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ORIGINAL ARTICLE

DOI: https://doi.org/10.4322/bds.2021.e2868

Oral ID® as an adjunctive tool for surgical margin assessment in patients with oral squamous cell carcinoma: a comparative study

Oral ID® como uma ferramenta adjuvante para avaliação da margem cirúrgica em pacientes com carcinoma oral de células escamosas: um estudo comparativo

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ABSTRACT

Objective: The condition of the resected margin in oral squamous cell carcinoma continues to be an important prognostic factor; the use of optic technology could help surgeons in determining the margin status at real time. This study aims to evaluate Oral ID, a hand held device that uses the principal of auto-fluorescence to determine surgical safe margins in patients with oral squamous cell carcinoma, and to compare the results with those of the conventional 1 cm margin method. **Material and Methods:** This study was a descriptive, comparative analytical study carried out at Khartoum Dental Teaching Hospital and Oral Histopathology Diagnostic Laboratory, Faculty of Dentistry, University of Khartoum. A total of 92 margins obtained from 31 patients, 46 margins were taken by Oral ID and the other 46 were taken by the traditional 1cm method. All margins were examined histologically with conventional Hematoxylin and Eosin stain. **Results:** It was found that all tumors showed fluorescence loss; A significant association was found between the use of Oral ID and obtaining a free margin P (0.02) the sensitivity of Oral ID was found to be 74% the specificity was found to be 89%. Ten out of the 46 margins obtained by fluorescence showed mild dysplasia and two margins showed high grade dysplasia. The 46 margins obtained by the traditional 1cm margin showed different field alterations two were involved, one was close, five showed high grade dysplasia and 14 showed mild dysplasia yielding a specificity of 52.2%. **Conclusion:** Using Oral ID for surgical margin assessment increases the accuracy to 74% compared to the conventional method which was found to be 52.2%. The results of the device are comparable to other auto-fluorescence devices of different trademarks. Further development of the device to help overcome its limitations is strongly advised.

KEYWORDS

Oral ID; Auto-fluorescence; Cancer; Diagnosis; Oral squamous cell carcinoma.

RESUMO

Objetivo: A condição da margem ressecada no carcinoma oral de células escamosas continua sendo um importante fator prognóstico; o uso de tecnologia óptica pode ajudar cirurgiões a determinar o status da margem em tempo real. O objetivo deste estudo é avaliar o Oral ID, um aparelho portátil que utiliza o princípio da autofluorescência para determinar margens de segurança cirúrgicas em pacientes com carcinoma oral de células escamosas, e comparar os resultados com o método convencional de margem de 1 cm. **Material e Métodos:** Este estudo foi um estudo descritivo, analítico e comparativo realizado no Khartoum Dental Teaching Hospital e no Laboratório de Diagnóstico de Histopatologia Oral da Faculdade de Odontologia, Universidade de Khartoum. Um total de 92 margens foram obtidas de 31 pacientes, 46 margens foram obtidas por Oral ID e as outras 46 foram obtidas pelo método tradicional de 1 cm. Todas as margens foram examinadas histologicamente com coloração convencional de Hematoxilina e Eosina. **Resultados:** Verificou-se que todos os tumores apresentaram perda de fluorescência; uma associação significativa foi encontrada entre o uso de Oral ID e a obtenção de uma margem

livre P (0,02), a sensibilidade de Oral ID foi de 74% e a especificidade de 89%. Dez das 46 margens obtidas por fluorescência mostraram displasia leve e duas margens mostraram displasia de alto grau. As 46 margens obtidas pela margem tradicional de 1cm apresentaram diferentes alterações de campo, duas estavam envolvidas, uma estava próxima, cinco apresentaram displasia de alto grau e 14 apresentaram displasia leve com especificidade de 52,2%. **Conclusão:** O uso de Oral ID para avaliação da margem cirúrgica aumenta a acurácia para 74% em comparação com o método convencional, que foi encontrado em 52,2%. Os resultados do dispositivo são comparáveis a outros dispositivos de autofluorescência de diferentes marcas comerciais. O desenvolvimento do dispositivo para ajudar a superar suas limitações é fortemente recomendado.

PALAVRAS-CHAVE

Oral ID; Autofluorescência; Câncer; Diagnóstico; Carcinoma oral de células escamosas.

