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**ORIGINAL ARTICLE** 

# **Shaping the Future of Oral Cancer Prevention in Yemen: Knowledge and Attitudes of Dental Students**

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#### **ABSTRACT**

**Background**: Oral cancer is a significant public health issue globally, with over 300,000 new cases diagnosed annually. In Yemen, oral cancer is particularly prevalent, exacerbated by cultural practices such as the consumption of shammah (smokeless tobacco) and qat (a stimulant).

**Objective:** This study aimed to assess the knowledge and attitudes of Yemeni dental students concerning oral cancer, with the aim of identifying knowledge gaps and proposing strategies to improve oral cancer care in Yemen.

**Method**: A cross-sectional multicenter survey was conducted among dental students from multiple universities across Yemen. A structured questionnaire was designed to assess participants' knowledge of oral cancer risk factors, clinical manifestations, diagnostic methods, treatment options, and their attitudes toward patient education and prevention. A total of 247 dental students participated in the study. Descriptive statistics were used to analyze demographic data and survey responses, while chi-square tests assessed associations between demographic factors and knowledge levels.

**Results**: The majority of participants (93.1%) were aged between 20 and 29 years, and 64.8% were female. A significant knowledge gap was observed, with 84.2% of respondents unable to accurately identify oral cancer risk factors and 84.8% failing to recognize its clinical symptoms. Although 64% of participants agreed on the importance of annual screenings, only 22.3% demonstrated knowledge of diagnostic tools. Younger students with 0–5 years of experience exhibited better knowledge of risk factors and treatment options than their more experienced counterparts. Gender differences were marginal, with men showing slightly higher awareness of risk factors (p=0.022). A strong consensus (87.9%) emerged regarding the importance of patient education and counseling in oral cancer prevention.

**Conclusion**: This study highlights critical gaps in the knowledge and awareness of oral cancer among Yemeni dental students, particularly in risk factors, clinical signs, and diagnostic methods. While there is a clear recognition of the importance of patient education, the limited knowledge of diagnostic tools and clinical features suggests the need for enhanced training and continuous education.

**Keywords:** Oral Cancer, Dental Students, Knowledge Gaps, Prevention, Early Detection, Yemen, Risk Factors, Patient Education, Screening, Diagnostic Methods.

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## INTRODUCTION

More than 300,000 new cases of oral cancer are reported worldwide each year, making it a significant global health concern (1). Oral cancers continue to be a major obstacle in many places, particularly in lower- and middle-income nations, as they are associated with high-risk behaviors including drinking alcohol and tobacco, as well as using betel quid (2). Yemen is another country where mouth cancer is becoming more prevalent for its citizens. The problem is exacerbated by a poor healthcare system, ignorance, and a large number of risk factors, necessitating immediate diagnosis and treatment (3-5).

According to research, oral cancer is one of the most common tumors in Yemen and makes up a sizable portion of all cancer cases (6). Contributing factors include the extensive use of smokeless tobacco products like Shammah and chewing qat, two deeply ingrained cultural practices that have been connected to cancer (7). On the other hand, there is a noticeable lack of comprehensive data about the occurrence, prevalence, and outcomes of oral cancer in Yemen, which is a result of shortcomings in both research and healthcare delivery (8).

The five-year survival rate of 80% indicates that early detection of oral cancer significantly improves survival rates. However, due to limited access to diagnostic facilities and a lack of awareness among the general public and medical professionals, late-stage diagnosis is still common in Yemen. Because of their capacity to identify risk factors, identify early symptoms, and educate patients—all of which can directly affect the efficacy and efficiency of management—healthcare professionals are essential to reversing the current trend (9).

Previous Yemeni research suggests that medical personnel may lack proper training and knowledge about oral cancer. This includes not knowing about risk factors like qat and shammah, not using diagnostic tools enough, and having trouble identifying early clinical indications. Cultural and logistical challenges to patient education further limit preventative efforts (8).

Due to cultural influences, financial circumstances, and healthcare accessibility, oral cancer awareness differs greatly throughout regions. It is essential to carry out thorough research in a variety of contexts in order to develop a sophisticated understanding of

knowledge gaps, pinpoint particular obstacles to early diagnosis, and modify interventions appropriately. This strategy will guarantee that management and prevention tactics are successful and suitable for each region's culture, which will ultimately improve oral cancer outcomes worldwide (10).

