low	Low	Low	Low	Low	Low

Table 3: Descriptive data of all the included studies

Author	Year	Country	Site	Lesion type	Number of cases	Number of controls	Frequency	Current	Voltage (mV)
Ching *et al*.	2010	Taiwan	Tongue	OSCC	5	5	20 Hz; 50 kHz; 1.3 MHz; 2.5 MHz; 3.7 MHz; and 5 MHz		200
Sun *et al*.	2010	Taiwan	Tongue	OSCC	12	12	20 Hz, 50 kHz, 1.3 MHz, 2.5 MHz, 3.7 MHz, and 5 MHz		200
Sarode *et al*.	2015	India	Oral	OSCC	50	50	20 Hz; 50 kHz; 1.3 MHz; 2.5 MHz; 3.7 MHz; and 5 MHz		200
Murdoch *et al*.	2014	United Kingdom	Oral	OSCC	47	51	0.076–625 kHz	<12 µA	
Tatullo *et al*.	2015	Italy	Tongue	OLP	52	11	50 kHz		

OSCC: Oral squamous cell carcinoma; OLP: Oral lichen planus

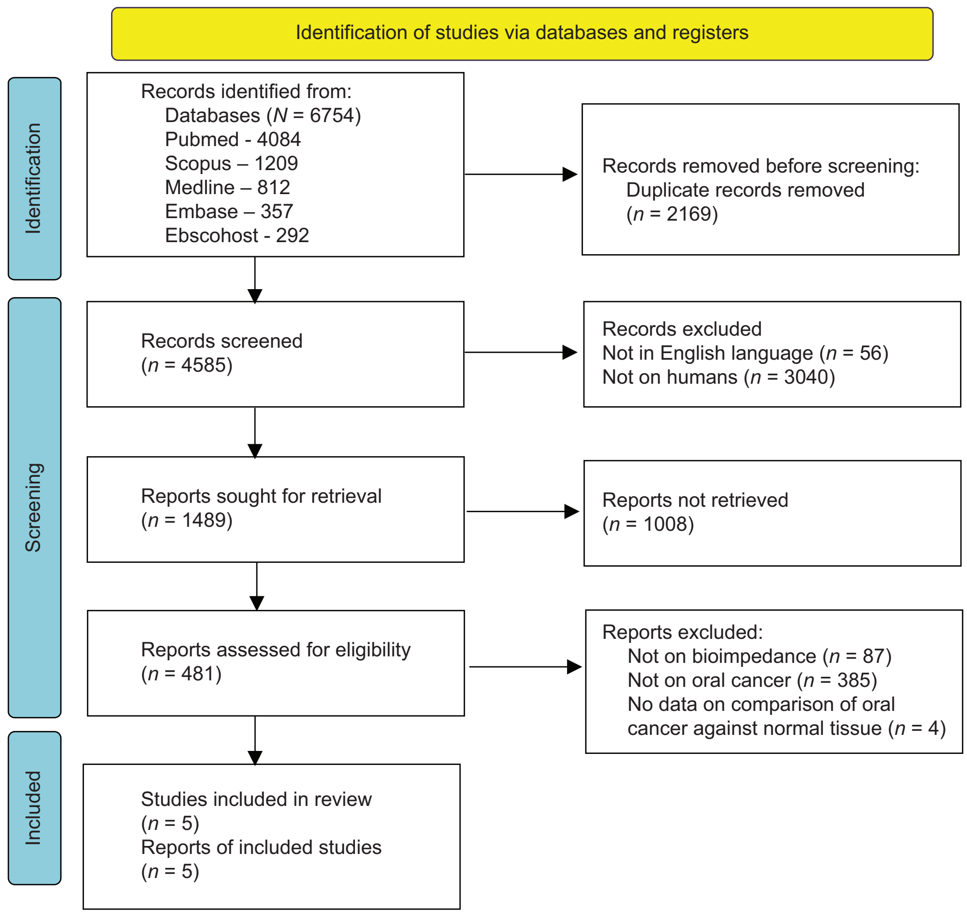

Figure 2: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram for new systematic reviews, which included searches of databases and registers only

in Taiwan and one in India) and two in Europe (one in the United Kingdom and one in Italy). Quality assessment was done for all the included studies using the QUADAS II tool [Table 2]. On scoring, two studies have an overall judgment of "low risk of bias," whereas three studies are at "risk of bias," and all five studies have "low risk regarding applicability." Bioimpedance devices used in the included studies are shown in Figure 3.