INTRODUCTION

Oral cancer is a major public health problem both in the Sudan and worldwide. Of all oral neoplasms squamous cell carcinoma is one of the most frequent tumors affecting the oral cavity. Recent studies have shown that more than 90% of malignant neoplasms affecting the oral cavity are of squamous cell carcinoma type [1,2]. In addition to the high prevalence of the disease; reports from local centers and worldwide indicate an ongoing increase in the incidence of the disease. The use of a local snuff "Toombak "and infection by HPV have shown to be the major causes of oral and orophararyngeal cancer in the Sudan [3-5]. The gold standard for the treatment of oral squamous cell carcinoma (OSCC) remains surgical excision with tumor free margins. The importance of obtaining free margins at surgery cannot be overemphasized as this directly affects the prognosis of the patient [6,7]; failing to do so will dramatically affect the rates of recurrence and survival [6-9]. It also exposes the patient to the hazards and complications of a second surgery or adjunctive therapy such as radiotherapy and chemotherapy, adding the burden of post therapeutic complications and extra cost on the patient.

A diagnostic aid to help the clinician to delineate surgical margins would be very useful [7,10]. Recent trials on using tissue auto-fluorescence as a sensitive method to detect surgical margins have been described in various tumors such as breast cancer (BC) and have shown accurate results [11,12]. Poh et al. [13] in Canada has used a similar device to detect field change around squamous cell carcinoma and found a positive correlation between loss of heterozygosity and fluorescence visualization loss. In this study we intended to investigate the ability of this method to delineate surgical margins at real time using a new auto-fluorescence device named Oral ID, a relatively cost effective device that detects cancerous and precancerous lesions by the principle of fluorescence [2,13]. Oral ID cancer screening device has gained the US food and drug administration clearance yet no studies on the general population have been carried out to assess the validity of this device. It uses a blue light with a wavelength (435-460nm) it is equipped with eyewear to use with the device [13]. The objective of this study was to investigate the value of Oral ID as an adjunctive tool to help delineate dysplastic changes around cancers and to calculate the sensitivity and specificity of the device in comparison to the traditional 1cm method and to other comparable auto-fluorescence hand held devices.

MATERIALS AND METHODS

Study sample

This is an observational, prospective, descriptive, comparative, cross sectional, analytical study conducted on thirty-one patients previously diagnosed with primary oral cancer that presented for treatment in Khartoum Dental Teaching Hospital. The patients were accrued to participate in the study that took place between July 2016 to June 2018 eligibility criteria included the presence of primary oral squamous cell carcinoma T1-T4.

Ethical considerations and confidentiality protection

All records were highly secured. The approval for the performance of the study was obtained from the Ethics Committee of the Postgraduate Medical & the Board of the Faculty of Dentistry University of Khartoum. Information was treated

with confidentiality, and no patient name was used, only the serial number. The purpose of the study was explained to all participants and an informed consent was obtained from all participants, except one eight-year-old participant, were the consent was obtained from the mother of the patient.

Oral ID device

Is a portable, battery operated, hand held device manufactured by forward science company a privately held biotechnology company based in Houstan, Texas. The device requires no consumables and has the additional advantage of not needing to rinse the mouth with a dye, like traditional devices. The device was designed to be used for screening of the oral mucosa it emits a blue light (435-460nm), the kit includes two pair of eyewear with filtered yellow lenses that allows the passage of green red autofluorescence; when illuminated with the device normal mucosa appears green and this is termed fluorescence visualization retained while abnormal dysplastic and cancerous mucosa looses the ability to retain the normal green appearance under fluorescence light and appears as dark patches and is termed fluorescence visualization loss [14,15].

Method

Surgical site assessment

- The Tumor surgical site was first assessed under operating room illumination and the lesion was documented using a digital camera (Sony Cybershot 20.1 megapixels, Model Name: DSC-W830, optical zoom ×8 with filter);
- The margins of the tumor were demarcated using a surgical marker 1cm away from the clinical tumor as judged by the surgeon. For T1 –T2 tumors anterior, posterior superior and inferior mucosal margins were used. For T3-T4 tumors only one mucosal margin was used for reasons of convenience in manipulation. Deep margins were not included in the study because bleeding affects the ability of the tissues to absorb light and therefore may give false results in addition to the relatively shallow penetration depth of the autofluorescence devices [16];
- Lights in the operating room were turned off;
- The surgical site of the tumor and the margin were examined using direct fluorescence visualization;
- The normal anatomic contralateral side was examined as a control due to the variation in the oral cavity fluorescence imaging characteristics that differ widely from one site to another [17]. If the area of the 1 cm surgical margin showed fluorescence loss the margin was extended into the fluorescence visualization retained area; on the other hand if the margin retained the normal fluorescence, the 1cm margin was considered sufficient;
- The lights were turned back on and the distance between the conventional 1cm tumor margin and the fluorescence margin was ascertained using a flexible ruler;
- The tumor was surgically resected according to the furthest margin (1cm vs fluorescence) and fixed in 10% buffered formalin and submitted to the Oral Pathology Lab in University of Khartoum;
- All steps were photographed for documentation;
- All procedures were done while the patient was under general anesthesia.

