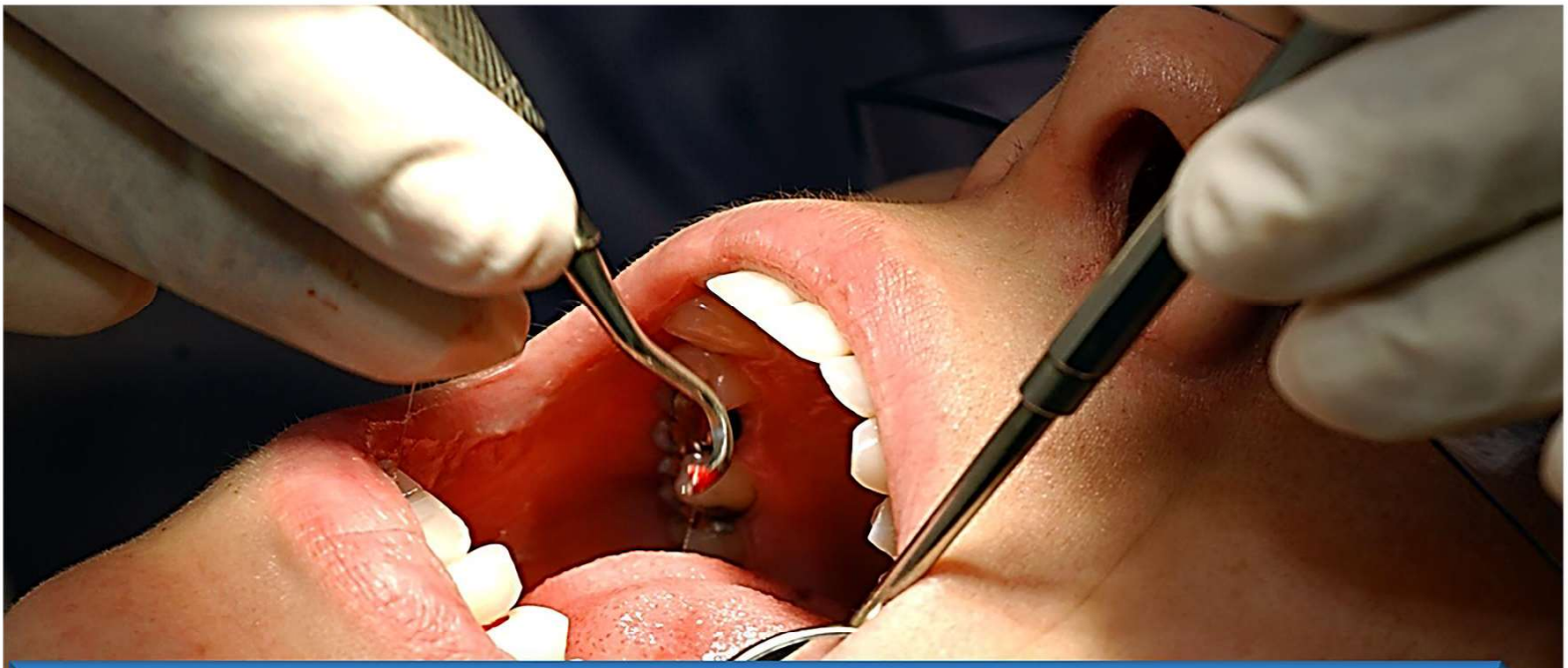
Universitat Autònoma de Barcelona

QUALITY ASSESSMENT OF SCIENTIFIC EVIDENCE ABOUT DIAGNOSIS AND TREATMENTS FOR ORAL CANCER

Meisser Vidal Madera Anaya



QUALITY ASSESSMENT OF SCIENTIFIC EVIDENCE ABOUT DIAGNOSIS AND TREATMENTS FOR ORAL CANCER

Doctoral thesis

MEISSER VIDAL MADERA ANAYA BDS MSc

Supervisors

Xavier Bonfill Cosp Ph.D.

Gerard Urrútia Cuchí Ph.D

Universitat Autònoma de Barcelona

Faculty of Medicine

Department of Paediatrics, Obstetrics and Gynaecology, and Preventive Medicine and Public Health

Ph.D. Program in Methodology of Biomedical Research and Public Health

Barcelona, September 2020

UNIVERSITAT AUTÒNOMA DE BARCELONA

Faculty of Medicine

Department of Paediatrics, Obstetrics and Gynaecology, and Preventive Medicine and Public Health

Ph.D. Program in Methodology of Biomedical Research and Public Health

DOCTORAL THESIS

QUALITY ASSESSMENT OF SCIENTIFIC EVIDENCE ABOUT DIAGNOSIS AND TREATMENTS FOR ORAL CANCER

Ph.D. Candidate

Meisser Vidal Madera Anaya BDS MSc

Supervisors

Xavier Bonfill Cosp Ph.D.

Gerard Urrútia Cuchí Ph.D.

Barcelona, September 2020

ACKNOWLEDGMENT

To Dr. Xavier Bonfill Cosp who provided me his kind support and knowledge during all the years of my doctoral studies. It has been a pleasure to be tutored by him.

To Dr. Gerard Urrútia Cuchí whom with his gentle way taught me a lot. Thank you for being a part of this process.

To all members of the Iberoamerican Cochrane Centre and the Department of Public Health and Clinical Epidemiology, Hospital de la Santa Creu i Sant Pau who helped me to achieve my goals.

To all co-authors of the publications that comprise this doctoral thesis whom with their contributions made this possible, specially Juan Franco who did a remarkable job in all publications.

To my colleagues during my doctoral studies, Claudia Vallí, Andrea Cervera, Stefanie Suclupe, and Karla Salas. Thank you so much for all the memorable moments that we lived together.

To "Bolivar Gana con Ciencia" Fellowship Program and Ceiba Foundation which provided me financial support to attend this doctoral program.

To the University of Cartagena which is my academic home, there my interest in research started, and where I intent to continue developing and expanding my knowledge in this area.

Finally, to my family, specially my parents Luis Madera Del Toro and Ana Anaya Arrieta who have encouraged me to follow my dreams. Despite the geographical distance, they always are with me, giving me their support and unconditional love.

¨Cancer is a word, not a sentence¨

John Diamond

CONTENT

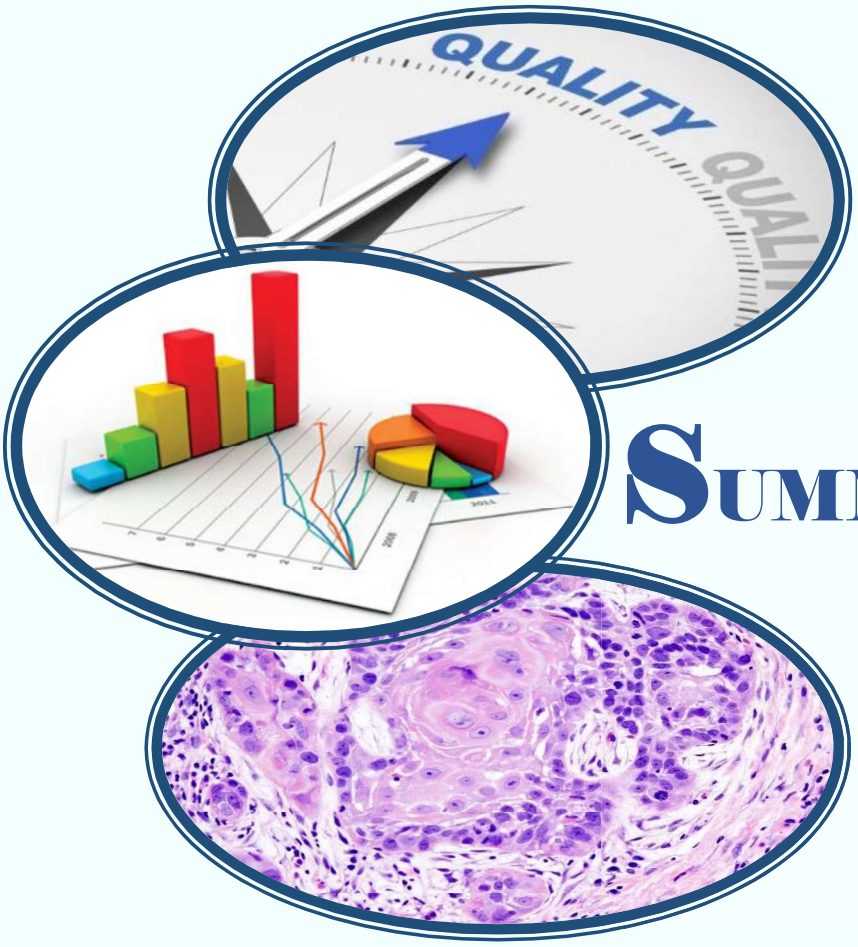
List of tables

List of figures

List of appendices

List of abbreviations

5-FU	5-fluorouracil
AGREE II	The Appraisal of Guidelines for Research & Evaluation Instrument-II
AMSTAR-2	The Assessing the Methodological Quality of Systematic Reviews tool-2
BCG-CWP	Bacillus Calmette-Guérin-cell wall preparation
CCRT	Concomitant chemo-radiotherapy
CI	Confidence interval
C-trial	Controlled trial
GEM	Global evidence mapping initiative
GRADE	Grading of Recommendations Assessment, Development and Evaluation framework
ICC	Intraclass coefficient
ICT	Induction chemotherapy
IQR	Inter-quartile range
MTX	Methotrexate
OSCC	Oral squamous cell carcinoma
PICO	Population-Intervention-Comparison-Outcomes
RCT	Randomized controlled trial
RT	Radiotherapy
TNM	Tumor-Node-Metastasis stage



Summary

ABSTRACT

Introduction: Oral cancer is considered a public health problem worldwide. It has a 5-year survival rate of 50% due to diagnosis are commonly performed at advanced stage of the disease. Its treatment usually involves a multidisciplinary team to provide comprehensive healthcare to people that suffer from this disease. Nowadays, there is a vast number of scientific publications suggesting the use of different therapeutic interventions and recommendations for its diagnosis, but their quality is unknown. Thus, a critical appraisal of evidence about diagnosis and treatments for oral cancer is needed.

Aim: To assess the quality of available scientific evidence about diagnosis and treatments for oral cavity cancer.

Methods: Three independent studies were carried out using different methodology designs. In order to describe and assess the quality of scientific evidence on diagnosis and treatments for oral cavity cancer, we designed and conducted: i) an evidence mapping study to describe the available evidence about the main therapeutic interventions for oral cancer; ii) a systematically critical assessment study to determine the quality of clinical practice guidelines on treatments for oral cavity cancer; and iii) a systematically critical assessment study to assess the quality of clinical practice guidelines on oral cancer diagnosis, and to describe their recommendations.

Results: The evidence mapping study included 15 systematic reviews involving 118 primary studies, of which 55.1% were randomized controlled clinical trials. Ten systematic reviews scored "critically low" methodological quality. We extracted 30 PICOs focusing on interventions such as surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy; 18 PICOs were for resectable oral cancer, of which 8 were reported as beneficial. There were 12 PICOs for unresectable oral cancer, of which only 2 interventions were reported as beneficial.

In the second study, 12 clinical practice guidelines were included. The mean scores for each AGREE II domain were the following: "scope and purpose" 88.4%±12.4%; "stakeholder involvement" 60.4%±25%; "rigor of development" 60.9%±25.3%; "clarity of presentation" 76.5%±19.8%; "applicability" 32.2%±30.7%; and "editorial independence" 61.6%±35.5%. Three guidelines were rated as "recommended"; six as "recommended with modifications"; and three as "not recommended".

In the last study, eight clinical practice guidelines were selected. The median scores of the six AGREE II domains were as follows: "scope and purpose" 97.9% (IQR: 96.2-100.0%); "stakeholder involvement" 86.1% (IQR: 69.8-93.1%); "rigor of development" 75.3% (IQR: 64.2-94.3%); "clarity of presentation" 91.7% (IQR: 82.6-94.4%); "applicability" 53.1% (IQR: 19.3-74.2%); and "editorial independence" 83.3% (IQR: 67.2-93.8%). Four guidelines were assessed as "recommended", four "recommended with modifications", and none "not recommended". Twenty-three recommendations were provided, mostly with a low or very low level of evidence.

Conclusions: Overall, the scientific evidence about treatments for oral cancer is limited and its quality is critically low. Likewise, the methodological quality of clinical practice guidelines on diagnosis and treatments for oral cancer was rated from suboptimal to moderate. Moreover, most recommendations were based on a low level of evidence. These findings highlight the need to address future research focused on new treatments and knowledge gaps identified in this field, and increased efforts are required to enable the development of high-quality evidence-based guidelines for oral cancer.

RESUMEN

Introducción: El cáncer oral es considerado un problema de salud pública globalmente**.** Este tiene una tasa de supervivencia a los 5 años del 50%, debido a que su diagnóstico se realiza comúnmente en estadios avanzados. En su tratamiento usualmente participa un equipo multidisciplinario para proporcionar una atención integral a los individuos que padecen esta enfermedad. Actualmente, existe un número considerable de publicaciones científicas que sugieren el uso de diferentes opciones terapéuticas y recomendaciones para su diagnóstico; sin embargo, la calidad de esta evidencia se desconoce. Por lo tanto, se requiere una evaluación crítica de la evidencia sobre el diagnóstico y tratamiento de cáncer oral.

Objetivo: Evaluar la calidad de la evidencia científica disponible sobre el diagnóstico y tratamientos del cáncer oral.

Métodos: Tres estudios independientes fueron realizados usando diferentes diseños metodológicos. Para describir y evaluar la calidad de la evidencia científica sobre el diagnóstico y tratamientos para el cáncer oral, se diseñó y realizó: i) un estudio de mapeo de la evidencia para describir la evidencia disponible sobre principales intervenciones terapéuticas para cáncer oral; ii) un estudio de evaluación crítica sistemática para determinar la calidad de guías de práctica clínica sobre tratamientos de cáncer oral, y iii) un estudio de evaluación critica sistemática para determinar la calidad de guías de práctica clínica sobre diagnóstico de cáncer oral, y describir sus recomendaciones.