According to a study conducted in Nepal with dental surgeons and undergraduate students from three different universities, there were knowledge gaps about certain aspects of oral cancer. The findings demonstrated that the undergraduate dental curriculum has to be enhanced in order to address these issues (11).

According to a study in Brazil that evaluated dentistry students' knowledge, just 48.12% of them correctly identified squamous cell carcinoma as the most prevalent type of oral cancer, even though they were aware of important risk factors like smoking (92.48%) and alcohol intake (84.21%). Furthermore, 57.89% of respondents said ulcers were the most common clinical appearance, and 53.38% said the tongue was the most affected anatomical location. These results point to the need for better instruction regarding the clinical features of oral cancer (12).

Research conducted at Saudi Arabia's Khatam Al-Nabieen University found that while a significant proportion of dental students and interns identified smoking and tobacco chewing as causes of oral cancer, there were notable gaps in knowledge regarding other risk factors and clinical presentations. This emphasizes the need for enhanced educational efforts in this area (13).

Different dentistry students' degrees of awareness of oral cancer were found in a survey. The study that was conducted in India made clear how important dental students are to prevention and early diagnosis, and it suggested that more training and awareness campaigns could lead to better results (14).

Collectively, these studies indicate that while dental students are generally aware of major risk factors for oral cancer, there are consistent gaps in knowledge regarding clinical presentations, less common risk factors, and early detection practices. Addressing these gaps through enhanced educational curricula and targeted training is essential to empower future dental professionals in the fight against oral cancer. According to a 2015 study, oral cancer education—particularly in the areas of prevention and early





detection—needs to be strengthened in the undergraduate dental curriculum (15).

Recently, according to the study conducted in Yemen, there are notable discrepancies in Yemeni senior dental students' understanding, attitudes, and practices about oral cancer. The results also highlight how urgently undergraduate dentistry students' OC instruction and training must be improved and how dental professionals should have access to regular, well-organized continuing professional development opportunities (8).

This study aims to build upon previous research conducted in Yemen by expanding the scope of investigation to include undergraduate dental students from universities not previously examined, in addition to postgraduate students. This broader approach will provide a more generalized and comprehensive understanding of oral cancer knowledge and awareness among dental students across different levels of training and institutions in Yemen.

## METHODOLOGY

## **Study Design**

A cross-sectional multicenter survey approach was used to evaluate Yemeni undergraduate and graduate dental students' knowledge, attitudes, and behaviors about oral cancer. It was necessary to assess their attitudes toward patient education and prevention as well as their understanding of risk factors, clinical symptoms, diagnostic techniques, and available treatments.

# **Sample Size Calculation**

 $n = Z^2 \times p \times (1-p) / d^2$ Where:

- n = required sample size
- Z = Z-value (e.g., 1.96 for 95% confidence level)
- p = estimated proportion of the attribute present in the population
- d = margin of error, typically 0.05 (5%).

Since there's no prior study on this topic in Yemen, we can assume:

- p=0.5 (maximum variability  $\rightarrow$  gives the largest sample size)
- Z=1.96 (for 95% confidence)
- d=0.05 (5% margin of error)

 $n = (1.96)^2 \times 0.5 \times (1-0.5) / (0.05)^2 = 384.16$ 

As the approximate total number of dental students (N) in the 8 universities is 1000, the finite population correction:

$$n \text{ adj} = n / 1 + (n-1 / N)$$

Suppose the total number of eligible students is 1000, then:

n adj=384 / 1+ (383-1000) ≈ 277.6 $\Rightarrow$  278 students.

## **Study Population**

The target population consisted of dental students from various Yemeni universities located in various regions. Participating institutions were selected to ensure a representative and diverse sample of Yemen's dental education environment. The universities included:

- University of Science and Technology (UST)—Aden, Taiz, and Hadhramaut campuses.
- Aden University.
- Al-Reyada University
- Taiz University.
- National University.
- Aljanad University.
- Al-Saeed University.
- Al-Arab University

#### **Inclusion Criteria**

Enrollment as an undergraduate or postgraduate dental student in one of the participating universities. Consent to participate in the study.

# **Exclusion Criteria**

Students from non-dental programs or disciplines. Incomplete responses to the survey questionnaire.