Histological assessment

One biopsy was taken from each margin. The margins obtained by fluorescence were marked with green ink while traditional margins were marked with blue ink. The margins were stained with routine H&E stain for histological examination. Each slide was evaluated by two investigators. The second investigator was not aware of the fluorescence status to reduce bias. The margins were treated according to the guidelines issued by the UK Royal College of Pathologists that consider distance from invasive carcinoma of 5mmor more away as free;1-5 as close, less than 1mm was considered involved [18]. Margins were considered clear when they contained no evidence of invasion or dysplasia otherwise they were considered involved. Histological differentiation of the tumor was recorded by the histopathologist using WHO grading system. Dysplasia was graded using the binary system that recognizes low grade and high grade dysplasia only to reduce bias. The pathologist attended each operation, and the

margins were marked in the operating theatre to insure accuracy of margin delineation.

Statistical assessment

Differences and associations were examined using chi square test for categorical variables. Descriptive statistics was used for frequencies. All tests were two-sided. $P < 0.05$ was considered to be statistically significant. Data was entered into computer master-sheet SPSS for window version 20.0.

RESULTS

During a period of two years 31 patients diagnosed with oral squamous cell carcinoma attending Khartoum Dental Teaching Hospital were included in this study. 58% of the participants were male with a mean age of 54 (Figures 1 and 2). Of the 31 cases included in this study 11 tumors were well differentiated (35.5%), 16 tumors were moderately differentiated (51.6%) 4 tumors were poorly differentiated (12.9%) with no previous history of chemotherapy and radiotherapy patients with recurrent disease were excluded from the study (Figure 3). 58% of the patients participating in the study were males with a mean age of 54 the most common affected sites were the tongue, the buccal mucosa and the gingiva which all showed an equal percentage of incidence at 25.8% (Figure 4). Twenty seven percent of the patients were toombak dippers and 6% were smokers whilst the majority did not admit any habits (Table I).

Table I - Distribution of cases according to habits

	Frequency	Percent
toombak dipping	7	22.6
toombak dipping + Smoking	1	3.2
toombak dipping + Smoking +Alcohol	1	3.2
toombak dipping+ Alcohol	1	3.2
smoking	1	3.2
none	20	64.5
Total	31	100.0

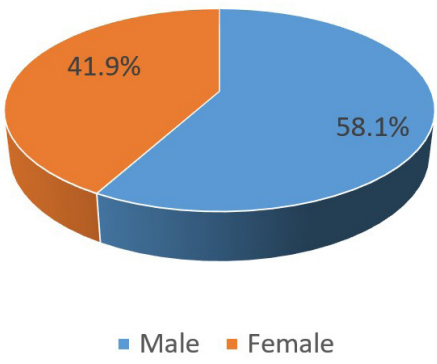


Figure 1 - Distribution of cases according to gender.

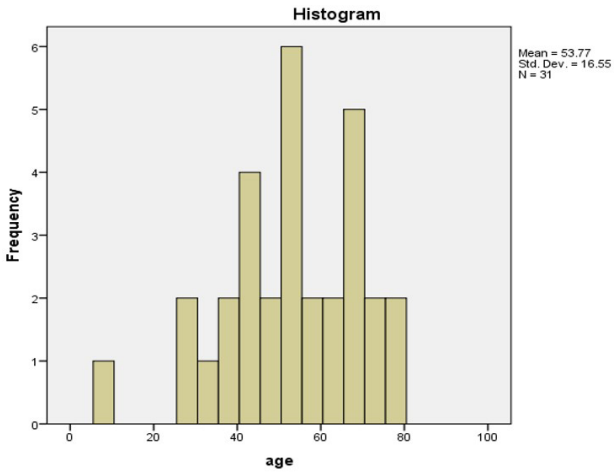


Figure 2 - Age of patients (8-80) with a mean 54 years (n=31).