Results of the selected studies are presented in two forms. First, the results of selected studies presented through four electrical properties of cancerous and precancerous tissue: impedance (Z); real (R) and imaginary (X) part of impedance, and phase angle (θ).

Impedance

Cancerous and normal tissue showed a decline in impedance, as measurement frequency spiked from 20 Hz to 5 MHz. At 20 Hz and 50 kHz, the impedance of normal tissue was significantly larger compared to cancerous tissue ($P < 0.001$)[14-16] as shown in Table 4. Whereas the study conducted by Tatullo *et al*. on oral lichen planus (OLP) at 50 kHz showed that the impedance

Table 4: Details of all four parameters in the studies investigating impedance in malignant tissue

Author	Frequency	Impedance (*Z*)		Phase angle (*θ*)		Real part of impedance (*R*)		Imaginary part of impedance (*X*)	
		Tissue							
		CT	NT	CT	NT	CT	NT	CT	NT
Ching *et al*.	20 Hz	4317.92	12,771.50	−22.74	−13.40	4049.90	12,432.41	−1440.95	−2918.89
	50 KHz	372.02	782.93	−37.97	−49.78	290.08	500.77	−228.91	−599.18
Sun *et al*.	20 Hz	4358.5	14,458.8	−21	−14.7	4115.2	13,946.3	−1387.8	−3732.2
	50 KHz	380.1	816.9	−37.5	−50.1	312.4	523.8	−183.9	−621.5
Sarode *et al*.	20 Hz	4493	15,490	−21.81	−14.56	4198	14,000	−1375	−3552
	50 KHz	370	817.1	−37.24	−50.35	315	523.7	−185.3	−620.8
Tatullo *et al*.	20 Hz	-	-	-	-	-	-	-	-
	50 KHz	1224.4	913.7	30.9	26	-	-	-	-

CT: Cancerous tissue; NT: Normal tissue

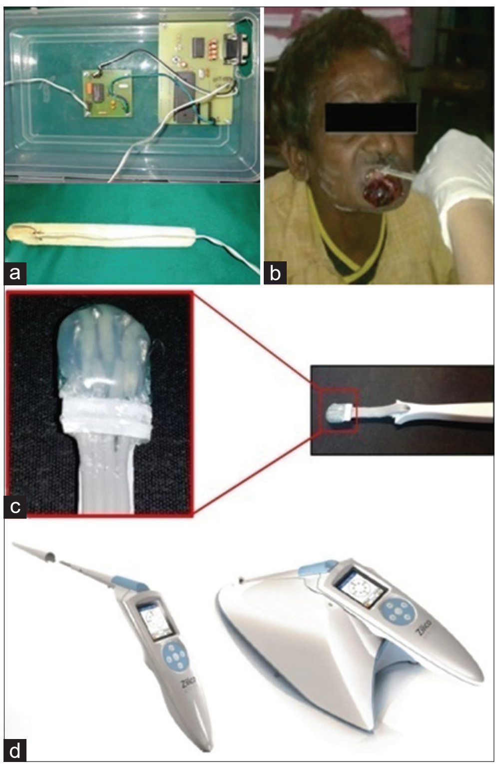

Figure 3: The image of the bioimpedance spectroscopy tool across the included studies. (a) Bioipedance device using ice cream stick as probe. (b) using the BIS device in an oral cancer patient. (c) BIS probe with in evidence the "head" containing the four micro-electrodes. (d) EIS device consists of a handheld unit, a base station for downloading data to a laptop, a single-use sheath covering the snout of the handheld unit

of normal tissue was significantly smaller compared to precancerous tissue ($P < 0.005$).[17]