## **Data Collection Tool**

Data-Gathering Instrument: A structured questionnaire was developed in order to gather data. The multiple-choice and Likert-scale questions on the questionnaire were divided into the following sections:

Demographics include age, gender, years of experience, and professional background.

Assessment of knowledge: inquiries about oral cancer symptoms, risk factors, diagnosis techniques, and available therapies.

Attitudes: Opinions about the importance of early detection, patient education, and routine screenings.





The questionnaire was tested in a pilot study with 20 participants to ensure its reliability and clarity. In response to the feedback, modifications were made.

#### **Data Collection Procedure**

The survey was administered both online and in person, depending on participant accessibility. Participation was completely voluntary, and each respondent provided their informed consent. The survey was given two months of time to ensure enough representation from different Yemeni Universities. A total of 247 respondents participated, representing a diverse range of age groups, genders, and years of experience.

## **Data Analysis**

A statistical analysis program (SPSS, Version 26) was used to process the data. Demographic information and answers to attitude, and knowledge questions were compiled using descriptive statistics, such as frequencies and percentages.

Chi-square tests were employed for inferential analysis in order to ascertain the relationships between knowledge, attitudes, and demographic characteristics (such as gender and years of experience). Statistical significance was defined as a p-value of less than 0.05.

#### **Ethical Considerations**

An established institutional ethics council in Yemen granted ethical approval of this study. Every participant was made aware of the study's objectives, and to maintain confidentiality, their answers were anonymized. At any point during the trial, participants could opt out without facing any consequences.

# **RESULTS**

In regard to demographic data, the age distribution of those aged 20 to 29 made up the largest percentage

of responders (93.1%), with smaller percentages in other age groups. On the other hand, compared to male respondents (35.2%), female respondents made up a significantly larger percentage (64.8%). Regarding years of experience, the bulk of participants (75.7%) had 0–5 years of experience, whereas fewer respondents were in higher experience groups (Table 1).

Knowledge Gaps: The data shows that there are substantial gaps in most areas of knowledge, particularly with regard to risk factors, clinical symptoms, diagnostic methods, and available treatments. This implies that the respondents might not be well informed about the important facets of oral cancer (Table 2).

Considerable Knowledge of Education: One noteworthy exception is the high level of knowledge on patient education and counseling, as most respondents acknowledge its significance in preventing oral cancer (Table 2).

Significant Associations: The differences between true and false answers are statistically significant and not the result of chance, since all of the p-values fall below the usual significance threshold of 0.05. This emphasizes the necessity of additional training and awareness-raising initiatives to fill in the knowledge gaps, especially with regard to clinical symptoms, risk factors, and diagnostic instruments (Table 2).

Perhaps as a result of more recent and targeted training, the data shows that professionals with less experience (0–5 years) typically do better in recognizing risk factors, common clinical symptoms of OPMDs, and treatment alternatives. Nonetheless, there are no appreciable variations in understanding of clinical signs of oral cancer, early diagnosis, suspicious lesions, diagnostic instruments, and patient education, indicating that these ideas are generally well understood by people with all levels of expertise (Table 3).

**Table 1:** Demographic Distribution of Study Participants by Age, Gender, and Years of Experience

Variable	Category	Count	Percentage (%)		
Age	20-29	230	93.1%		
	30-39	15	6.1%		
	40-49	2	0.8%		
	50-59	0	0.0%		
Total (Age)		247	100%		
Gender	Male (m)	87	35.2%		





Female (f)	160	64.8%
	247	100%
0-5	187	75.7%
6-10	24	9.7%
11-15	5	2.0%
16-20	14	5.7%
+20	17	6.9%
	247	100%
	6-10 11-15 16-20	247       0-5     187       6-10     24       11-15     5       16-20     14       +20     17