Resultados: El estudio de mapeo de la evidencia incluyó 15 revisiones sistemáticas abarcando 118 estudios primarios; de estos 55,1% fueron ensayos clínicos controlados aleatorizados. Diez revisiones sistemáticas tuvieron una calidad metodológica "muy baja"**.** Treinta preguntas PICOs fueron extraídas, las cuales se enfocaron en intervenciones como cirugía, radioterapia, quimioterapia, terapia dirigida e inmunoterapia; 18 PICOs eran para cáncer oral operable, de las cuales ocho fueron reportadas como beneficiosa. Hubo 12 PICOs para cáncer oral inoperable, de las cuales solo dos fueron reportadas como beneficiosas.

En el segundo estudio se incluyeron 12 guías de práctica clínica. Los puntajes promedio para cada dominio del AGREE II fueron: "alcance y propósito" 88,4%±12,4%; "participación de los interesados" 60,4%±25%; "rigor de desarrollo" 60,9%±25,3%; "claridad de presentación" 76,5%±19,8%;

"aplicabilidad" 32,2%±30,7%; y "independencia editorial" 61,6%±35,5%. Tres guías fueron clasificadas como “recomendada”, seis como “recomendada con modificaciones”; y tres como “no recomendada”.

En el último estudio ocho guías de práctica clínica fueron seleccionadas. Los puntajes en mediana para los seis dominios del AGREE II fueron: “alcance y propósito” 97,9% (RIC: 96,2-100%); "participación de los interesados" 86,1% (RIC: 69,8-93,1%); "rigor de desarrollo" 75,3% (RIC: 64,2-94,3%); "claridad de presentación" 91,7% (RIC: 82,6-94,4%); "aplicabilidad" 53,1% (RIC: 19,3-74,2%); y "independencia editorial" 83,3% (RIC: 67,2-93,8%). Cuatro guías fueron clasificadas como “recomendada”, cuatro como “recomendada con modificaciones” y ninguna como “no recomendada”. Se identificaron 23 recomendaciones, en su mayoría basadas en nivel de evidencia “baja” o “muy baja”.

Conclusiones: En general, la evidencia científica sobre los tratamientos de cáncer oral es limitada y su calidad es muy baja. Asimismo, la calidad metodológica de guías de práctica clínica sobre diagnóstico y tratamientos para el cáncer oral fue considerada desde subóptima hasta moderada. Además, la mayoría de sus recomendaciones fueron basadas en un nivel de evidencia “baja”. Estos hallazgos resaltan la necesidad de realizar futuras investigaciones sobre nuevos tratamientos y vacíos del conocimiento identificados en esta área; asimismo mayores esfuerzos son necesarios para permitir el desarrollo de guías basadas en evidencia de alta calidad para cáncer oral.

RESUM

Introducció: El càncer oral és considerat, globalment, un problema de salut pública. Aquest té una taxa de supervivència al cap de 5 anys del 50%, ja que el seu diagnòstic es realitza, en general, en estadis avançats. Pel que fa al seu tractament, normalment, hi participa un equip multidisciplinari per tal de proporcionar una atenció integral als individus que pateixen aquesta malaltia. Actualment, hi ha un nombre considerable de publicacions científiques que suggereixen l'ús de diferents opcions terapèutiques; però, la qualitat d'aquesta evidència es desconeix. Per tant, es requereix una avaluació crítica de l'evidència sobre el diagnòstic i el tractament del càncer oral.

Objectiu: Avaluar la qualitat de l'evidència científica disponible sobre el diagnòstic i els tractaments del càncer oral.

Mètodes: Es van realitzar tres estudis independents que utilitzaven diferents dissenys metodològics. Per descriure i avaluar la qualitat de l'evidència científica sobre el diagnòstic i els tractaments per al càncer oral, es va dissenyar i realitzar: i) un estudi de mapatge de l'evidència per tal de descriure l'evidència disponible sobre les principals intervencions terapèutiques per a càncer oral; ii) un estudi d'avaluació critica sistemàtica per determinar la qualitat de guies de pràctica clínica sobre tractaments de càncer oral, i iii) un estudi d'avaluació critica sistemàtica per determinar la qualitat de guies de pràctica clínica sobre diagnòstic de càncer oral, i descriure les seves recomanacions.

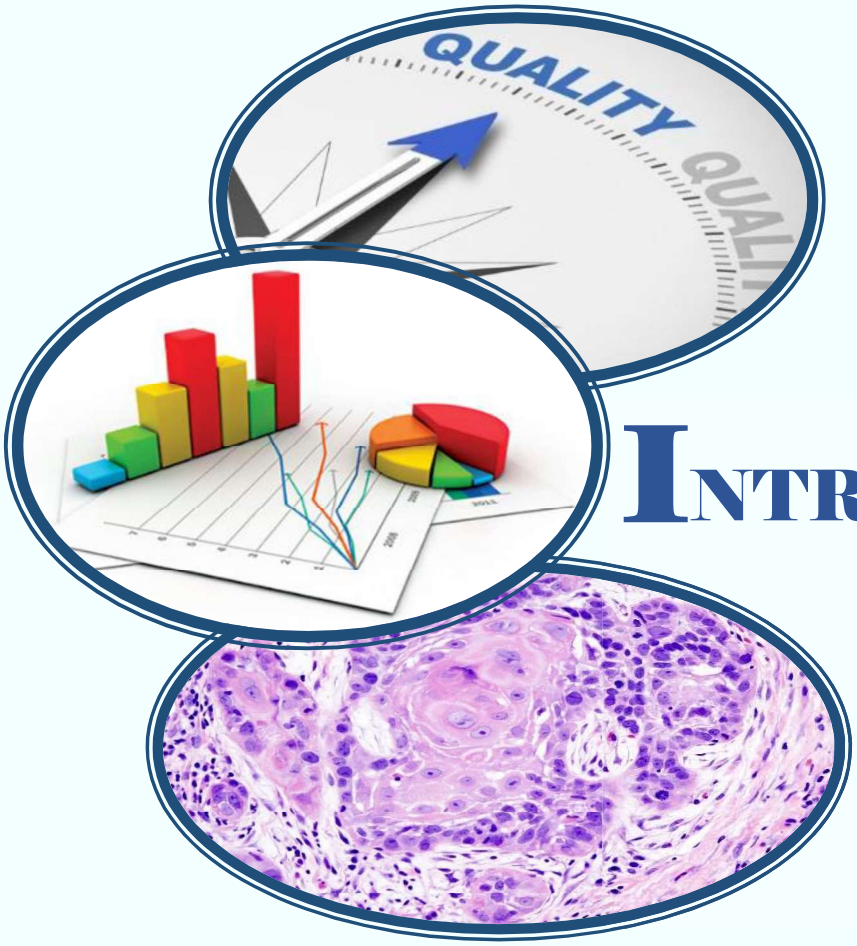
Resultats: L'estudi de mapatge de l'evidència va incloure 15 revisions sistemàtiques que incloïen 118 estudis primaris; d'aquests, el 55,1% van ser assaigs clínics controlats aleatoritzats. Deu revisions sistemàtiques van tenir una qualitat metodològica "summament baixa". Es van extreure trenta preguntes PICOs, les quals es van enfocar en intervencions com ara cirurgia, radioteràpia, quimioteràpia, teràpia dirigida i immunoteràpia; 18 PICOs eren per càncer oral operable, de les quals vuit van ser reportades com a “beneficiosa”. Hi va haver 12 PICOs per càncer oral inoperable, de les quals només dos van ser reportades com a “beneficiosa”.

En el segon estudi, es van incloure 12 guies de pràctica clínica. La mitjana de la puntuació per a cada domini de l'AGREE II van ser: "abast i propòsit", 88,4% ± 12,4%; "Participació dels interessats", 60,4% ± 25%; "Rigor de desenvolupament", 60,9% ± 25,3%; "Claredat de presentació", 76,5% ± 19,8%; "Aplicabilitat", 32,2% ± 30,7%; i "independència editorial", 61,6% ± 35,5%. Tres guies van ser

classificades com a "recomanada", sis com a "recomanada amb modificacions"; i tres com a "no recomanada".

En l'últim estudi, es van seleccionar vuit guies de pràctica clínica. La mitjana de la puntuació per als sis dominis de l'AGREE II van ser: "abast i propòsit", 97,9% (RIC: 96,2-100,0%); "Participació dels interessats", 86,1% (RIC: 69,8-93,1%); "Rigor de desenvolupament", 75,3% (RIC: 64,2-94,3%); "Claredat de presentació", 91,7% (RIC: 82,6-94,4%); "Aplicabilitat", 53,1% (RIC: 19,3-74,2%); i "independència editorial", 83,3% (RIC: 67,2-93,8%). Quatre guies van ser classificades com a "recomanada", quatre com a "recomanada amb modificacions" i cap com a "no recomanada". Es van identificar 23 recomanacions, majoritàriament basades en nivell d'evidència "baixa" o "molt baixa".

Conclusions: En general, l'evidència científica sobre els tractaments de càncer oral és limitada i la seva qualitat és summament baixa. Així mateix, la qualitat metodològica de guies de pràctica clínica sobre diagnòstic i tractaments per al càncer oral va ser considerada des de subòptima fins a moderada. A més, la majoria de les seves recomanacions es van basar en un nivell d'evidència "baixa". Aquestes troballes ressalten la necessitat de realitzar futures investigacions sobre nous tractaments i buits del coneixement identificats en aquesta àrea; així mateix, són necessaris més esforços per permetre el desenvolupament de guies basades en evidència d'alta qualitat per al càncer oral.



Introduction

1. INTRODUCTION

1.1 ORAL CAVITY CANCER

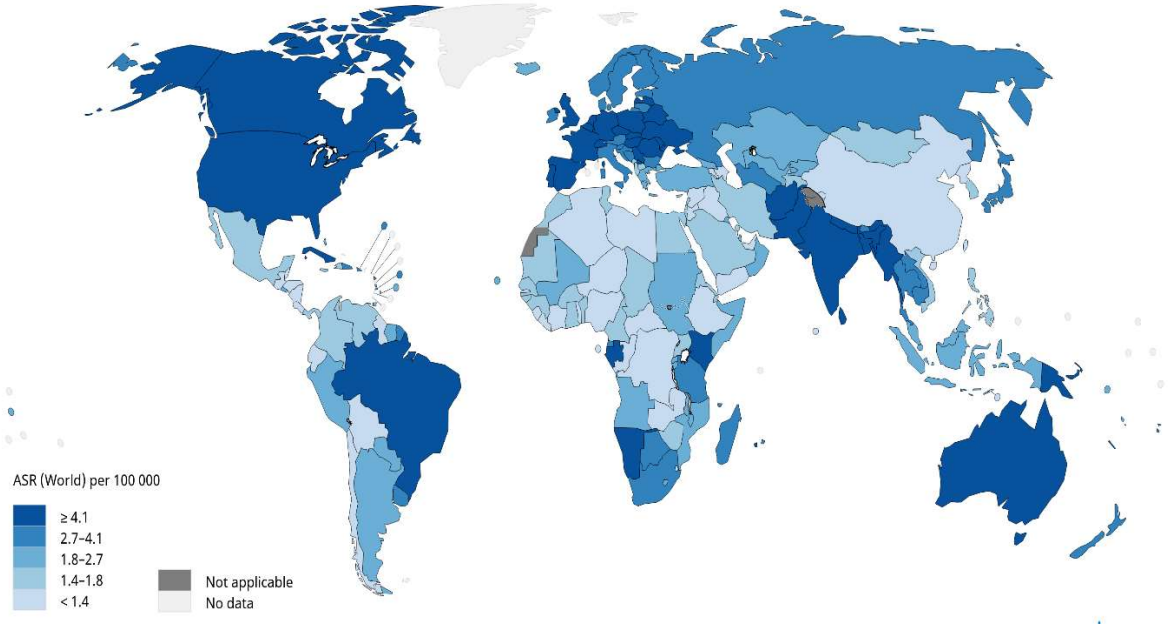
1.1.1 Epidemiology of oral cancer: a priority public health problem

Oral cavity cancer is a health issue globally. It fully meets criteria to be considered a public health problem such as high mortality rate, the impact of the condition on an individual level, impact on wider society, and there are effective treatments for it (1). To illustrate, it has been reported that around 650,000 new cases are diagnosed per year; although it represents about 2% of the tumor incidence worldwide, its high mortality rate around 50% is the most important reason for concern (2). This disease stands amongst the six most common cancers worldwide, and about 40% of head and neck tumors are oral squamous cell carcinomas (OSCC) (3), which is the most common type of mouth cancers. Moreover, this disease has a substantial financial burden on the healthcare system and produce both physical and psychological impacts on affected population such as speech difficulties, swallowing function, and self-image issues (4).