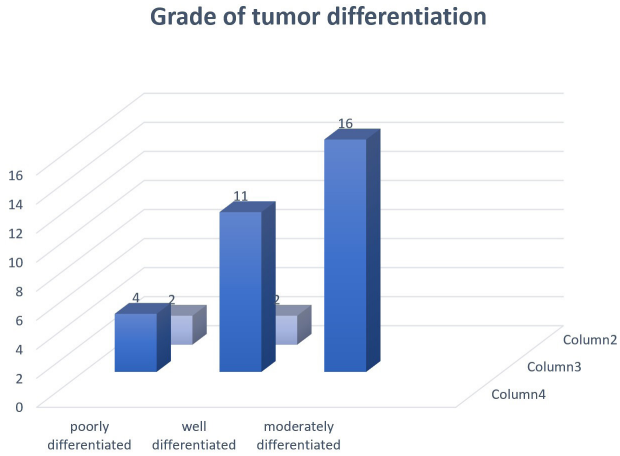


Figure 3 - Grade of tumor differentiation.

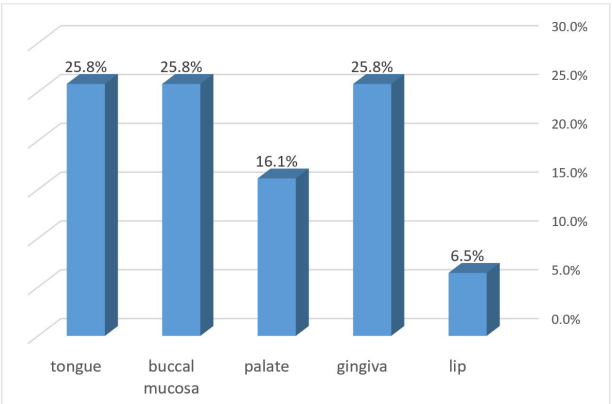


Figure 4 - Site of distribution in the oral cavity.

Table II - Field alteration at the margin

Margin histology		free	involved	close	dysplasia at the margin	Total
Fluorescence margin	Count	34	0	0	12	46
	%	73.9%	0.0%	0.0%	26.1%	100.0%
Traditional 1cm margin	Count	24	1	2	19	46
	%	52.2%	2.2%	4.3%	41.3%	100.0%
Total	Count	58	1	2	31	92
	%	63.0%	1.1%	2.2%	33.7%	100.0%

Table III - Dysplasia at the margin

		high grade dysplasia	low grade dysplasia	Total
1cm margin	Count	8	14	22
	%	36.4%	63.6%	100.0%
Oral ID	Count	2	10	12
	%	16.7%	83.3%	100.0%
Total	Count	10	24	34
	%	29.4%	70.6%	100.0%

The sample was selected conveniently. A total of 92 margins were obtained from the patient samples; 46 margins were obtained by fluorescence and the remaining 46 margins were obtained by the traditional method. The samples were conventionally processed and examined histologically by H&E. The mean distance of fluorescence margin in this study was 1.2cm with a standard deviation of 0.2cm with the highest value being 1.5cm and the lowest value being 1cm. All examined tumors showed fluorescence loss. Thirty-four out of the 46 margins obtained by fluorescence were clear of alteration or tumor, yielding a sensitivity of (74%). No margins were involved and none were close, twelve margins showed dysplasia (26%), only two of them (4%) showed high grade dysplasia. On the other hand, 24 (52%) of the margins obtained by the traditional method were free, 2 margins were involved **(**4.3%) and one margin was close (2.2%). Nineteen out of the 46 margins taken by the traditional method were dysplastic (41.3%), 8 of the dysplastic lesions (17.4%) were high grade dysplasia (Table II). In forty-four percent of the cases the fluorescence margin was equal to traditional method.

There was a significant association between the use of fluorescence and obtaining a free margin ($Z = 2.213$, P-Value = 0.027). The sensitivity of Oral ID in this study was approximately 74% whereas the specificity for Oral ID was found to be 89% (Table II).

The device detected five false positives out of the total number margins taken by fluorescence 46, yielding a specificity of 89%. We compared the percentage of high grade lesions (carcinoma, carcinoma in situ (CIS), high grade dysplasia) out of the total amount of involved margins in both the margins obtained by Oral ID and the traditional method we found the amount of high grade dysplasia's at the traditional method to be 36.4% compared 16.7% for the Oral ID (Table III).