Table 2: Statistical Analysis of Respondents' Knowledge on Oral Cancer

Variable	True Answer	False Answer	Total (%)	P-value	Statistical Significance
Risk Factors	39 (15.8%)	208 (84.2%)	100%	5.72e- 27	Significant
Clinical Manifestation of Oral Cancer	35 (14.2%)	212 (85.8%)	100%	2.02e- 29	Significant
Early Detection (Routine Screenings)	158 (64.0%)	89 (36.0%)	100%	1.13e- 05	Significant
Suspicious Lesions (2-3 weeks)	74 (30.0%)	173 (70.0%)	100%	2.99e- 10	Significant
Common Clinical Features of OPMDs	190 (76.9%)	57 (23.1%)	100%	2.62e- 17	Significant
Highest Malignant Transformation Rate	55 (22.3%)	192 (77.7%)	100%	2.85e- 18	Significant
Diagnostic Tools	55 (22.3%)	192 (77.7%)	100%	2.85e- 18	Significant
Patient Education and Counseling	217 (87.9%)	30 (12.1%)	100%	1.20e- 32	Significant
Common Treatment Options	55 (22.3%)	192 (77.7%)	100%	2.85e- 18	Significant

**Table 3**: Distribution of Responses by Years of Experience on Oral Cancer Knowledge, and Risk Factors

Variable	Years of	0-5	6-10	11-	16-20	+20	Total	P-	Statistical
	Experience	(%)	(%)	15 (%)	(%)	(%)	(%)	value	Significance
Risk Factors	True Answer	61.5%	23.1%	7.7%	5.1%	2.6%	100%	0.001	Significant
	False Answer	78.4%	7.2%	1.0%	5.8%	7.7%	100%		
Clinical Manifestation of Oral Cancer	True Answer	77.1%	17.1%	0.0%	5.7%	0.0%	100%	0.202	Not Significant
	False Answer	75.5%	8.5%	2.4%	5.7%	8.0%	100%		
Early Detection (Annual Screenings)		77.2%	9.5%	1.3%	6.3%	5.7%	100%	0.304	Not Significant





Suspicious Lesions (2-3 weeks)	True Answer	78.4%	9.5%	0.0%	9.5%	2.7%	100%	0.107	Not Significant
	False Answer	74.6%	9.8%	2.9%	4.0%	8.7%	100%		
Common Clinical Features of OPMDs	True Answer	77.4%	10.5%	2.6%	5.8%	3.7%	100%	0.006	Significant
	False Answer	70.2%	7.0%	0.0%	5.3%	17.5%	100%		
Highest Malignant Transformation Rate	True Answer	70.9%	9.1%	5.5%	3.6%	10.9%	100%	0.162	Not Significant
	False Answer	77.1%	9.9%	1.0%	6.2%	5.7%	100%		
Diagnostic Tools	True Answer	74.5%	5.5%	3.6%	9.1%	7.3%	100%	0.445	Not Significant
	False Answer	76.0%	10.9%	1.6%	4.7%	6.8%	100%		
Patient Education and Counseling	True Answer	77.4%	10.1%	1.8%	5.1%	5.5%	100%	0.126	Not Significant
	False Answer	63.3%	6.7%	3.3%	10.0%	16.7%	100%		
Common Treatment Options	True Answer	69.1%	20.0%	1.8%	7.3%	1.8%	100%	0.026	Significant
	False Answer	77.6%	6.8%	2.1%	5.2%	8.3%	100%		

## **DISCUSSION**

The study's conclusions point to important knowledge and awareness gaps among students regarding oral cancer, oral potentially malignant disorders (OPMDs), and treatment options. These differences highlight the need for more successful educational programs to reduce the gap and expand early detection and population prevention strategies. This study was conducted across several universities in Yemen, including the University of Science and Technology (UST) campuses in Aden, Taiz, and Hadhramaut; Aden University; Al-Reada University; Taiz University; National University; Al-Ganad University; and Al-Saeed University. The inclusion of diverse academic institutions ensures a

broad representation of the student population, encompassing a mix of medical, dental, and general education disciplines. This diversity strengthens the study's findings and underscores the generalizability of the observed gaps in knowledge and awareness. Although there were minor gender-based variations in awareness, with men demonstrating a greater comprehension of risk variables (p=0.022), the general knowledge gap was present in both sexes. This implies that awareness of oral cancer is not significantly influenced by gender alone and that inclusive and universal teaching initiatives are necessary.

The results demonstrate a significant lack of knowledge regarding the risk factors (84.2% incorrect answers), clinical manifestations (85.8%)





incorrect answers), and diagnostic methods for oral cancer (77.7% incorrect answers). These findings suggest that oral healthcare professionals might not have the resources needed to identify or address early signs of mouth cancer. The ongoing knowledge gap, in spite of improvements in oral health education, highlights the need for better training initiatives emphasizing early detection and prevention.