According to global cancer statistics 2018 (5), the countries with highest age-standardized incidence rates (per 100000 people) of oral cavity cancer are: Papua New Guinea (20.4), Pakistan (12.2), Bangladesh (9.5), India (9.1), Sri Lanka (7.6), Hungary (7.5), Australia (7.1), Afghanistan (7.0), Latvia (6.9), and France (6.3) (Figure 1). Regarding the region-specific incidence age-standardized rates by sex for this cancer in the same period, the six regions with the highest incidence are Melanesia (Males 21.2; Females 12.0), South Central Asia (Males 12.9; Females 4.5), Australia/New Zealand (Males 9.4; Females 3.7), Eastern Europe (Males 8.0; Females 1.8), Western Europe (Males 6.9; Females 3.2),

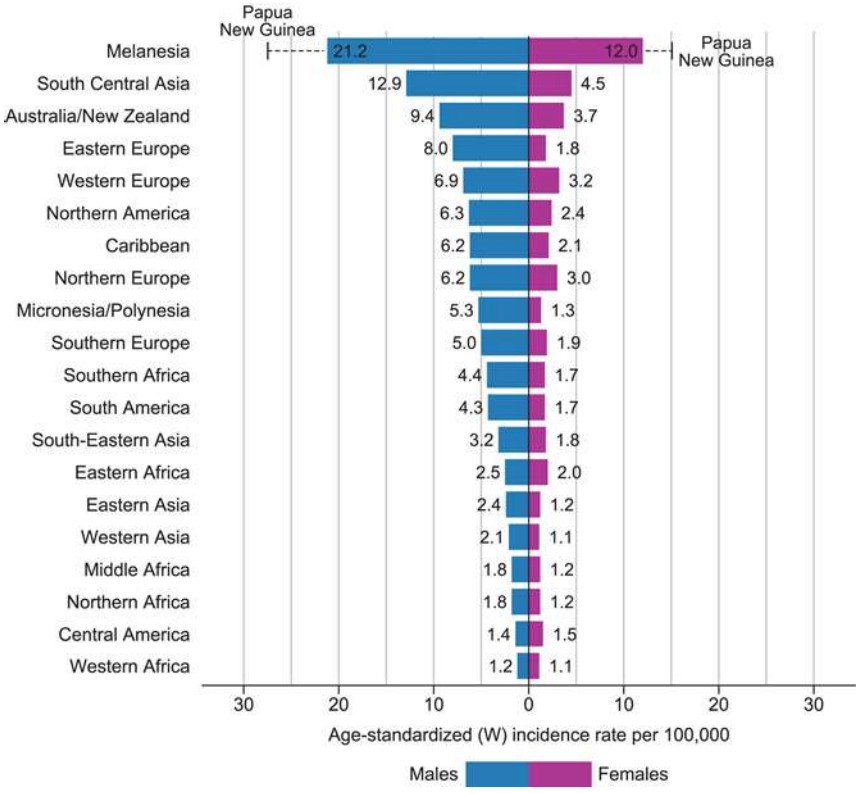
and Northern America (Males 6.3; Females 2.4) (Figure 2). Overall, there is a higher incidence of oral cancer for males than women in all regions globally.

Figure 1. *Estimated age-standardized incidence rates globally for oral cavity cancer in 2018, both sexes, all ages*



Source: GLOBACAN 2018 (5).

Figure 2. *Region-specific incidence age-standardized rates by sex for oral cavity cancer in 2018.*

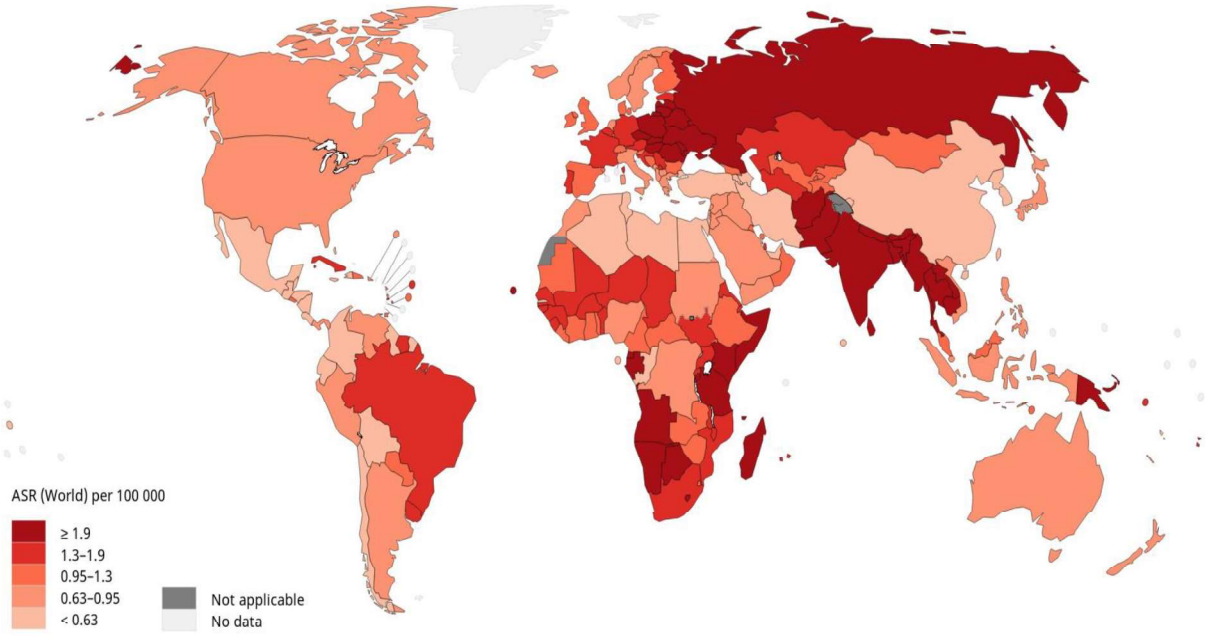


Source: GLOBACAN 2018 (5).

Oral cavity cancer accounts for over 140 000 deaths annually worldwide. Its age-standardized mortality rates can vary depending on geographical regions, being in 2018 higher in countries such as Pakistan (8.7/100000), Papua New Guinea (8.4/100000), Bangladesh (6.2/100000), Afghanistan (5.7/100000), India (5.6/100000), Namibia (4.6/100000), Sri Lanka (3.8/100000), Hungary (3.6/100000), Kenya (3.5/100000), and Gabon (3.4/100000); whereas that countries as Democratic Republic of Korea, French Guiana, Nicaragua, Bolivia, and United Arab Emirates, there are less than 0.5 deaths per

100000 people (Figure 3) (5). Likewise, it has been reported that the mortality rate of oral cancer in Colombia is around 0.6 deaths per 100000 people, and in Spain is 1.1 deaths per 100000 people (5).

Figure 3. *Estimated age-standardized mortality rates globally for oral cavity cancer in 2018, both sexes, all ages*



Source: GLOBACAN 2018 (5).

The high mortality rate of oral cancer has been related to different factors, one of the main ones is the diagnosis in advanced stages. Frequently, mouth lesions are easy to access and should not have a diagnostic delay in order to receive an opportune treatment (6). However, people are commonly diagnosed in an advanced stage of the disease. Diagnostic delays are associated with the fact that patients do not seek treatment or do not have easy access to professionals who can establish the

diagnosis (7). Consequently, it affects the survival of these patients. In this sense, it has been reported that oral cancer has a 5-year survival rate around 41% among Asian population (8). To illustrate, a study (8) conducted in Malaysia including people from different ethnic groups, found that oral cancer 5-year survival rate was 45.7%, 44.0%, 41.3%, and 27.7% for Malays, Chinese, Indians, and Indigenous populations, respectively. Moreover, the same authors concluded that there is no statistically significant difference between oral cancer survival rates and ethnicities.

Regarding the latest report by the Surveillance, Epidemiology, and End Results (SEER) Program (9), which provides information on cancer statistics in an effort to reduce the cancer burden among the United States population, oral cancer had a 5-year period survival of 66.5% in 2016, suggesting that there is an improvement on survival rates for this oral disease in the last decades. To illustrate, the oral cancer survival rate was 52.5% in 1975-1977, while that it was 69.2% in 2010-2016 for all races and both sexes, being statistically significant this difference. Likewise, that report (9) suggests that oral cancer survival was 66.2% for all stages at diagnosis, all races, and both sexes in 2010-2016 period. However, it can vary depending on the stage of disease. For example, it was higher for those with localized cancers (85.1%), whereas that those with distant neoplasms had the lowest survival rate (40.1%) (Table 1). Also, it has been suggested that some factors are associated with poor survival such as increased tumor size, lymph node involvement and advanced lesions (8).

Table 1. *Oral cancer 5-year relative survival (percent) 2010-2016 by stage at diagnosis*

Stage at diagnosis	All races			Whites			Blacks		
	Both sexes	Males	Females	Both sexes	Males	Females	Both sexes	Males	Females
All stages	66.2	65.6	67.7	67.6	67.3	68.3	49.5	47.6	53.8
Localized	85.1	84.3	86.1	85.3	85.1	85.7	77.3	72.6	81.6
Regional	66.8	68.1	62.2	68.1	69.6	62.6	51.7	52.2	50.2
Distant	40.1	40.5	38.7	41.1	41.8	38.4	29.3	28.9	30.4
Unstaged/Unknown	54.0	54.0	53.4	51.5	51.6	51.0	39.2	40.9	36.1

Source: SEER 2020 (9)

1.1.2 Risk factors

It has been suggested that tobacco smoking and alcohol consumption are the major risk factors of developing mouth cancers (10). Evidence from a systematic review suggests that the synergistic use of tobacco and alcohol significantly increases the likelihood to have oral cancer (11). Moreover, vast risk factors have been proposed such as occupational exposure, poor oral hygiene, chronic irritation, viral infection, diet (low consumption of fruits and vegetables), and genetic factors (12, 13).

According to Warnakulasuriya (14) the oral cancer risk factors can be classified into three categories: i) not modifiable (age, ethnicity, social-economic status); ii) modifiable (smoking, alcohol consumption, diet, lifestyle/betel quid); and III) emerging risk factors (human papillomavirus infection, immunosuppression, mate drinking). Likewise, this author stated that there are other controversial factors with limited evidence (oral hygiene and dentition, indoor air pollution) and no evidence

(hereditary and family risk, cannabis use, khat chewing, nicotine replacement therapy, HIV infection and alcohol in mouthwashes).

Given most OSCC are associated with two preventable factors such as smoking and alcohol misuse (15), the differences in the incidence of this oral disease across the world may be related to the different lifestyles, cultures, and social behaviors (11). To illustrate, smoked forms of tobacco are mainly used in countries as the United States (16), while smokeless tobacco is commonly used in Asian countries (17). Moreover, it has been reported that people who smoke have almost five times more chance to develop oral cancer compared with those who do not (18). Likewise, it has been suggested that both the intensity and duration of tobacco smoking are related to mouth cancer risk (19). Overall, the occurrence of oral cavity cancer has been attributed to a complex carcinogenic process that involves the interaction of many environmental and genetic factors (20).

In this sense, it has been reported that there are more than 70 carcinogenic compounds in the tobacco such as nitrosamines, volatile aldehydes, aromatic amines, and polycyclic aromatic hydrocarbons (21). These compounds are related to mutations of genes, reduction of apoptosis, an increase of angiogenesis, and loss of cell cycle control mechanisms (22). Likewise, alcohol abuse has been associated with the production of reactive oxygen species, resulting in deoxyribonucleic acid damage due to the production of acetaldehyde (23). Moreover, alcohol rises the oral mucosa permeability, acting as a solvent for tobacco products, so it can increase its carcinogenic effect (24).

1.1.3 Diagnosis

Despite easy self-examination and physical examination, patients often present with advanced-stage disease. For patients with suspected oral cancer cavity, a comprehensive head and neck examination is compulsory. Visual inspection and palpation allow an accurate impression of the extent of the disease, the third dimension of the tumor, the presence of bone invasion, or skin breakdown. Appropriate documentation with drawings and photographic records of the tumor are useful in staging, decision-making, and further follow up (25).

Most mouth cancers are presented as new lumps, persistent ulcers, and a red or white patch on the oral mucosa (26). However, since that other oral conditions may have similar signs, these clinical presentations could be considered unspecific; thus, detecting early oral lesions suggesting the presence of oral cancer may be difficult, especially for those dentists without expertise. Overall, a tissue biopsy along its histopathological study is still considered as the gold standard for confirmation of a mouth neoplasm (26). Accessible lesions may be adequately biopsied in the clinic using punch forceps, core needle, or fine-needle aspiration (25).

The clinical TNM (tumor, node, metastasis) stage should be recorded at first encounter and modified as the evaluation progresses. The TNM system is the most widely accepted method due to its relatively simple design and user-friendliness. The clinical staging of the oral cavity tumors consists of primary tumor characteristics, the neck, and assessment for distant metastases (Table 2), which allows TNM stage grouping for the tumor (27). Moreover, radiographic imaging is essential to consider the relation of the tumor to the adjacent bone and for evaluating regional lymph nodes. Likewise, the computerized tomography scan is useful for the evaluation of bone and neck nodes, especially where there are early

cortical involvement and extracapsular nodal spread. Similarly, magnetic resonance imaging provides complementary information about soft tissue extent and perineural invasion and is also helpful for evaluating the extent of medullary bone involvement because adult marrow is normally replaced by fat (25).

It is useful to mention that to contribute to the early diagnosis of oral cavity cancer or potentially malignant disorders, some adjunctive aids have been developed and are commercially available for clinical use. Their main goal is to assist clinicians in visualizing clinical changes that may be found in the mouth, suggesting suspected oral cancer. According to Warnakulasuriya (26), these adjunctive aids can be divided into the following categories: i) optical imaging devices (VELscope, Vizilite, Microlux), those with high resolution microscopy (microendoscopy), and vital staining techniques (toluidine blue, Lugol's iodine). The use of these tools can vary depending on the expertise of the operator and other factors (26). However, since the reliability of the use of some of these tools is controversial, the detection of mouth neoplasm must be based on clinical visual inspection and palpation of the affected site and neck.

Table 2. *TNM classification and staging for oral cavity cancer*

TNM classification for oral cavity cancer																
T - Primary tumor																
TX	Primary tumor cannot be assessed															
T0	No evidence of primary tumor															
Tis	Carcinoma in situ															
T1	Tumor 2 cm or less in greatest dimension															
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension															
T3	Tumor more than 4 cm in greatest dimension															
T4a (lip)	Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose)															
T4a (oral cavity)	Tumor invades through cortical bone, into deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face															
T4b (lip and oral cavity)	Tumor invades masticator space, pterygoid plates, or skull base; or encases internal carotid artery															
Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a as T4.																
N - Regional Lymph Nodes																
NX	Regional lymph nodes cannot be assessed															
N0	No regional lymph node metastasis															
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension															
N2	Metastasis as specified in N2a, 2b, 2c below															
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension															
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension															
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension															
N3	Metastasis in a lymph node more than 6 cm in greatest dimension															
Note: Midline nodes are considered ipsilateral nodes.																
M – Distant metastasis																
MX	Distant metastasis cannot be assessed															
M0	No distant metastasis															
M1	Distant metastasis															
Oral cavity cancer staging																
Stage	**0**	**I**	**II**	**III**				**IVA**							**IVB**	**IVC**
T	Tis	T1	T2	T3	T1	T2	T3	T4a	T4a	T1	T2	T3	T4a	Any T	T4b	Any T
N	N0	N0	N0	N0	N1	N1	N1	N0	N1	N2	N2	N2	N2	N3	Any N	Any N
M	M0	M0	M0	M0	M0	M0	M0	M0	M0	M0	M0	M0	M0	M0	M0	M1

Source: Adapted from Montero 2015 (25)

1.1.4 Treatment

Despite technology advances in oncology research and cancer treatments, oral cavity cancer still has a poor prognosis and its management involves commonly severe physical and psychological after-effects (28, 29). Amongst the mainly therapeutic interventions for oral cavity cancer, are surgical therapies, radiotherapy, and chemotherapy which can be used alone or in combination depending on different factors.