DISCUSSION

Oral ID is a hand held, optical device that detects tissue auto-fluorescence. It was manufactured by Forward Science Technology Company. Autofluorescence originates from a variety of fluorophores in the oral cavity. Fluorophores are components of the tissue which absorb light at a particular wave length and re-emit this light at a longer one. The three main fluorophores that react with light are collagen, elastin and Flavin adenine dinucleotide (FAD) a coenzyme involved in cellular metabolism. During carcinogenesis the intensity of tissue fluorescence is reduced due to the altered state of these fluorophores [16].Various methods have been used to delineate and assess surgical margins. Traditionally thickness of surgical margins both clinically and histologically has been regarded as a major method for assessment, where clinical

margins are about 1-1.5cm whereas The prognostic value of clinical margin is still controversial .Pathological margins of 5mm are considered involved and tend to show better prognostic value than clinical margins although no universal agreement on this has been reached [7,19]. Another drawback of surgical margin thickness is that it is an operator dependent procedure related to the experience of the surgeon [20].

A second technique is the use of histology which for a long time has been considered the gold standard for surgical margin assessment but histology remains time consuming, and is affected by the sampling technique [9,21]. Furthermore studies concluded that local recurrence occurs in up to half of the patients with microscopically negative surgical margins.

Frozen section analysis is also a technique that has long been used for surgical margin assessment, it is a valuable intraoperative guide in the management of SCC; as it helps to make important decisions that may prevent surgical re-intervention, or postoperative therapy [7]. But according to Olson et al. [23] its main disadvantage is that it is an expensive technique that requires extensive machinery such as cryostat and special microtomes to be available and also to some degree depends on the sampling technique of the pathologist [7,22].

Iodine has been recently introduced as a promising method for intraoperative surgical margin assessment.

The principle of iodine is that it depends on the detection of glycogen content of the normal epithelial cells. This glycogen content is altered in cases of dysplasia and malignancy; so normal epithelium takes iodine stain whereas dysplastic epithelium fails to do so [24,25]. In 2013 Nomura and Shibahara from Japan investigated the correlation between the iodine unstained (IU) area and the malignant potentiality of the lesion by examining the Existence of glycogen using PAS and correlated that with the expression of P53 and proliferative cellular nuclear antigen(PCNA). They concluded that the IU areas surrounding the OSCC showed various degrees of dysplasia. This correlated with the decrease in glycogen content as noted by PAS and increased expression of PCNA and p53 [25].

But iodine isn't without its drawbacks such as the fact that it is difficult to detect clear margins with IU areas; in addition to this, certain areas in the oral cavity such as the gingiva and the hard palate, which have keratinized epithelium were less reactive to iodine than other sites in the oral cavity; areas of chronic inflammation were found to be less reactive to iodine. Some patients also reported hypersensitivity to iodine [25,26]

The usefulness of auto-fluorescence in detecting oral potentially malignant disorders in primary care setting has been well described in the literature by many authors such as Farah et al. [27,28]. In this study we intended to evaluate the usefulness of the device to help surgeons taking critical decisions at real time. This is very important as the literature states that high grade dysplasia at the mucosal margins correlates positively with secondary tumors and local recurrences [29]. The device was used to evaluate surgical margins and the results were compared to those of the traditional method. This study was carried out on a sample of 31 patients all of whom were operated on by a single surgeon to limit confounding factors (Figures 5, 6 and 7).

The most common habit reported amongst the patients in this series was toombak dipping as ten patients (32.2%) reported the use of toombak (Table I). This fact adds to the cumulative evidence and findings about the relation between toombak and cancer; indicating the need for a national strategic plan to help condemn and eliminate its use [3,5,30].

In the present study, the mean distance of extension of fluorescence loss beyond clinically visible tumors was found to be 1.2 cm with a standard deviation of 0.2cm. The study of Poh et al. [13] in 2016 found a mean distance of 1.3cm with a standard deviation of 0.57cm. This finding indicates that the use of the traditional 1 cm method is not sufficient to eradicate disease. The findings of Poh et al. [13] supports this, as they have stated that if the traditional technique was used in their study; half of the margins would have cancer or dysplasia.

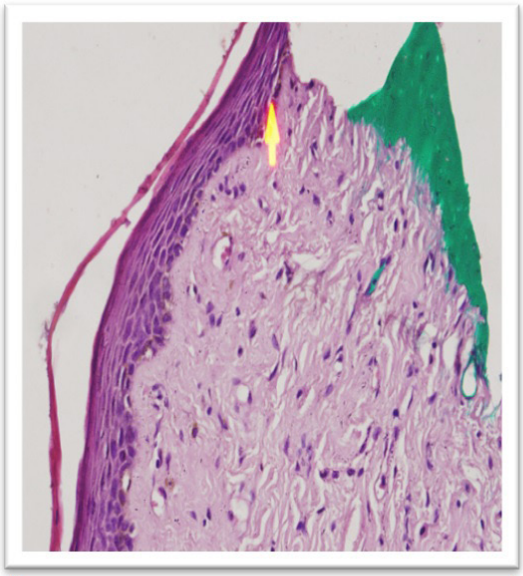
In forty-four percent of the cases the fluorescence margin was equal to 1cm. These findings are very different from those of Poh et al. [13] where only 1 out of 66 margins obtained by fluorescence showed dysplasia yielding a sensitivity of 98% [13]. Certainly differences in the results of the two studies can be attributed to the differences in the criteria of inclusion of patients; as Poh et al. [13]