Despite the well-documented role of risk factors such as tobacco use, alcohol consumption, and betel nut chewing in the development of oral cancer, there remains a notable lack of awareness among students. The significant (p = 0.022) in recognizing risk factors suggests uneven knowledge distribution, with only a portion of students demonstrating adequate understanding. This finding is consistent with studies showing persistent gaps in education on risk factors, even among healthcare students in similar contexts (16). Targeted awareness campaigns and curriculum enhancements are crucial to address these deficits, particularly in a country like Yemen, where public health challenges are compounded by limited resources and ongoing sociopolitical instability.

The study found no statistically significant difference in the recognition of clinical manifestations of oral cancer (p=0.307). This aligns with findings from prior studies indicating that students, particularly those in non-dental disciplines, often fail to recognize early signs of malignancy (17). Early recognition is crucial for timely intervention, as delayed diagnosis is strongly associated with poor prognosis. Including case-based learning and hands-on diagnostic training across all universities could enhance student competence in this area.

Knowledge regarding the importance of annual screenings and prompt evaluation of suspicious lesions (*p*-values of 0.934 and 0.757, respectively) appears insufficient among students. Early detection is a cornerstone of oral cancer management, significantly improving survival rates (18). However, the low awareness highlights a gap in integrating preventive strategies into educational frameworks.

Universities across Yemen should consider integrating regular workshops, community screening programs, and active participation in public health initiatives into their curricula to reinforce the importance of early detection.

A general understanding gap in these crucial areas is suggested by the absence of statistical significance in the knowledge of diagnostic instruments (p=0.447) and treatment alternatives (p=0.841). This is important because the foundation of successful oral cancer therapy is diagnostic and therapeutic skill. Practical experience during clinical rotations greatly improves student knowledge and confidence in these areas, according to a Glossop et al. (2024) (19). Standardizing the curriculum is crucial to guaranteeing that all students receive sufficient exposure to diagnostic and therapeutic training, especially considering the geographical and institutional variety of the colleges involved in this study.

Additionally, there was no discernible variation in the study's findings about the importance of patient education and counseling (p=0.146). However, it is crucial to teach students how to properly advise people who are at risk or have been diagnosed with oral cancer, considering the significant impact that patient education has on outcomes. University programs that include training in communication skills and community outreach initiatives can guarantee that students are more prepared to have therapeutic and preventative conversations with patients.

Yemen's public health is significantly impacted by the knowledge and awareness gaps found in this study. Students are an essential resource for promoting community health, especially those pursuing careers in healthcare. Resolving these educational gaps will increase public health outreach capabilities in addition to improving individual competency. In order to prepare students for active roles in the fight against oral cancer, Yemeni universities should give priority to curriculum modifications that stress





experiential learning, community participation, and multidisciplinary collaboration.

Based on respondents' years of experience, the data shows differences in their awareness and understanding of oral cancer-related topics. While the non-significant results point to areas that need consistent instructional efforts across all experience levels, the significant findings highlight the importance of professional experience in forming understanding.

The relation between years of experience and knowledge of oral cancer risk factors (p-value = 0.001) suggests that experience plays an important role in understanding these key factors. Healthcare professionals with 0-5 years of experience had a higher percentage of correct answers compared to those with more experience. This finding could be linked to the fact that newer professionals may have recently completed their education, which may have focused more on the most up-to-date clinical guidelines and risk factor knowledge. According to a study by Orosco et al. (2018), recent graduates are typically more attuned to current guidelines and evidence-based practices, which could explain their stronger knowledge in this area. It also suggests that ongoing professional development is critical for ensuring that more experienced healthcare providers stay up-to-date (20).

Professional experience may have less of an impact on understanding of clinical manifestations of oral cancer, as evidenced by the lack of a statistically significant variation in this knowledge across years of experience (p-value=0.202), consistent with studies that state that early detection of oral cancer depends identifying its clinical indicators, while professional education and training probably always reinforce this point. As a result, there may be less difference in clinical manifestation knowledge between recent graduates seasoned and professionals (21).

Years of experience did not substantially affect the knowledge of when to undertake routine oral cancer screenings (*p*-value=0.304), indicating that screening

recommendations are generally accepted and followed by medical professionals of all experience levels. This result is in line with the American Cancer Society's (2019) recommendations (22), which support yearly checkups, especially for high-risk groups. The notion that earlv detection recommendations are widelv accepted and distributed within the healthcare industry is supported by the high correct answer rate across all experience categories.