Surgery

Surgical treatment is an important part of the management of oral cavity cancer regarding both the removal of the primary tumor and removal of lymph nodes in the neck (30). Surgery alone may be the treatment for early-stage disease or surgery may be used in combination with radiotherapy, chemotherapy, and immunotherapy for advanced tumors (30). Surgical resection allows accurate pathologic staging, with information about the status of margins, tumor spread, and histopathologic characteristics which can then be used to inform subsequent management based upon the assessment of risk versus benefit (25). Overall, smaller cancers may be removed through minor surgery, while larger tumors may require more-extensive procedures. For instance, removing a larger tumor may involve removing a section of the mouth such as jawbone or a portion of the tongue.

Radiotherapy

Radiotherapy uses high-energy beams to eradicate cancer cells (31). This is commonly used after surgery. However, sometimes it might be used alone, especially in early-stage mouth cancers. In other situations, the radiotherapy may be combined with chemotherapy; this combination improves the effectiveness of it, but it also increases the side effects (32). It has been reported that in cases of advanced mouth cancer, radiotherapy may help relieve signs and symptoms caused by cancer, such as pain (31). Moreover, among the side effects of this treatment are dry mouth, tooth decay, and damage to the jawbone.

Chemotherapy

Chemotherapy involves the administration of cytotoxic' drugs, which work by attacking rapidly dividing cancer cells, disrupting the growth of the cancer cells, and destroying them. The drugs used in chemotherapy affect the life cycle of the cancer cells, most commonly by damaging the deoxyribonucleic acid of the cells so that they can no longer reproduce (33). Different types of chemotherapeutic agents interrupt the life cycle of cancer cells at different stages; thus, combining two or three different agents into a chemotherapy regimen may produce a greater and/or longer lasting effect on the tumor than single agent chemotherapy (33). However, as well as increased benefits, combinations of chemotherapeutic agents may also be associated with increased toxicity, effects that may be exacerbated by the simultaneous use of radiotherapy. It has been reported that the side effects of chemotherapy depend on which drugs you receive. Moreover, among the common side effects, we can mention nausea, vomiting, and hair loss (34).

Other therapies

Other therapeutic interventions have been proposed to treat oral cavity cancer, such as targeted therapy and immunotherapy (35). The first one alters specific aspects of cancer cells that fuel their growth. Targeted drugs can be used alone or in combination with chemotherapy or radiotherapy. Cetuximab is one targeted therapy used to treat mouth cancer in certain situations. This drug stops the action of a protein that has found in many types of healthy cells but is more prevalent in certain types of cancer cells (36). Among their side effects are skin rash, itching, headache, diarrhea, and infections. Similarly, immunotherapy uses the immune system to fight cancer (35). It is generally reserved for people with advanced mouth cancer that are not responding to standard treatments.

Overall, a multidisciplinary team is essential to ensure a favorable outcome. Multiple factors should be considered in selecting treatment for an individual patient. The risk of treatment-related complications should be assessed based on physiological age, comorbid conditions, lifestyle, surgical resectability, and patient expectations (25).

1.2 SYNTHESIZING SCIENTIFIC EVIDENCE

1.2.1 Systematic reviews

Among the options to organize and critically evaluate published studies are systematic reviews, which summarize the results of the evidence from healthcare primary studies in order to answer a specific research question (37). According to the Cochrane handbook “a systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question. It

uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made"(37).

It has been reported that the key features of a systematic review are: i) a clearly stated set of objectives with pre-defined eligibility criteria for studies; ii) an explicit and reproducible methodology; iii) a systematic search that attempts to identify all studies that would meet the eligibility criteria; iv) an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and v) a systematic presentation, and synthesis, of the characteristics and findings of the included studies (37). It is useful to highlight that it is common confuse systematic and narrative literature reviews since both are used to provide a summary of the existent literature or research on a specific topic. However, there are significant differences between them, which are described in Table 3.

In addition, there are new tools for evidence synthesis such as evidence mapping, scoping reviews, and rapid reviews, which have been developed to help clinicians, patients, researchers, and other stakeholders to make evidence-based decisions (38). These new options are appropriate to address issues that may be too extensive for a systematic review (39).

***Table 3**. Comparison of narrative and systematic reviews*

Components of a review	Narrative review	Systematic review
Focus of review and formulation of the question	Introduces context and current thinking, often without a specific question, is general and covers several aspects of a topic.	Uses a precise and focused question to produce evidence to underpin a piece of research. A stand-alone piece of research, it should be conducted prior to undertaking further research, particularly in higher degree theses
Methods section	Usually not present, or not well-described	Clearly described with pre-stated criteria about participants, interventions, comparisons, and outcomes. All methods are reported in a protocol in advance
Search strategy to identify studies	Usually not described; mostly limited by reviewers' abilities to retrieve relevant studies; usually not reproducible and prone to selective citation	Clearly described and usually exhaustive; transparent, reproducible, and less prone to selective citation. It involves several specified databases using precise search Terms. A similar systematic search of grey literature also is included
Quality assessment of identified studies	Usually all identified studies are included without explicit quality assessment	Only high-quality studies are included using pre-stated criteria; if lower-quality studies included, the effects of this are tested in subgroup analyses
Data extraction	Methods usually not described	Usually undertaken by more than one reviewer onto pre-tested data forms; attempts often made to obtain missing data from authors of primary studies
Data synthesis	Qualitative description employing the "vote counting" approach, where each included study is given equal weight, irrespective of study size and quality	Recognized, referenced, methods for data analysis; includes analysis of methods, rigor of conduct of research, strength of evidence, and so on. It may include a meta-analysis that assigns higher weights to effect measures from more precise studies; pooled, weighted effect measures with confidence limits provide power and precision to results
Heterogeneity	Usually dealt with in a narrative fashion	Heterogeneity dealt with by graphical and statistical methods; attempts are often made to identify sources of heterogeneity
Interpreting results	Prone to cumulative systematic biases and personal opinion	Less prone to systematic biases and personal opinion
Outcome	Actions/directions informed by evidence of various kinds drawn from included papers.	Actions/directions are based on evidence from reviewed papers

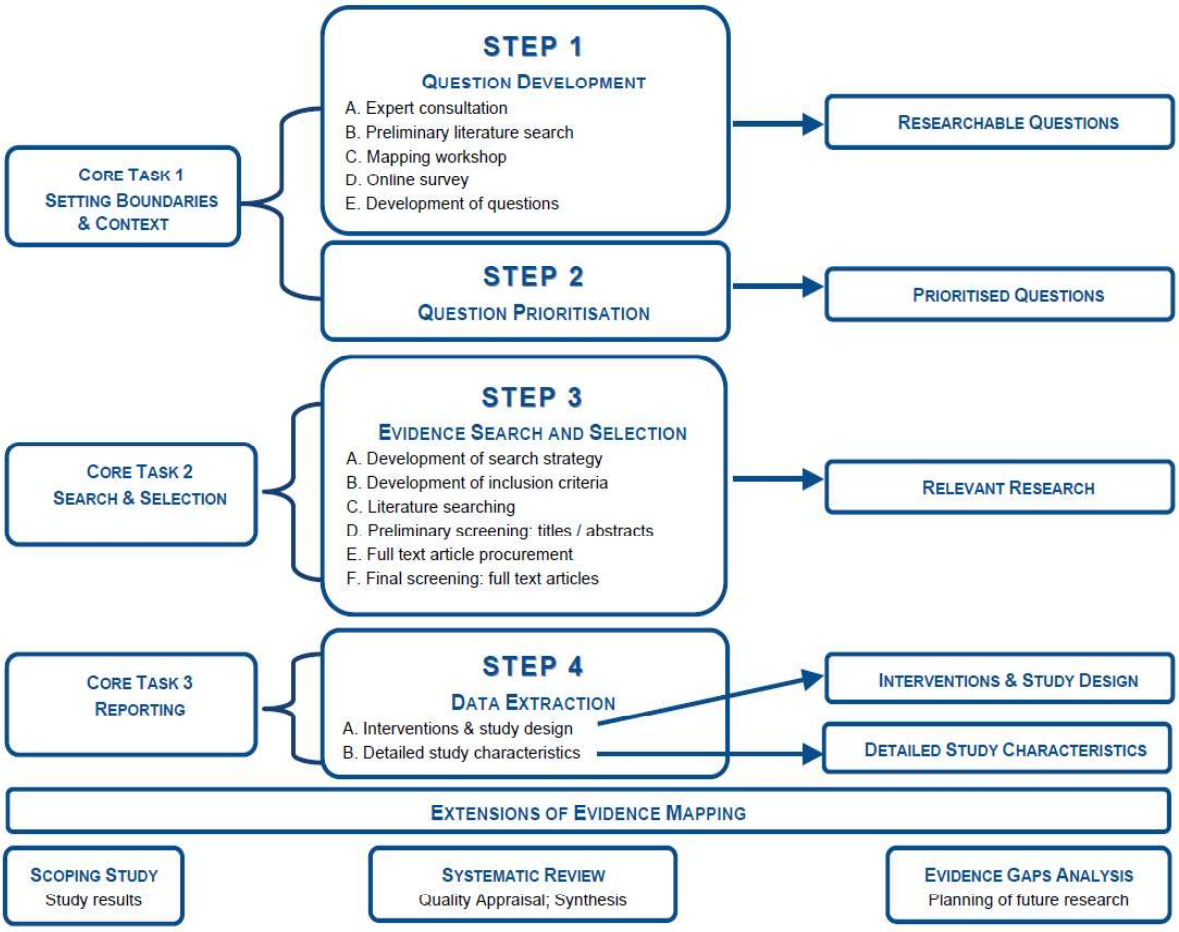
Source: Pai 2004 (40) and Robison 2015 (41)

1.2.2 Evidence mapping methodology

In 2007, the Global Evidence Mapping (GEM) initiative was established as a collaboration of clinical research and policy stakeholders to provide an overview of existing research about traumatic brain injury and spinal cord injury (42). Evidence mapping provides an innovative and visual approach to establish what we know and do not know about the effects of interventions on a thematic area. It can support evidence-informed decision-making by facilitating evidence from existing systematic reviews in a user-friendly format (38, 43). Thus, drawing evidence maps of research fields may help policy-makers to make well-informed decisions and estimate the feasibility and potential costs of a systematic review (44).

According to the GEM initiative (42), the methodology to conduct an evidence mapping comprises three consecutive core tasks (Figure 4). So initially, the boundaries and context of the map must be set by the development of researchable questions. This can be done by expert consultations, preliminary literature searches, a mapping survey, an online survey, or a combination of these. Then, the prioritization of questions must be undertaken. The second core task involves an evidence search and selection as known by the systematic review methodology (37). Finally, reporting task, in which data concerning interventions and study design as well as detailed study characteristics must be extracted. Likewise, extensions of evidence maps may include scoping studies, systematic reviews, and planning future research.

Figure 4. *Evidence mapping methods by GEM initiative*



Source: Bragge 2011(42).

1.3 CLINICAL PRACTICE GUIDELINES

1.3.1 Relevance of clinical practice guidelines to practice

Given growing pressure to provide evidence-based health care, the use of clinical practice guidelines has been increasing globally in past years (45, 46). Clinical practice guidelines are a summary of evidence-based recommendations that were developed using systematic methods of literature review. Thus, they can be considered as helpful tools for the translation of research evidence into practice (47).

Overall, most beneficial therapies are included in clinical practice guidelines, assisting practitioners' and patients' decisions on appropriate healthcare in specific clinical circumstances (47).

The main goals of clinical practice guidelines are to provide explicit recommendations for healthcare professionals involved in clinical practice and to diminish inappropriate clinical discrepancies in order to improve results, reduce risks, and support a cost-effective practice (48). The advantages of using clinical practice guidelines based on the best evidence include the fact that they guide healthcare professionals in decision-making, reducing inadequate variability in clinical practice, promote effective and safe patient outcomes, and that their development involves a multidisciplinary team using the most relevant up-to-date available evidence (45, 49). It is useful to highlight that despite all these benefits, it has been reported that low-quality clinical practice guidelines may also harmfully influence patient care or be of questionable applicability (50, 51). Likewise, some have reported that many clinical practice guidelines are lacking quality and that there is a wide vast of heterogeneity among their recommendations (49, 52).

Although the importance of clinical practice guidelines is widely well recognized, it continues to be ongoing confusion with regards to terminologies used to describe various tools to inform clinical practice, which aim to standardize clinical practice, and thereby improve processes and outcomes of care (53). Often the term "clinical practice guideline" may be interchangeably used with "clinical pathway", "practical protocol" and "practice points". However, they are all uniquely different (54). Overall, the high-quality clinical practice guidelines are developed following a rigorous process and

include recommendations based on the best available evidence (53), while others may not follow explicit criteria (Table 4).