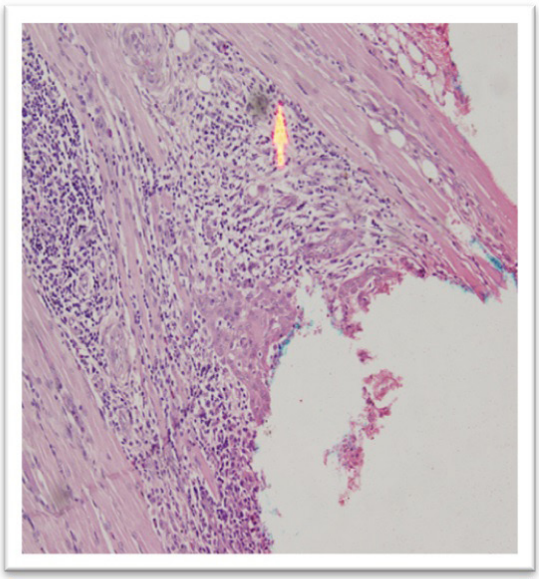
A: Preoperative picture with initial assessment under white light showing ill-defined squamous cell carcinoma surgical margin delineated 1cm away from the tumor.



B: Picture of patient under fluorescence light showing loss of fluorescence at the margin, initial surgical margin marked in blue the margin was increased by 0.4cm to include the area of fluorescence loss new margin marked in green.



C: high power view H&E stain Fluorescence margin free with no evidence of tumor or dysplasia.



D: high power view H&E stain Conventional 1cm margin involved showing tumor nest at the margin.

Figure 5 - A: Preoperative picture with initial assessment under white light showing ill-defined squamous cell carcinomasurgical margin delineated 1 cm away from the tumor; **B:** Picture of patient under fluorescence light showing loss of fluorescence at the margin, initial surgical margin marked in blue the margin was increased by 0.4 cm to include the area of fluorescence loss new margin marked in green; **C:** high power view H&E stain Fluorescence margin free with no evidence of tumor or dysplasia; **D:** high power view H&E stain Conventional 1 cm margin involved showing tumor nest at the margin.

restricted their study to T1-T2 lesions only. The literature also states that the penetration depth of auto-fluorescence illumination is relatively shallow, and is therefore best used to evaluate superficial margins [31]. Accessibility of the tumor also affects the results as the boundaries of posterior tumors are very difficult to delineate. Fluorescence qualities also differ from site to site, and the best results were obtained when the device was used on the tongue and gingiva.

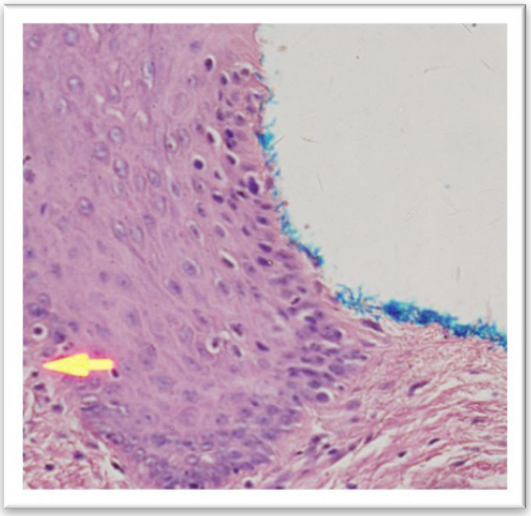
Awan et al. [32] in their study which used a similar device found a sensitivity of 84% and a specificity as low as 15% but Awan et als' study was conducted to evaluate the device as a screening tool which could explain the relatively higher sensitivity very low specificity found in his study [25,32]. Chenzhou Wu et al. [31] in China 2018 meta-analysis on in-vivo optical imaging in the head and neck that included 12 different studies in their research found the mean sensitivity and specificity for auto-fluorescence