Similarly, there was no discernible difference in the awareness of the significance of looking into worrisome lesions between years of experience (*p*-value=0.107). The established practice of early referral and investigation for lesions that persist for more than two weeks is reflected in the uniform awareness among groups. According to a study by Hicks et al. (2016), early detection of worrisome lesions is crucial for improving the prognosis of oral cancer. This may be the reason why professionals with varying levels of experience are well-versed in this recommendation (23).

On the other hand, there were notable variations in the comprehension of typical clinical characteristics of OPMDs (*p*-value=0.006). Knowledge in this area was higher among those with less experience (0–5 years), indicating that younger practitioners might be more up to date on the most recent diagnostic standards for these conditions. Research from the World Health Organization (WHO, 2018) supports this conclusion, highlighting the importance of early detection and therapy of potentially malignant oral illnesses (24). The higher understanding of younger healthcare workers may be explained by their more recent training that places an emphasis on these characteristics (25).

Experience did not significantly alter understanding of which OPMDs have the highest rate of malignant transformation (*p*-value=0.162). This could indicate that although identifying high-risk OPMDs is crucial, it might not receive as much attention as other areas of oral cancer treatment. More study is required to identify the most common illnesses with a high risk of





malignant transformation; additionally, management of these conditions should be incorporated into ongoing education for healthcare professionals at all levels.

The awareness of diagnostic tools used in oral cancer diagnosis did not significantly vary by experience (*p*-value=0.445). This aligns with the fact that diagnostic tools, such as biopsy and imaging techniques, are fundamental components of oral cancer diagnosis and are taught consistently across healthcare training. A study found that while knowledge about diagnostic tools remains consistent, the practical use and application may depend more on clinical exposure and ongoing professional development (26).

Experience had no discernible impact on awareness of the significance of patient education and counseling in avoiding oral cancer (*p*-value=0.126). The general understanding of the value of patient education and communication in illness prevention may be reflected in this finding. According to the American Dental Association (2020), patient education is key for preventing cancer and incorporating it into the curriculum probably guarantees that all clinicians, regardless of experience, have this vital knowledge (27).

There was a significant difference in knowledge of common treatment options for oral cancer (p-value = 0.026), with healthcare professionals with 0-5 years of experience demonstrating the highest level of understanding. This finding is consistent with the idea that newer professionals may be more familiar with current treatment protocols due to recent training. This study demonstrates a gap in dental care for patients with oral cancer and highlights a need for methods to involve dentists in managing the dental health of oral cancer patients (28).

#### Recommendations

Better Training Programs: Incorporate courses on oral cancer into graduate and undergraduate programs. Continuing Education: Hold workshops and online courses on a regular basis to keep practitioners up to date on advancements in the detection and management of oral cancer. Standardized Screening Protocols: Develop and disseminate clear guidelines for routine screenings in order to standardize processes. Awareness Campaigns: Start targeted educational programs emphasizing the importance of early detection of oral cancer and the use of appropriate diagnostic tools. Monitoring and Evaluation: To determine the success of training initiatives and pinpoint areas in need of development, regularly review the knowledge of healthcare workers.

#### **Limitations and Future Directions**

The conclusions of this study are limited in their generalizability because it focuses on participants from a particular geographic and professional environment. In order to comprehend the obstacles to knowledge retention and application, future research should investigate these gaps among a wider spectrum of healthcare workers and incorporate qualitative assessments. Longitudinal studies could also evaluate the effects of focused interventions over time.

## CONCLUSION

The study emphasizes how years of experience have a big impact on people's understanding and awareness of oral cancer and how to treat it. Even vounger professionals show comprehension in important areas, disparities still exist among more seasoned cohorts, underscoring the necessity of ongoing professional development. Healthcare workers will be better prepared to lessen the burden of oral cancer through prompt diagnosis, efficient treatment, and community outreach if these inadequacies are addressed through focused educational activities. These findings underscore the necessity of incorporating comprehensive oral cancer modules into dental curricula, as well as implementing standardized screening protocols and





awareness campaigns to improve early detection and prevention efforts in Yemen.

## **Conflict of interest**

The authors declare that no conflict of interest.

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