Table 4. *Differences between clinical practice guidelines and protocols*

Clinical practice guidelines	Protocols
Developed following explicit criteria	Developed without explicit criteria
A multidisciplinary team	A group of experts
Systematic review of literature	Narrative review of literature
Assessing the quality of evidence and its levels of recommendations	There is no assessment of evidence
With an external critical appraisal	Without an external critical appraisal

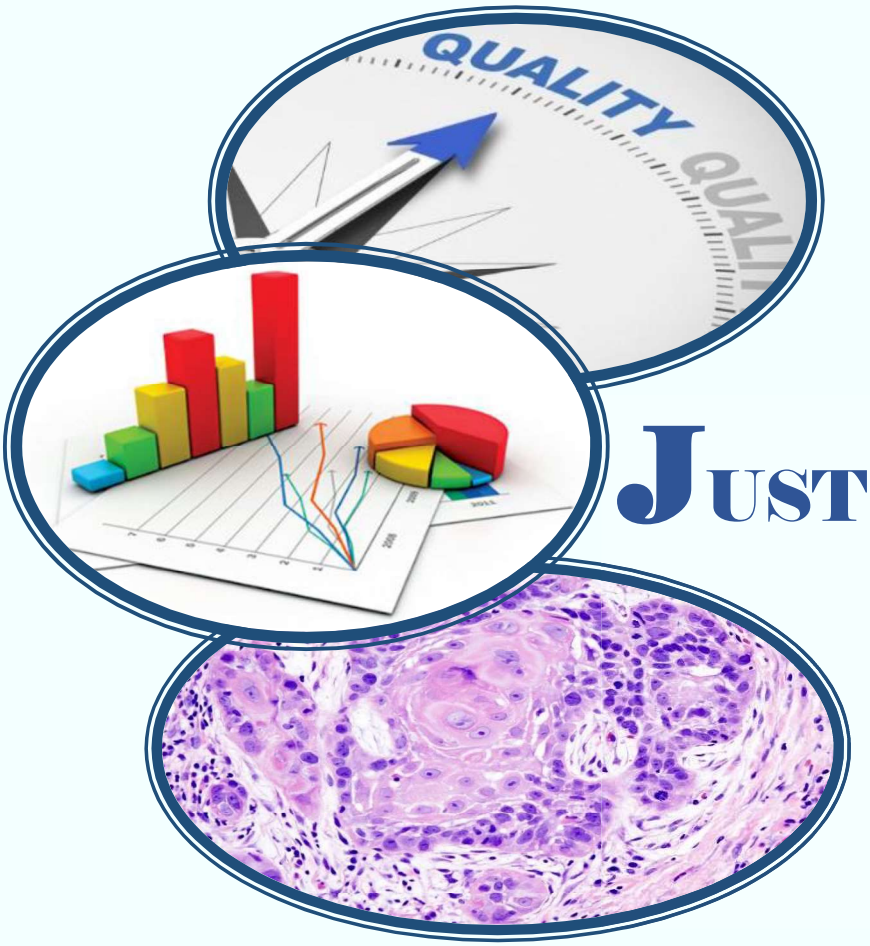
Source: Adapted from Román 2012 (54)

1.3.2 Assessment of clinical practice guidelines

The applicability of any clinical practice guidelines depends on several factors such as rigorous development, clarity of presentation, editorial independence, adequate dissemination, and implementation strategy (48). Multiple tools have been proposed to assess these characteristics (55); however, the most comprehensively validated appraisal tool is the Appraisal of Guidelines Research and Evaluation (AGREE) instrument, which was developed to address the variability issue in clinical practice guidelines quality (56).

In 1988, the AGREE initiative was established by an international group of researchers and clinical practice guidelines developers; the original AGREE instrument was first published in 2003 by the AGREE Collaboration (57). This instrument was updated later, resulting in the new AGREE II published

in 2010 (58, 59). The new AGREE II replaced the original one as the preferred valid reliable international tool to assess the quality of clinical practice guidelines, and can be used as part of an overall quality strategy aimed to improve healthcare (56). All items included in the AGREE II are presented by domains in the Appendix 1.



JUSTIFICATION

2. JUSTIFICATION

Oral cancer has low survival rates due to diagnosis commonly performed in advanced stages (60, 61), and its management is multidisciplinary involving the active participation and collaboration between dentists, physicians, pathologists, maxillofacial surgeons, and oncologists (62, 63). Therefore, any effort focus on the identification of new knowledge that allows improving diagnosis, treatment, and life expectancy of people suffering from this oral disease will be valuable.

The relevance of this doctoral thesis is based on describe and assess the available scientific evidence on diagnosis and treatments for oral cancer. That evidence could be helpful in healthcare, improving transcendental aspects such as survival and quality of life of people suffering from oral cancers. The high mortality rate of oral cancer may be associated with many factors, one of the main ones being the diagnostic delay (60). Commonly, oral suspicious lesions are easy to assess and should be diagnosed early for therapeutic intervention to be effective. Nonetheless, patients are often diagnosed in advanced stages of disease; this might be due to the lack of consultation, or the barriers to adequate healthcare accessibility.

Therefore, these issues need to be addressed using reliable and high-quality clinical practice guidelines, including specific evidence-based recommendations. Moreover, other aspects should be considered. To illustrate, nowadays there are many guidelines including recommendations on

diagnosis and treatments for oral cancer. However, little is known about the quality, applicability, and potential impact of those because their quality has not been systematically evaluated.

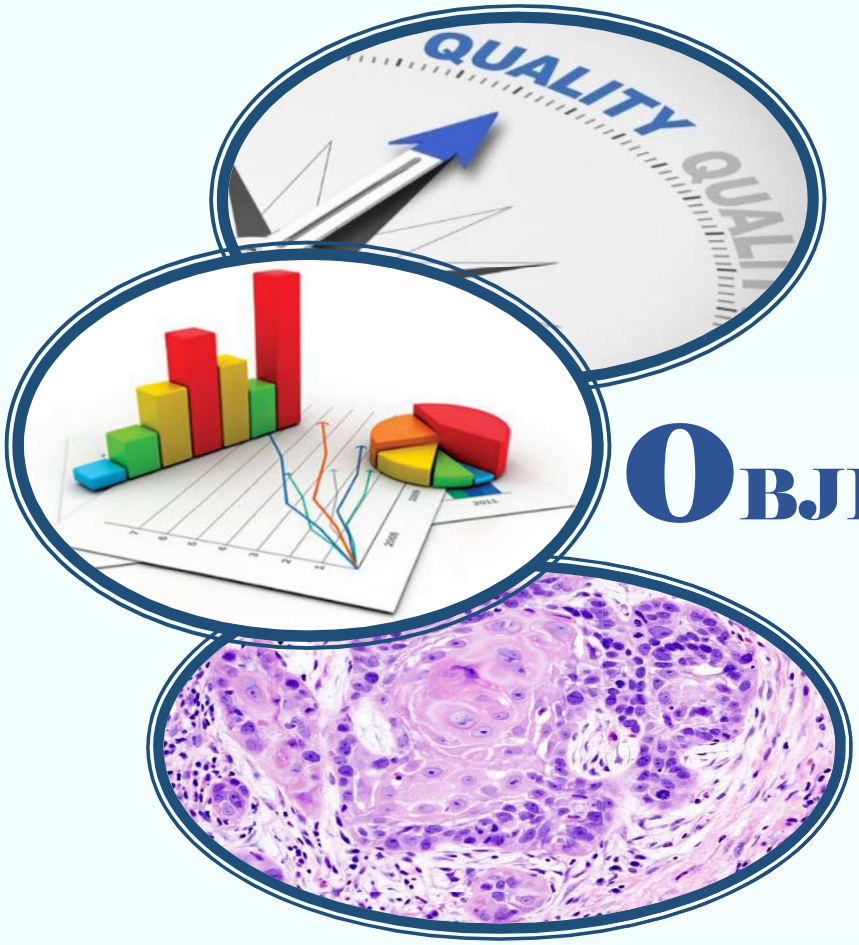
Regarding the treatment of oral cancer, although the complete surgical removal of carcinoma is the first choice, it is not always possible due to various factors such as tumor size, affected structures, and expansion to other organs (62, 63). Basically, the selected therapeutic intervention depends on the type of carcinoma, location, and tumor stage (62). Currently, there are a variety of protocols that combine several therapeutic options such as surgery, radiotherapy, and chemotherapy. However, despite all available different options, some of them may cause adverse effects, impacting the prognosis of the disease; therefore it is necessary to know the effectiveness of these therapies based on available evidence in terms of cure, survival, recurrence, and adverse effects.

Similarly, currently there is a vast published scientific literature proposing a variety of treatment approaches for oral cancer. This fact may hinder knowing the effectiveness of such therapies and when they should be used. Furthermore, some research may be influenced by conflicts of interest. Hence, critical analysis and a methodological quality assessment of the available evidence are required. In this sense, it is pertinent to review, organize and evaluate the available evidence in systematic reviews on therapeutic interventions for patients with oral cancer, and show it in a user-friendly format and helpful for both healthcare professionals and potential patients.

Finally, it is useful to highlight that no previous studies have evaluated the quality of clinical practice guidelines including recommendations on diagnosis and treatments for oral cancer. Likewise, there is no previous report using the evidence mapping methodology to describe the evidence about therapeutic interventions for this oral disease.

The findings of this doctoral thesis will allow having innovative knowledge about the quality of clinical practice guidelines on diagnosis and treatments for oral cancer. Likewise, it will identify the main therapeutic interventions for this disease along with their effectiveness. Thus, this information could be useful to different processes such as elaboration of new clinical practice guidelines or their update, researching on possible gaps that could be identified in this field, and contribute to the decision-making process.

According to this context, the following research question has been formulated as a guiding thread for this doctoral thesis, which will be developed as compendiums of publications: how is the quality of available scientific evidence about diagnosis and treatments for oral cancer?



OBJECTIVES

3. AIM AND OBJECTIVES

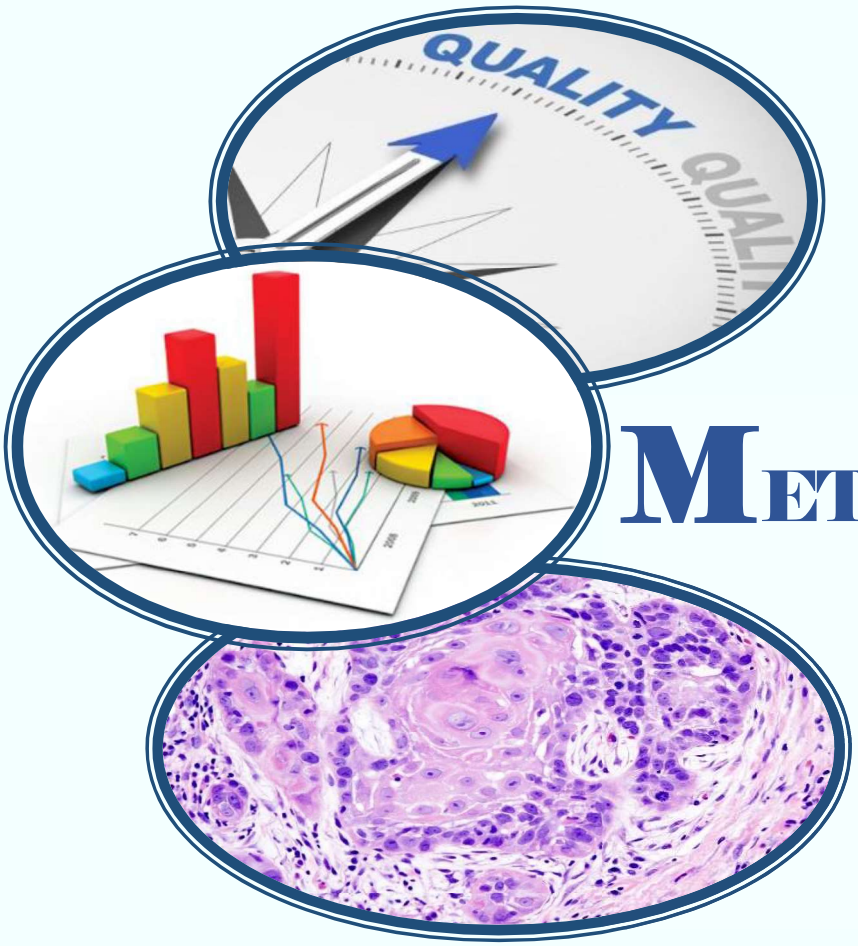
3.1 AIM

The aim of this doctoral thesis is to assess the quality of available scientific evidence about diagnosis and treatments for oral cavity cancer.

3.2 SPECIFIC OBJECTIVES

The specific objectives of this doctoral thesis are the following ones:

1. To identify, organize, and describe the available scientific evidence about the effectiveness of therapeutic interventions for oral cancer.
2. To determine the quality of clinical practice guidelines including recommendations on treatments for oral cancer.
3. To determine the quality of clinical practice guidelines on the diagnosis of oral cancer, and to describe their recommendations.



Methods

4. METHODS

This doctoral thesis is presented through a compendium of scientific publications. Its methods correspond to each study conducted. Likewise, the design of each study was carefully chosen in accordance with the research questions stated.

In order to describe and assess the quality of scientific evidence on diagnosis and treatment about oral cavity cancer, we designed an evidence mapping to describe the available evidence about the main therapeutic interventions for oral cancer. Moreover, systematically critical assessments were performed to determine the quality of clinical practice guidelines including recommendations about diagnosis and treatments for oral cavity cancer.

4.1 STUDY 1. EVIDENCE MAPPING ON THERAPEUTIC INTERVENTIONS FOR ORAL CAVITY CANCER

Study design

An evidence mapping was carried out in accordance with the methodology proposed by the GEM initiative (42).

Search strategy and studies selection

We searched MEDLINE, EMBASE, Epistemonikos, The Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects and Health Technology Assessments. The last search was performed in October 2018. MeSH descriptor and free text terms were used to oral cavity cancer

such as "mouth neoplasms", “oral carcinoma”, “oral cancer”, “oral tumor”, “buccal carcinoma”. No language restrictions were applied.

We included systematic reviews with or without meta-analysis, assessing any treatments in patients diagnosed with oral cavity cancer defined by the International Classification of Diseases for Oncology (C01-C06) (64). These systematic reviews had conducted a comprehensive search in at least two different databases, and reported the assessment of risks of bias or quality of their included studies (37). Conversely, systematic reviews about prognosis, safety or cost-effectiveness were excluded.

Quality assessment of studies and data extraction

The methodological quality of included systematic reviews was assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR-2) tool (65). Moreover, two authors independently extracted data on the general characteristics and research questions addressed in each systematic review. The PICO (Population-Intervention-Comparison-Outcome) framework was used to draw the research questions. In addition, the conclusions of the systematic reviews were classified into five (beneficial, probably beneficial, harmful, no differential effect, inconclusive) categories following previously reported criteria (66).