Phase angle

Cancerous and normal tissues showed a decline in the phase angle, as measurement frequency spiked from 20 Hz to 5 MHz. Moreover, at 50 kHz, the phase angle of surrounding normal tissue was significantly smaller than cancerous tissue ($P < 0.05$)[14-17] as shown in Table 4. Whereas at 20 Hz, according to Sun *et al*., the phase angle of cancerous tissue was analyzed to be significantly smaller compared to normal tissue ($P < 0.001$);[14] however, according to Sarode *et al*., the phase angle of cancerous tissue was significantly larger than normal tissue ($P < 0.001$).[16]

Real part of impedance

Cancerous and normal tissue showed a decline in the real part of impedance, as measurement frequency increased from 20 Hz to 5 MHz. At 20 Hz and 50 kHz, the real part of impedance of normal tissue was significantly larger than that of cancerous tissue ($P < 0.05$) as shown in Table 4.[14-16]

Imaginary part of impedance

Cancerous and normal tissue showed an increase in the imaginary part of impedance, as measurement frequency increased from 20 Hz to 5 MHz. At 20 Hz and 50 kHz, the imaginary part of impedance of normal tissue was significantly smaller than that of cancerous tissue ($P < 0.05$) as shown in Table 4.[14-16]

Cancer versus normal tissue

The impedance readings for OSCC and moderate-to-severe dysplastic lesions showed a significant difference from healthy mucosa ($P = 0.0002$, $P = 0.0067$, and $P = 0.0338$, respectively). Whereas impedance reading taken from normal tissue showed no significant difference compared to reading from mild dysplastic and benign lesions. Murdoch *et al*. also stated that the readings for the high-risk lesion group (OSCC + high-risk dysplasia) were significantly higher when compared to the low-risk lesion group (low-risk dysplasia and benign) ($P = 0.0408$) and the identical anatomical location in the healthy controls ($P = 0.0001$); however, the difference was not significant in the readings from the low-risk lesion group and the identical anatomical location in the healthy controls. Impedance readings taken from the healthy controls showed no significant differences from the nonlesional contralateral side of the mouth.[18]

To evaluate the performance of impedance readings as a way of diagnosing disease, receiver operating characteristic (ROC) curves were prepared from the impedance records with the area under the curve (AUC) of 0.674 ($P = 0.0411$), specificity 62.5%, sensitivity 65.2%, and positive likelihood ratio of 1.74. Whereas, lesions when compared with normal mucosa on the opposite part of the oral cavity, the AUC was 0.776 (P = 0.001), sensitivity 65.2%, specificity 91.7%, and positive likelihood ratio 7.83.[18]

Lichen planus

Patients with OLP lesions on the tongue showed a significant increase in the impedance (1740.5) and phase angle (19.6) for the affected part of the tongue compared to the healthy tongue (Z: 806 and θ: 29.5). Patients diagnosed with intraoral reticular OLP, who developed hyperkeratotic plaques, showed a significant increase in the impedance values (2060.5) and a significant decrease in the phase angle (23) values compared to normal mucosa (Z: 1224.4, θ: 30.9). Whereas among patients with erosive OLP lesions, the impedance value (913.7) was significantly reduced compared to reticular lesions and hyperkeratotic plaque of other patients. Bioimpedance appears to be a good predictor model with a sensitivity of 90%, specificity of 85%, and AUC = 0.89 (AUROC curve).[17]

After treatment

A statistically nonsignificant increase in the impedance values (1445) was observed for previously treated OLP lesions compared to the surrounding healthy mucosa (1224.4); whereas the phase angle (32) was similar to the healthy mucosa (30.9).[17]

Heterogeneity test

Forest plot [Figure 4] of the sensitivity and specificity, regarding the diagnostic accuracy of bioimpedance in differentiating OSCC from healthy tissue, showed the heterogeneity of the applicable studies.