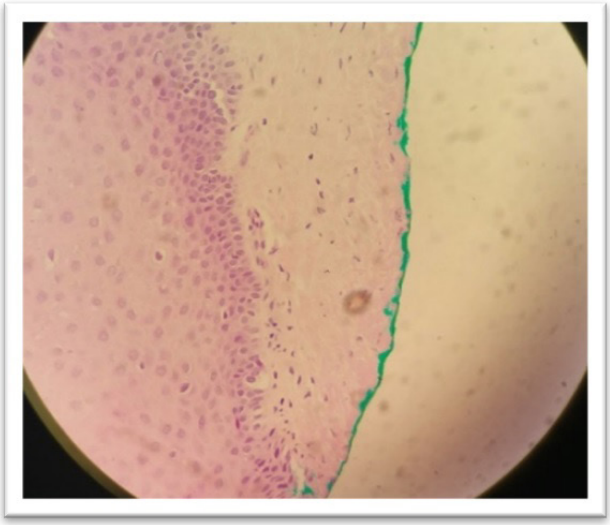
A: Preoperative picture with initial assessment under white light Traditional margin



B: Picture of patient under fluorescence light Fluorescence margin 1.3 cm



C: H&E stain High power view of traditional margin margin showing high grade dysplasia



D: H&E stain High power view of fluorescence margin free

Figure 6 - A: Preoperative picture with initial assessment under white light Traditional margin; **B:** Picture of patient under fluorescence light Fluorescence margin 1.3 cm; **C:** H&E stain High power view of traditional margin margin showing high grade dysplasia; **D:** H&E stain High power view of fluorescence margin free.

devices to be 72.4% and 63.79%, respectively. The sensitivity of the present study was within the range of study which was found to be from 20% to 100% and the specificity ranged from 15.3% to 100%.

The low level of specificity in the meta-analysis can be explained by the fact that most of studies included in the analysis were conducted to evaluate the device as a screening tool. Lane at al. conducted a pilot study on 44 patients using histology as the gold standard, the device achieved a sensitivity of 98% and specificity of 100% when discriminating normal mucosa from severe dysplasia/carcinoma in situ (CIS) or invasive carcinoma [33]. In the present study, the ability of Oral ID to discriminate high grade lesions from normal mucosa was approximately 96% (Table IV).

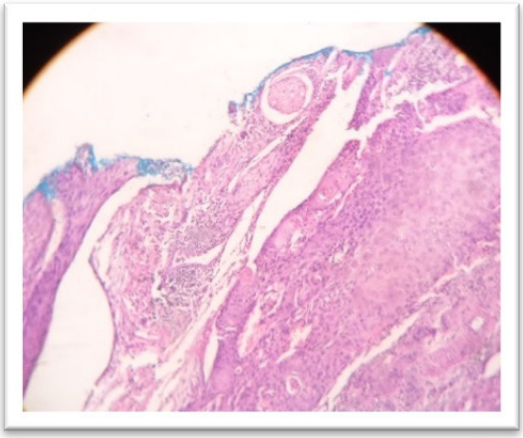
A significant association between the use of fluorescence and obtaining a free margin was found in this study, with a P value of (0.02). Poh et al. [13] in 2006 showed that there was



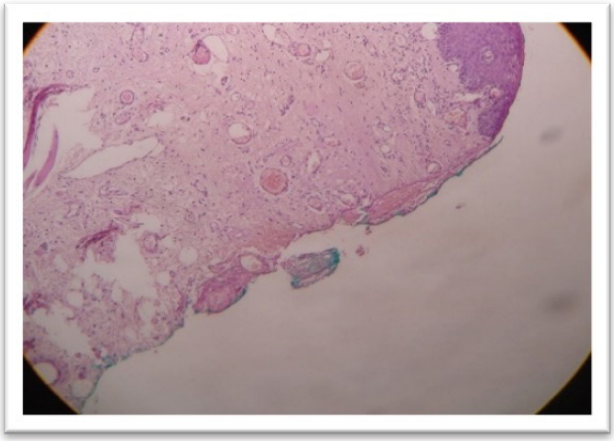
A: Preoperative picture with initial assessment under white light 1 cm surgical margin



B: Picture of patient under fluorescence light traditional margin contained dark patches, margin was extended 0.5cm Fluorescence margin 1.5 cm



C: H&E stain 1 cm surgical margin high power view showing tumor at the margin (Involved)



D: H&E stain Fluorescence margin free

Figure 7 - A: Preoperative picture with initial assessment under white light 1 cm surgical margin; **B:** Picture of patient under fluorescence light traditional margin contained dark patches, margin was extended 0.5 cm Fluorescence margin 1.5 cm; **C:** H&E stain 1 cm surgical margin high power view showing tumor at the margin (Involved); **D:** H&E stain low power view Fluorescence margin free