Data analysis and synthesis of results

We presented the evidence mapping on tables describing the characteristics of the included systematic reviews and all PICOs identified. A narrative description of the PICOs, stratified by disease severity

was performed. Moreover, a bubble plot was designed to display the evidence in three dimensions (authors' conclusions, quality and number of primary studies included in each systematic review).

4.2 STUDY 2. QUALITY OF CLINICAL PRACTICE GUIDELINES ON TREATMENTS FOR ORAL CAVITY CANCER

Study design

A systematic assessment of the quality of clinical practice guidelines

Search strategy and guidelines selection

We searched MEDLINE, EMBASE, TRIP, Clearinghouses, prominent clinical practice guidelines developer groups, and scientific societies in this field in order to identify eligible clinical practice guidelines. We used specific terms for oral cavity cancer such as "mouth neoplasms", "oral carcinoma", "oral cancer", "oral tumor", "buccal carcinoma", with no language restrictions. The last search was conducted in October 2017.

Clinical practice guidelines providing recommendations for the treatment of primary oral cancer in adult population were included. We only selected guidelines published between 2005 and 2017, with an explicit description of their methodology. Conversely, documents without recommendations or guidelines only focused on screening or diagnosis were excluded.

Quality assessment of guidelines and data extraction

Two reviewers independently extracted general characteristics of each clinical practice guidelines. Moreover, four appraisers independently assessed the quality of each guideline using the AGREE II instrument (56, 58). This tool includes 23 items on a seven-point Likert scale across six domains (scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence).

Data analysis

A descriptive analysis of the characteristics of clinical practice guidelines was performed. We calculated the domain scores by adding up all the scores of the individual items in a domain, and by scaling the total as a percentage of the maximum possible score for that domain (56). Consequently, standardization was calculated as follows: (obtained score − minimum possible score) / (maximum possible score − minimum possible score). The range of standardized score for each domain was 0% to 100%. We considered 60% as a threshold of acceptable quality. Descriptive statistics (mean, median, standard deviation, range) were calculated for each domain score for each CPG. In addition, we calculated the intraclass coefficient (ICC) with its 95% confidence interval (95% CI) as an indicator of overall agreement between appraisers. Statistical analyses were performed using SPSS® version 20.0 (SPSS Inc, Chicago, IL).

4.3 STUDY 3. QUALITY OF CLINICAL PRACTICE GUIDELINES ON DIAGNOSIS OF ORAL CAVITY CANCER

Study design

A systematic critical assessment of the quality and recommendations of clinical practice guidelines

Search strategy and guidelines selection

We systematically searched EMBASE, MEDLINE, Clinical practice guidelines' websites and dentistry and oncology scientific societies to identify potential guidelines. We used keywords and terms related to oral cavity tumor and clinical guidelines such as "oral cancer", "oral tumor", "oral carcinoma", "mouth neoplasms", "buccal carcinoma", "guideline", "practice guideline", "guidance", "recommendation". The last search was conducted in May 2018.

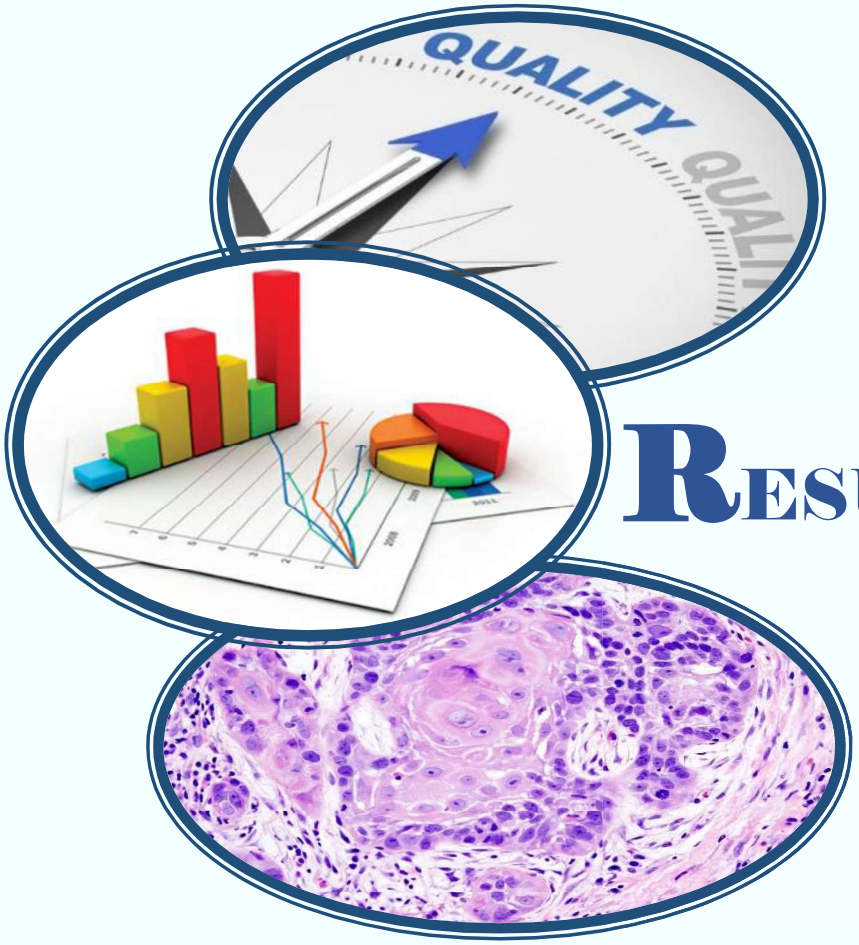
The eligibility criteria were: i) clinical practice guidelines providing recommendations for screening, suspicion or diagnosis of primary oral cavity cancer in adults; ii) guidelines about other cancers were selected if they provided at least two clear recommendations for oral cancer; iii) inclusion of an explicit methods section; iv) publication since 2006; and v) the most recent version from a clinical practice guideline developer.

Quality assessment of guidelines and data extraction

The quality of clinical practice guidelines was independently assessed by four appraisers using the AGREE II instrument (56, 58). Moreover, two authors independently extracted data from each clinical practice guideline such as title, country, year of publication, authoring organization, language, level of development, funding source, whether or not it is an update, recommendations, methods used to determine the recommendations, level of evidence, and grading of the recommendations.

Data analysis

Inter-appraiser agreement was assessed using the ICC with a 95% IC (67). We calculated the domain scores by adding up all the scores of the individual items within a domain, and calculated the percentage of the maximum possible score for that domain (56). Standardized scores (range, 0% to 100%) for each domain were calculated. We used 60% as a cut-off point for adequate quality. Median and the interquartile range were calculated for each domain score for each clinical practice guideline. Moreover, a descriptive analysis of the guidelines' recommendations was conducted. Statistical analyses were performed with SPSS® version 20.0 software (SPSS Inc, Chicago, IL).



RESULTS

5. RESULTS

The results of this doctoral thesis correspond to each study conducted, which have been published in international scientific journals.

SCIENTIFIC PUBLICATIONS COMPRISING THIS DOCTORALTHESIS

Publication 1. Madera Anaya M, Franco JVA, Ballesteros M, Solà I, Urrútia Cuchí G, Bonfill Cosp X. Evidence mapping and quality assessment of systematic reviews on therapeutic interventions for oral cancer. Cancer Manag Res. 2019;11:117–130. doi:10.2147/CMAR.S186700. Impact Factor (IF): 2.886

Publication 2. Madera Anaya MV, Franco JV, Merchan-Galvis AM, Gallardo CR, Bonfill Cosp X. Quality assessment of clinical practice guidelines on treatments for oral cancer. Cancer Treat Rev. 2018; 65:47-53. doi: 10.1016/j.ctrv.2018.03.001. IF: 8.885.

Publication 3. Madera, M., Franco, J., Solà, I. Bonfill J., Alonso-Coello, P. Screening and diagnosis of oral cancer: a critical quality appraisal of clinical guidelines. Clin Oral Invest. 2019; 23:2215-2226. doi.org/10.1007/s00784-018-2668-7. IF:2.812.

5.1 PUBLICATION 1. EVIDENCE MAPPING ON THERAPEUTIC INTERVENTIONS FOR ORAL CAVITY CANCER

5.1.1 SUMMARY OF RESULTS

Characteristics of the included systematic reviews

Fifteen systematic reviews (33, 68-81) met the eligibility criteria, which of 13 systematic reviews (33, 68, 69, 71-79, 81) included a meta-analysis. Nine systematic reviews (68, 72, 74-78, 80, 81) had focused on oral cavity cancer, exclusively. Eight systematic reviews (68, 70, 72, 74, 76, 79-81) assessed surgical interventions; three systematic reviews (69, 73, 77) assessed radiotherapy; three systematic reviews (33, 75, 78) assessed chemotherapy; and one (71) assessed targeted therapy and immunotherapy. The primary studies included in the systematic review were conducted from 1969 to 2015. This evidence mapping included 118 reports of primary studies with 10 423 participants after considering the overlapping or duplication of studies. These studies included 65 (55.1%) RCTs (n = 5 724), 48 (40.7%) observational studies (n = 42 396) and five (4.2%) controlled clinical trials (n = 460).

Methodological quality of systematic reviews

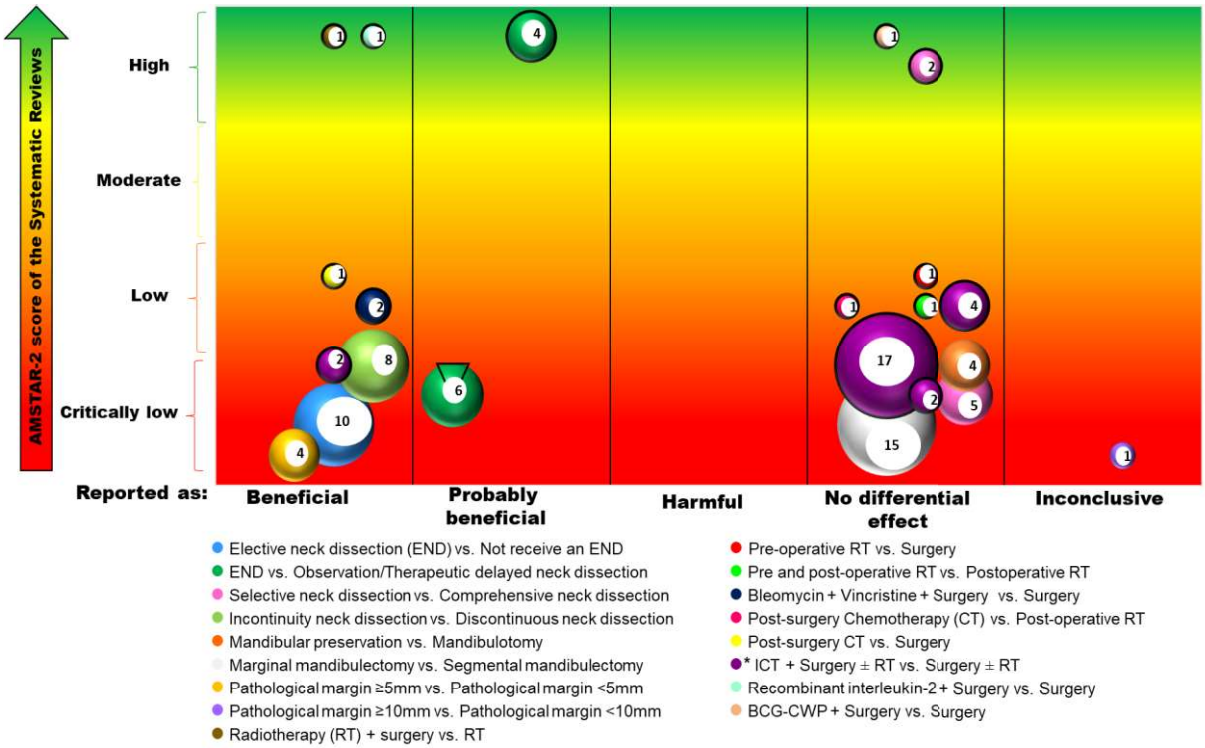
Ten systematic reviews (68, 72, 74-81) scored “critically low”, three systematic reviews (33, 69, 73) scored “low” and only two systematic reviews (70, 71) scored “high” methodological quality, according to AMSTAR-2 critical appraisal criteria. The systematic reviews were downgraded mainly because the authors did not explain their selection of the study designs for inclusion in the review (33, 69-75, 77-81), sources of funding for the included studies were not clearly stated (68, 69, 72, 74-81), there was

no reference to a protocol (68, 72, 74-81) and the list of excluded studies was not provided (68, 72, 74, 76-79, 81).

Characteristic of PICOs from systematic reviews

We extracted 30 PICOs focusing on interventions such as surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy. For resectable oral cancer, thirteen systematic reviews (33, 68, 70-76, 78-81) were conducted including 18 PICOs, of which eight were reported as “beneficial”, one PICO was reported as “probably beneficial”, eight PICOs were reported as “no differential effect”, and one PICO was reported as “inconclusive” (Figure 5).

Figure 5. *Evidence mapping of the therapeutic interventions for resectable oral cancer*



Bubble plots where each bubble represents one systematic review. The number of individual studies included in the systematic review is shown in each bubble and it also is represented by the bubble size. Each bubble also represents a pie showing the proportion of randomized controlled trials included with a black bold line. BCG-CWP: Bacillus Calmette-Guérin-cell wall preparation; ICT: induction chemotherapy; *Two PICOs included this comparison, but the intervention only was reported as "beneficial" in the PICO for patients with positive neck nodes level II.

Regarding the unresectable oral cancer, six systematic reviews (33, 69, 71, 73, 75, 77) were conducted including 12 PICOs, of which only two interventions were reported as "beneficial", two PICO were reported as "probably beneficial", and eight PICOs were reported as "no differential effect" (Table 5).