Discussion

The first study depicting the role of bioimpedance in cancer detection was done in 1926. However, Surowiec *et al*.,[19] in 1988, were able to determine the difference between breast carcinoma and healthy tissue through *in vitro* study using bioimpedance. In 1998, Emtestam *et al*.[11] employed bioimpedance for the investigation of BCC. In 1999, Chauveau *et al*.[20] assessed the bioimpedance values over a range of frequency values from 10 kHz to 10 MHz between *in vitro* samples of pathological and normal tissues. Thereafter in 1999, Lee *et al*.[12] used bioimpedance at frequency ranging from 100 kHz to 4 MHz for prostate cancer localization. Later in 2000, Brown *et al*.[13] used electrical impedance spectra through pencil probe (diameter 5 mm) among 124 females with cervical pathology. Further, Prakash *et al*.[21] in 2015, measured point-wise *ex vivo* EIS using a linear four-electrode impedance probe on hepatic tissue excised from patients with metastatic colorectal cancer.[7]

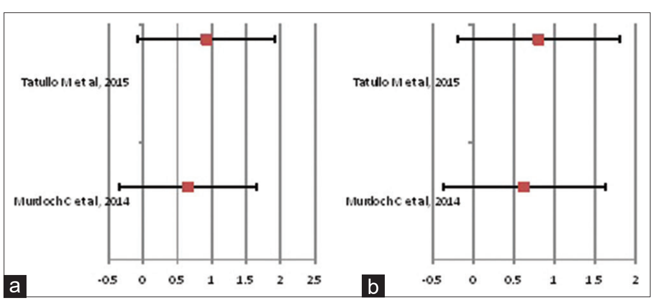

Figure 4: Forest plot depicting the diagnostic accuracy of bioimpedance in differentiating OSCC from healthy tissue. (a) Forest plot of sensitivity regarding the diagnostic accuracy of bioimpedance in differentiating OSCC from healthy tissue, (b) Forest plot of specificity regarding the diagnostic accuracy of bioimpedance in differentiating OSCC from healthy tissue. OSCC: Oral squamous cell carcinoma

After a detailed literature search, using different databases, bioimpedance has been assessed as a screening tool for various cancers throughout the body; however, there is a scarcity of studies on OSCC.

In the review, to measure bioimpedance, four electrical parameters: phase angle (θ), impedance (Z), real part (R), and imaginary part (X) of impedance were assessed through voltage at 200 mV at six frequencies ranging between 20 Hz–5 MHz: 5 MHz; 3.7 MHz; 2.5 MHz; 1.3 MHz; 50 kHz; and 20 Hz. OSCC tissue might significantly be differentiated from the healthy tissue at 20 Hz and 50 kHz frequencies.[7]

The impedance value is lower in cancerous tissue compared to normal tissue because cancerous tissue has more cellular water and salt content compared to normal tissue, packing density, transformed membrane permeability, and cell orientation, and thus, increased conductivity. Conductivity is inversely related to impedance.[1]

Oral cancer has a poor prognosis compared to many other cancers, with a maximum 5-year mortality rate, as until the late stages oral malignancies are not diagnosed. For a better prognosis, the disease should be identified in its premalignant phase as it depends to a large amount on the stage of diagnosis.[2]

Over the years, bioimpedance has appeared as a superior screening device over the existing screening techniques due to immediate results, being cost-effective, and involving little guidance. Hence, bioimpedance can be simply used at the grassroots level in countries, where various obstacles limit countrywide screening programs. The probable merits of immediate screening tests are reduced patient apprehension, enhanced patient compliance, and the ability to reiterate erroneous tests instantly.[22]

According to our search, so far, no study has assessed the bioimpedance values and their significance among patients with OPMDs/precancerous lesions. Further, the impact on tobacco chewers has not been studied. We suggest that a follow-up study should be done assessing the change in bioimpedance after tobacco cessation counseling. Further sensitivity and specificity of the device should be assessed to make it fit for use at the community level in community screening programs.

Conclusion

To date, no literature is available on the comparison of bioimpedance values among individuals with tobacco habit; however, no lesions and individuals diagnosed with oral premalignant and malignant conditions due to tobacco chewing. Bioimpedance appears to be a promising tool for oral cancer screening. Due to its noninvasiveness, reliability, immediate results, low cost, and portability of the whole system, bioimpedance can be used at the community level in developing countries, where conducting national screening programs is a challenge.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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