Table IV - Ability to discriminate high grade lesions from normal mucosa

Ability to discriminate high grade lesions from normal mucosa		
1cm margin	Count	38
	Percentage	82%
Oral ID	Count	44
	Percentage	96%

a significant association between the areas of (FVL) and (LOH) even in histologically clear margins with a P value of (0.04); from the above findings one can speculate that if molecular studies were performed in this study a significant difference in (LOH) between the fluorescence and conventional one cm margin would have likely been found

Oral ID has given relatively good results as it was able to increase the sensitivity of the traditional 1cm margin from (52.2%) to approximately (74%) achieving a (21.8%) improvement in sensitivity Table III, it also has a high ability in distinguishing high grade lesions and invasive carcinoma from normal mucosa (Table IV) and does not require consumables so no per patient cost; the device itself is of medium cost, which makes it relatively economic (compared to other similar commercial products); it is easily disinfected, portable and allows the detection of a big number of lesions.

The strengths of the study were that it was restricted to a single operator to reduce confounding factors as much as possible. Two operators decided the area of fluorescence loss to reduce subjectivity. To the best of the investigators knowledge no studies have been carried out on Oral ID in particular.

On the other hand the limitations are; the contrast between normal and abnormal is not always clear, suggesting the need for intensifying screens or adjustment of the wavelength of the light to increase the contrast [31]. Interpreting the fluorescence findings is highly subjective, and depends on the experience of the operator which jeopardizes the reproducibility of the results. Keratin is auto-fluorescent so hyper-keratinized areas may not show loss of fluorescence even in the presence of dysplastic lesion which also serves as a source of decreased accuracy [24]. The device only assesses lateral spread of cancer and cannot assess the depth of cancer extension. Another limitation was that fluorescence diascopy was not used in this study. The study strongly recommends a multicenter double blind experimental clinical trial a with larger sample size and follow up of the operated patients is also recommended to correctly assess the accuracy of the device. We also recommend molecular studies and IHC staining on low risk margins of both Oral ID and 1cm margins for proper risk assessment.

CONCLUSION

- Using the principal of fluorescence gave an accuracy of 74% whereas the conventional method gave an accuracy of 52%. Thus this method is more sensitive and specific in detecting field change in surgical margins;
- Oral ID can help delineate dysplastic changes around cancerous lesions;
- The device may be useful in taking intraoperative decisions but should not by any means be considered a substitute for traditional histology;
- The results obtained with Oral ID device are comparable to results obtained by other auto-fluorescence devices with different tradenames.

Acknowledgments

First and foremost I would like to acknowledge the blessings and support of Allah the almighty who enabled me to complete this research and whom without him the completion of the research would have been an impossible task. I would also like to express my sincere gratefulness and gratitude to my Supervisor, Professor Ahmed Mohammed Suleiman for his continuous support, guidance, valuable advice and useful critics that have actively contributed to this research. A special thanks to Professor Ali Abdalsatir who introduced me to the principles of surgical histopathology practice; his willingness to give his time so generously has been much appreciated I would like to also mention Karary University for their endless support during this postgraduate study. It gives me great pleasure to express my appreciation to my consultant pathologist Dr. Neimat Mohammed for teaching me the necessary skills to be a successful pathologist. I would also like to acknowledge the great help, support and sustainable presence of Dr. Nazik Omer Albasheer and Dr. Amal Sahnoon I would like to thank all my colleagues in the department of Oral Pathology University of Khartoum especially Dr. Mohamed Abdallah, Dr. Omar Abdoun and Dr. Najla Ahmed Abdalmalik for their helpful advice and material that made part of this research. I would also like to thank the staff of Khartoum Dental Teaching Hospital for their kind help and support. And last but not by any means least; I would like to express my unlimited gratefulness to my family, especially mentioning my parents who made me what I am today; and my dear sister Sarah Abdullah for her social help, encouragement and understanding.

Conflict of Interest

The authors whose names are listed certify that they have no affiliations or involvement in any organization with financial interest in the subject discussed in the manuscript.

Funding

None.

Regulatory Statement

Ethical Considerations Confidentiality Protection: All records were highly secured. Institutional Ethical Clearance: The approval for the performance of the study was obtained from the Ethics Committee of the Postgraduate Medical & the Board of the Faculty of Dentistry.

Information was treated with confidentiality, and no patient name was used, only the serial number. Participants were given informed written consent and the purpose of the study was explained.

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Date submitted: 2021 March 13
Accept submission: 2021 May 25