Table 5. *Therapeutic interventions for unresectable oral cancer by PICO framework*

Systematic reviews	Population	Intervention	Comparison	Outcomes	Primary studies		Conclusion
					RCT	C-Trial	
Baujat 2010**(69)**	Oral squamous cell carcinoma, M0.	Altered fractionated RT	Conventional RT	Survival	Marcial 1987, Dische 1997, Horiot 1997, Jackson 1997, Dobrowsky 2000, Fu 2000, Skladowski 2000, Poulsen 2001, Overgaard 2003, Bourhis 2006.		Beneficial
Chan 2015**(71)**	Primary oral cavity cancers	Gefitinib + RT	RT alone	Disease-free survival Adverse effects	Singh 2013.		No differential effect
Furness 2011(33)	Primary oral cavity and oropharyngeal cancers*	MTX + RT	RT alone	Total mortality	Nervi 1978.		Probably beneficial
Furness 2011(33)	Primary oral cavity cancers	Cisplatin + 5-FU + RT	RT alone	Total mortality Overall survival Disease free survival Recurrent disease	Lewin 1997, Licitra 2003.		No differential effect
Furness 2011(33)	Primary oral cavity and oropharynx cancers*.	Bleomycin + RT	RT alone	Total mortality Locoregional control Disease free survival	Shanta 1980, Morita 1980, Parvinen 1985.		No differential effect
Furness 2011(33)	Primary oral cavity and oropharynx cancers*	Pepleomycin + RT	RT alone	Locoregional control	Krishnamurthi 1990.		Probably beneficial
Furness 2011(33)	Primary oral cavity cancers	Bleomycin	MTX	Tumor regression	Molinari 1982.		Beneficial
Furness 2011(33)	Primary oral cavity cancers	Platin + 5FU	Platin + Vinorelbine	Mortality Disease free survival Toxicity	Segura 2002.		No differential effect
Furness 2011(33)	Primary oral cavity cancers, stage T2 to T4	Induction simultaneous MTX + 5-FU	Sequential MTX + 5-FU	Total mortality	Browman 1986.		No differential effect
Glenny 2010**(73)** Liu 2013**(77)**	Oral cancer, stage T1 to T3, negative neck nodes	High dose rate brachytherapy	Low dose rate brachytherapy	Local recurrence Overall mortality Complications Total mortality Cause specific survival	Inoue 2001.	Inoue 1998, Kakimoto 2003, Umeda 2005, Arrate 2010, Ghadja 2012.	No differential effect
Lau 2016**(75)**	Primary oral cavity cancer	ICT + RT	RT alone	Overall survival Disease free survival Loco-regional recurrence Distant metastasis	Richard 1974, Fazekas 1980, Pearlman 1985, Carugati 1988, Szpirglas 1988, Brunin 1992, Jaulerry 1992, Mazeron 1992, Salvajoli 1992, Martin 1994, Paccagnella 1994, Lewin 1997.		No differential effect
Lau 2016**(75)**	Primary oral cavity cancer	ICT+ CCRT	CCRT	Overall survival Disease free survival Loco-regional recurrence Distant metastasis Adverse effects	Chhatui 2015.		No differential effect

*At least 50% of participants had oral cavity cancer; 5-FU: 5-fluorouracil; CCRT: Concomitant chemo-radiotherapy; ICT: Induction chemotherapy; MTX: Methotrexate; RCT: Randomized controlled trial; C-trial: controlled trial RT: Radiotherapy.

PUBLICATION 1

Madera Anaya M, Franco JVA, Ballesteros M, Solà I, Urrútia Cuchí G, Bonfill Cosp X. Evidence mapping and quality assessment of systematic reviews on therapeutic interventions for oral cancer. *Cancer Manag Res*. 2019;11:117–130.

Cancer Management and Research. 2019.

Impact Factor: 2.886. Q2(163/368). Oncology

Cancer Management and Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Evidence mapping and quality assessment of systematic reviews on therapeutic interventions for oral cancer

This article was published in the following Dove Press journal:
Cancer Management and Research

Meisser Madera Anaya[1–3]
Juan Victor Ariel Franco[4]
Mónica Ballesteros[2]
Ivan Solà[2,3]
Gerard Urrútia Cuchí[2,3]
Xavier Bonfill Cosp[2,3,5]

[1]Department of Research, Faculty of Dentistry, University of Cartagena, Cartagena, Colombia; [2]Iberoamerican Cochrane Centre, Institute of Biomedical Research Sant Pau (IIB Sant Pau), Barcelona, Spain; [3]Department of Public Health and Clinical Epidemiology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; [4]Department of Research, Cochrane Argentina, Instituto Universitario Hospital Italiano, Buenos Aires, Argentina; [5]CIBER de Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain

Purpose: This evidence mapping aims to describe and assess the quality of available evidence in systematic reviews (SRs) on treatments for oral cancer.

Materials and methods: We followed the methodology of Global Evidence Mapping. Searches in MEDLINE, EMBASE, Epistemonikos and The Cochrane Library were conducted to identify SRs on treatments for oral cancer. The methodological quality of SRs was assessed using the Assessing the Methodological Quality of Systematic Reviews-2 tool. We organized the results according to identified Population–Intervention–Comparison–Outcome (PICO) questions and presented the evidence mapping in tables and a bubble plot.

Results: Fifteen SRs met the eligibility criteria, including 118 individual reports, of which 55.1% were randomized controlled clinical trials. Ten SRs scored "Critically low" methodological quality. We extracted 30 PICOs focusing on interventions such as surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy; 18 PICOs were for resectable oral cancer, of which 8 were reported as beneficial. There were 12 PICOs for unresectable oral cancer, of which only 2 interventions were reported as beneficial.

Conclusion: There is limited available evidence on treatments for oral cancer. The methodological quality of most included SRs scored "Critically low". The main beneficial treatment reported by authors for patients with resectable oral cancer is surgery alone or in combination with radiotherapy or chemotherapy. Evidence about the benefits of the treatments for unresectable oral cancer is lacking. These findings highlight the need to address future research focused on new treatments and knowledge gaps in this field, and increased efforts are required to improve the methodology quality and reporting process of SRs on treatments for oral cancer.

Keywords: mouth neoplasms, oral carcinoma, buccal tumor, evidence synthesis, evidence-based medicine

Introduction

Oral cancer is one of the most prevalent cancers worldwide. Oral squamous cell carcinoma is the most common cancer occurring in the mouth, with an estimate of 300,000 new cases globally each year; only in the US, there were around 50,000 new cases expected in 2017.[1] Oral cancer is posing an ever-increasing threat to global health and represents a growing burden on health services, which is a major problem in some parts of the world, especially in developing countries. Risk factors for oral cancer are frequently associated with lifestyle habits, such as smoking, alcohol abuse, poor nutrition and the use of betel quid.[2]

Unfortunately, the overall prognosis in these patients is low, with a 5-year survival rate of 50%, which has not changed over the last decades despite the advances in oncology treatment.[3] Locoregionally advanced oral cavity cancers are

Correspondence: Meisser Madera Anaya
Iberoamerican Cochrane Centre, Carrer Sant Antoni Maria Claret 167, Pavello 18, Planta 0, CP: 08025, Barcelona, Spain
Tel +34 93 553 7808
Email mmaderaa@unicartagena.edu.co

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/CMAR.S186700

aggressive tumors with high probabilities of relapse after definitive treatment with surgery or radiotherapy. Therefore, a multimodal approach, combining surgery and postoperative radiotherapy or chemoradiotherapy, has been suggested.[4,5]

Currently, there is a vast published scientific literature proposing a variety of treatment approaches for oral cancer. This fact may hinder knowing the effectiveness of such therapies and when they should be used. Furthermore, some research may be influenced by conflicts of interest. Thus, a critical analysis and a methodological quality assessment of the available evidence are required. In this sense, one of the options to organize and critically assess published studies is systematic reviews (SRs), which summarize the results of the evidence from health care primary studies in order to answer a specific research question.[6]

Likewise, there are new tools for evidence synthesis, such as evidence mapping, scoping reviews and rapid reviews, which have been developed to help clinicians, patients, researchers and other stakeholders to make evidence-based decisions.[7] These new options are appropriate to address issues that may be too extensive for an SR.[8]

In 2007, the Global Evidence Mapping (GEM) initiative was established as a collaboration of clinical research and policy stakeholders to provide an overview of existing research about traumatic brain injury and spinal cord injury.[9] Evidence mapping provides an innovative and visual approach to establish what we know and do not know about the effects of interventions on a thematic area. It can support evidence-informed decision making by facilitating evidence from existing SRs in a user-friendly format.[7,10]

The aim of this evidence mapping is to identify, describe and organize the current available evidence in SRs regarding therapeutic interventions for oral cancer. This approach purposes to determine the clinical questions assessed in the scientific literature and the corresponding quality of the supporting evidence, as well as to give general information about their claimed effectiveness. This information shall facilitate detecting research gaps and help stakeholders in the decision-making process.

Materials and methods

Study design

This evidence mapping adhered to the PRISMA-Extension for Scoping Reviews.[11] It was carried out in accordance with the methodology proposed by GEM,[9] adding some previously suggested tasks.[12] All methods were specified a priori in a protocol (available on request).

Eligibility criteria

We included SRs published any year, with or without meta-analysis, assessing any therapeutic interventions in patients diagnosed with oral cavity cancer defined by the ICD for Oncology[13] with codes C01–C02, C03, C04 and C05–C06. SRs related to head and neck cancer (C00–C14) with cases of oral cancer were included (as long as at least 50% of the participants had oral cavity cancer, or data for this cancer alone were available separately). Included SRs had conducted a comprehensive search in at least two different databases and reported the assessment of risks of bias or quality of their included studies.[6] When several articles published by the same team were identified, we considered the most recent publication. Conversely, SRs about prognosis, safety or cost-effectiveness were excluded.

Search strategy

We searched for systematic literature in MEDLINE (via PubMed), EMBASE (via Ovid), Epistemonikos, The Cochrane Database of Systematic Reviews (via The Cochrane Library) and Database of Abstracts of Reviews of Effects and Health Technology Assessments (via The Cochrane Library). The latest search was conducted on October 25, 2018.

We used MeSH descriptor and free text terms for oral cavity cancer, such as "mouth neoplasms", "oral carcinoma", "oral cancer", "oral tumor", "buccal carcinoma", and thesaurus terms when available. We adapted the search strategy in accordance with the specific characteristics of each database (Supplementary material 1) with no language restrictions. In addition, a cited reference search was conducted.

SR selection

We managed all retrieved titles and abstracts with the reference manager software EndNote® (Version X7, Thomson Reuters). After removing duplicates, two reviewers (MMA and JVAF) independently screened all titles/abstracts to exclude irrelevant studies. Then, full articles were obtained for a final decision. Detailed reasons for exclusion of any study considered relevant were clearly stated.

Methodological quality assessment

The report of methodological quality for each SR was assessed with the Assessing the Methodological Quality of Systematic Reviews (AMSTAR)-2 tool, a validated 16-item instrument for critically appraising SRs.[14] It has an overall rating based on weaknesses in critical domains (items: 2, 4, 7, 9, 11, 13 and 15). Briefly, the overall confidence in the results of the SR is rated in the following four categories: "High", no or one non-critical weakness;

"Moderate", more than one non-critical weakness; "Low", one critical flaw with or without non-critical weaknesses and "Critically low", more than one critical flaw with or without non-critical weaknesses.

Data extraction

General characteristics of the SR: authors, publication year, type of SR (with or without meta-analysis), objective, search date, design and number of included studies, and number of included participants.

Characteristics of research questions: we identified the research questions of each SR based on the aims stated by the authors, the eligibility criteria and the conclusions of the SR. The research questions were drawn using the PICO framework, which specifies the four key components of a well-defined therapeutic question: population, intervention, comparison and outcomes.[6] A research question was considered if all the elements of the PICO framework were provided and a conclusion about the direction of the effect was described anywhere in the SR. We extracted details on the population characteristics (eg, adult population, type of cancer, stage and cancer location), the intervention and comparator (eg, type of intervention and comparison broadly categorized as chemotherapy, surgery, radiotherapy, immunotherapy and targeted therapy) and the outcomes.

The conclusions of the SR authors were classified into five categories following previously reported criteria.[12] Briefly, the "beneficial" category was used if there were conclusions with evidence of a positive effect and SR authors used a language clearly indicative of a beneficial effect without major concerns regarding the existing evidence. The "probably beneficial" category was used for those conclusions where the evidence base was insufficient to draw firm conclusions despite the positive treatment effect and the reporting suggested a benefit. The "harmful" category was used when the reporting of the conclusions was clearly indicative of a harmful effect. The "no differential effect" category was used for conclusions that provided evidence for no difference between the intervention and the comparator. Finally, the "inconclusive" category was used if the direction of results was different across or within reviews due to conflicting results or limitations of individual studies.

Two authors (MMA and JVAF) independently performed all processes of study selection, methodological quality assessment and data extraction. If there were any disagreements, these were resolved by consensus, and when necessary, an additional reviewer (GUC) participated in the discussion until an agreement was reached. If needed, we contacted the SR authors for clarification or to obtain missing information.

Evidence mapping presentation

We presented the evidence mapping on tables describing the characteristics of the included SRs and on other tables providing the characteristics of all identified PICOs. We performed a narrative description of the PICOs stratified by disease severity (resectable and nonresectable cancers). In addition, we designed a bubble plot where each bubble represents one SR. This chart displays information in three dimensions: 1) the rating of authors' conclusions represented in the x-axis as "beneficial", "probably beneficial", "harmful", "no differential effect" and "inconclusive"; 2) AMSTAR-2 assessment in y-axis and 3) the number of primary studies included in the SR, which is shown in each bubble and is represented by the bubble size. Each bubble also represents a pie showing the proportion of randomized controlled trials (RCTs) included using a black bold line.

Results

Studies selected

The research yielded 2,547 records after removing duplicates. After title and abstract screening, 127 articles were obtained for final full-text review; 15 SRs[15–29] met the eligibility criteria (Figure 1). The list of excluded studies along with exclusion rationale is available in Supplementary material 2.

Characteristics of the included SRs

Thirteen SRs[15,16,18–27,29] included a meta-analysis, and all SRs[15–29] were published in English between 2010 and 2018. Nine SRs[15,19,22–26,28,29] had focused on oral cavity cancer exclusively, whereas other six SRs[16–18,20,21,27] had focused on head and neck cancers, with the oropharyngeal cancer being the most frequent among them. Eight SRs[15,17,19,22,24,27–29] assessed surgical interventions, three SRs[16,21,25] assessed radiotherapy, three SRs[20,23,26] assessed chemotherapy and one SR[18] assessed targeted therapy and immunotherapy. SRs included primary studies conducted from 1969 to 2015; the number of patients included in each SR ranged from 309 to 16,767 adult individuals. This evidence mapping included 118 reports of primary studies (Supplementary material 3) with 10,423 participants after considering the overlapping or duplication of studies. These studies included 65 (55.1%) RCTs (n=5,724), 48 (40.7%) observational studies (n=42,396) and 5 (4.2%) controlled clinical trials (n=460). Table 1 shows the characteristics of included SRs.

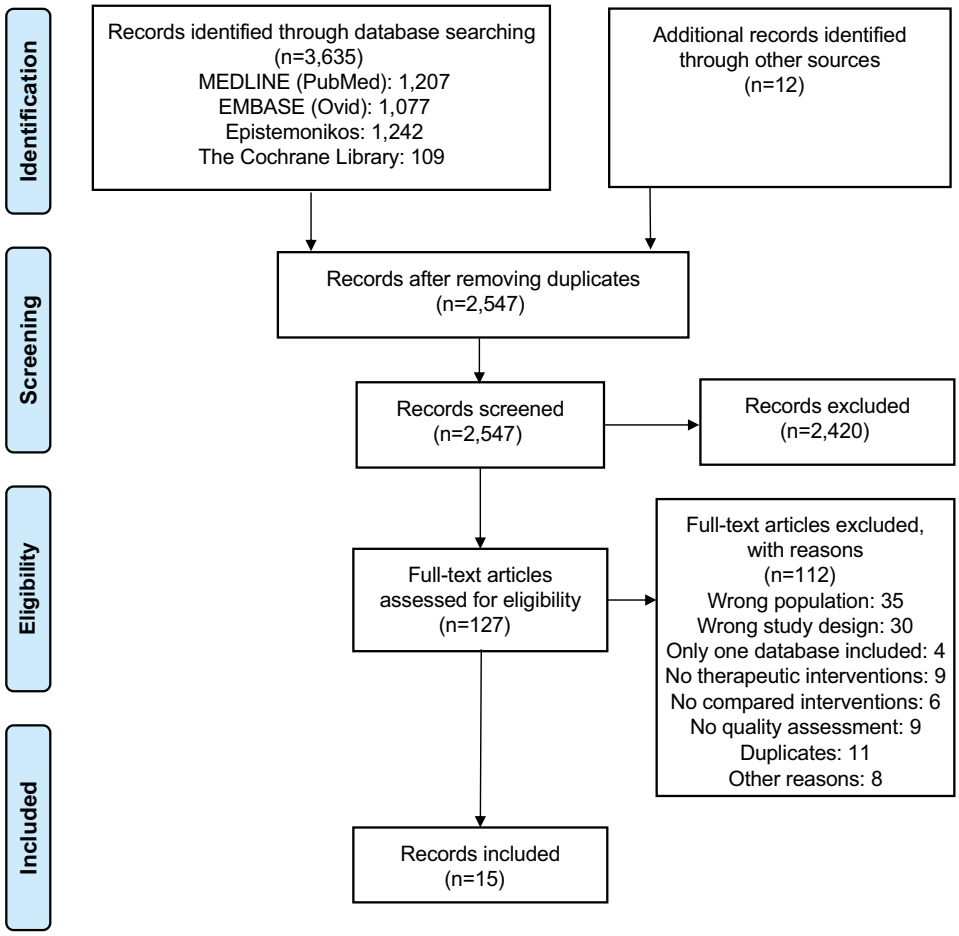


Figure 1 PRISMA flow diagram detailing the selection process.

The methodological quality of SRs

Ten SRs[15,19,22–29] scored "Critically low", three SRs[16,20,21] scored "Low" and only two SRs[17,18] scored "High" methodological quality, according to the AMSTAR-2 critical appraisal criteria (Figure 2). The SRs were downgraded mainly because the SR authors did not explain their selection of the study designs for inclusion in the review,[16–23,25–29] sources of funding for the included studies were not clearly stated,[15,16,19,22–29] there was no reference to a protocol,[15,19,22–29] and the list of excluded studies was not provided.[15,19,22,24–27,29]

Characteristics of PICOs from SRs

The evidence mapping of the therapeutic interventions for oral cancer is presented in Figure 3; 30 PICOs were extracted, which focused on two population groups: patients with resectable oral cancers and patients with unresectable cancer.

Patients with resectable oral cancers

Thirteen SRs[15,17–24,26–29] were conducted including 18 PICOs. Eight PICOs evaluated surgical interventions,[17,19,22,24,27–29] five PICOs assessed chemotherapy,[20,23,26] three PICOs assessed radiotherapy[17,21] and two PICOs assessed immunotherapy.[18] Eight PICOs were reported as "beneficial", one PICO as "probably beneficial", eight PICOs as "no differential effect" and one PICO was reported as "inconclusive" (Table 2).

Interventions reported as "beneficial" were as follows: 1) the elective neck dissection was better than no elective neck dissection in patients with negative neck nodes in terms of cervical metastasis rate, overall 5-year survival rate and occult cervical metastasis;[28] 2) the incontinuity neck dissection was better than discontinuous neck dissection in terms of local recurrence;[29] 3) a wider pathological margin (≥5 mm) was better than a narrow pathological margin (<5 mm) in terms of local recurrence rates in patients with oral squamous cell carcinoma treated by primary surgery without adjuvant therapy;[15] 4) radiotherapy combined with surgery was better than radiotherapy alone in terms of total mortality;[17] 5) the use of intra-arterial bleomycin and vincristine combined with surgery was better than surgery alone in terms of overall survival;[20] 6) post-surgery chemotherapy using methotrexate as chemotherapy drug was better than surgery alone in terms of total mortality;[20] 7) induction chemotherapy followed by surgery with or without radiotherapy was better than surgery with or without radiotherapy in patients with positive

Table 1 Characteristics of the included SRs

Author and year	Study design	Search date	Objective	Design and number of included studies	Participants (n)	AMSTAR-2 score
Anderson et al, 2015[15]	SRM	Not given	To determine whether a wider pathological margin reduces local recurrence rates in patients with OSCC treated by primary surgery without adjuvant therapy	Cohort: 5	539	Critically low
Baujat et al, 2010[16]	SRM	August 2010	To study the effects of altered fractionation radiotherapy vs conventional radiotherapy on overall survival rates	RCT: 15	6,515	Low
Bessell et al, 2011[17]	SR	February 2011	To determine which surgical treatment modalities for oral cavity and oropharyngeal cancers result in increased overall survival, disease-free survival, progression-free survival and reduced recurrence	RCT: 7	669	High
Chan et al, 2015[18]	SRM	February 2015	To assess the effects of molecularly targeted therapies and immunotherapies, in addition to standard therapies, for the treatment of oral cavity or oropharyngeal cancers	RCT: 12	2,488	High
Ding et al, 2018[19]	SRM	November–December 2017	To compare elective neck dissection with observation or therapeutic neck dissection specifically in patients with early-stage OSCC and clinically N0 neck to explore the potential benefits of elective neck dissection	RCT: 5 Case–control: 1	865	Critically low
Furness et al, 2011[20]	SRM	December 2010	To determine whether chemotherapy, in addition to radiotherapy and/or surgery for oral cavity and oropharyngeal cancer, results in increased overall survival, disease-free survival, progression-free survival, locoregional control and reduced recurrence	RCT: 89	16,767	Low
Glenny et al, 2010[21]	SRM	July 2010	To determine which radiotherapy regimens for oral cavity and oropharyngeal cancers result in increased overall survival, disease-free survival, progression-free survival and locoregional control	RCT: 30	6,536	Low
Gou et al, 2018[22]	SRM	May 2016	To explore the survival rate and disease control in patients with histological evidence of bone invasion and to compare the differences in survival rate and disease control between patients who underwent marginal mandibular resection and those who underwent segmental mandibulectomy	Cohort: 15	1,672	Critically low
Lau et al, 2016[23]	SRM	March 2016	To analyze the effect of induction chemotherapy in OSCC treatment by performing an updated SR and cumulative meta-analysis	RCT: 27	2,872	Critically low
Liang et al, 2015[24]	SRM	April 2015	To access the feasibility of selective neck dissection in oral cancer patients with positive neck nodes	Cohort: 5	443	Critically low
Liu et al, 2013[25]	SRM	June 2012	To compare the efficacy and safety of high-dose rate and low-dose rate brachytherapy in treating early-stage oral cancer	RCT: 1 Controlled trial: 5	607	Critically low
Marta et al, 2015[26]	SRM	January 2015	To assess the effectiveness and safety of induction chemotherapy prior to surgery for untreated OSCC patients	RCT: 2	451	Critically low

(*continued*)

Table 1 (*continued*)

Author and year	Study design	Search date	Objective	Design and number of included studies	Participants (n)	AMSTAR-2 score
Pang et al, 2016[27]	SRM	September 2016	To compare the prognoses outcomes of mandibular preservation method and the mandibulotomy approach in oral and oropharyngeal cancer patients	Cohort: 6	309	Critically low
Tang and Leung, 2016[28]	SR	February 2015	To answer the clinical question, "When should elective neck dissection be performed in maxillary gingival and alveolar squamous cell carcinoma with negative neck nodes?"	Cohort: 10	506	Critically low
Wang et al, 2018[29]	SRM	March 2017	To perform a meta-analysis to compare discontinuous neck dissection with incontinuity neck dissection as a treatment modality for SCC of the tongue and floor of the mouth	Cohort: 8	796	Critically low

Abbreviations: AMSTAR-2, Assessing the Methodological Quality of Systematic Reviews-2; OSCC, oral squamous cell carcinoma; RCT, randomized controlled trial; SCC, squamous cell carcinoma; SR, systematic review; SRM: systematic review with meta-analysis.

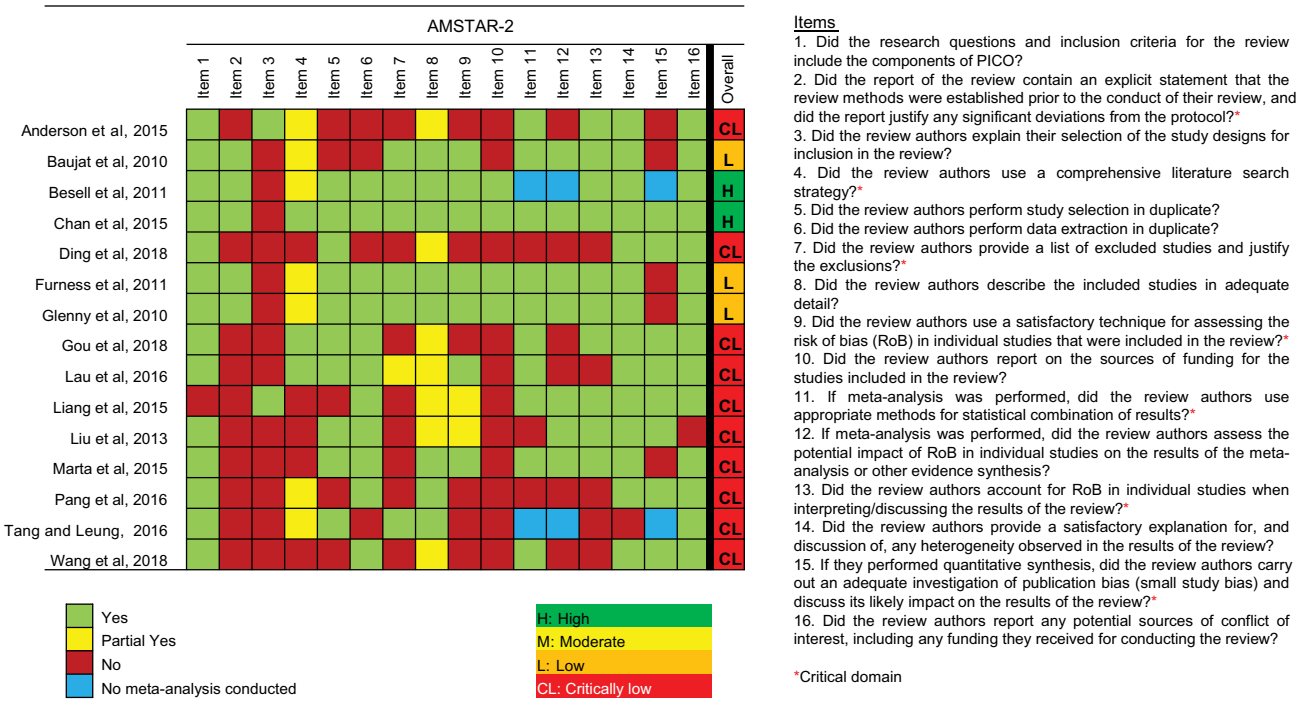


Figure 2 Methodological quality of the included systematic reviews.
Abbreviation: AMSTAR-2, Assesing the Methodological Quality of Systematic Reviews-2; PICO, Population–Intervention–Comparison–Outcome.

nodules classified as level II, in terms of overall survival[26] and 8) the use of recombinant interleukin-2 plus surgery was better than surgery alone in terms of overall survival.[18]

Patients with unresectable cancer

Six SRs[16,18,20,21,23,25] were conducted including 12 PICOs. Nine PICOs assessed chemotherapy,[20,23] two PICOs assessed radiotherapy[16,21,25] and one PICO assessed targeted therapy.[18] Two PICOs were reported as "beneficial", two PICOs as "probably beneficial" and eight PICOs were reported as "no differential effect" (Table 3).

The interventions reported as "beneficial" were: 1) altered fractionation radiotherapy was better than conventional radiotherapy in terms of overall survival[16] and 2) bleomycin was better than methotrexate in terms of tumor regression.[20]

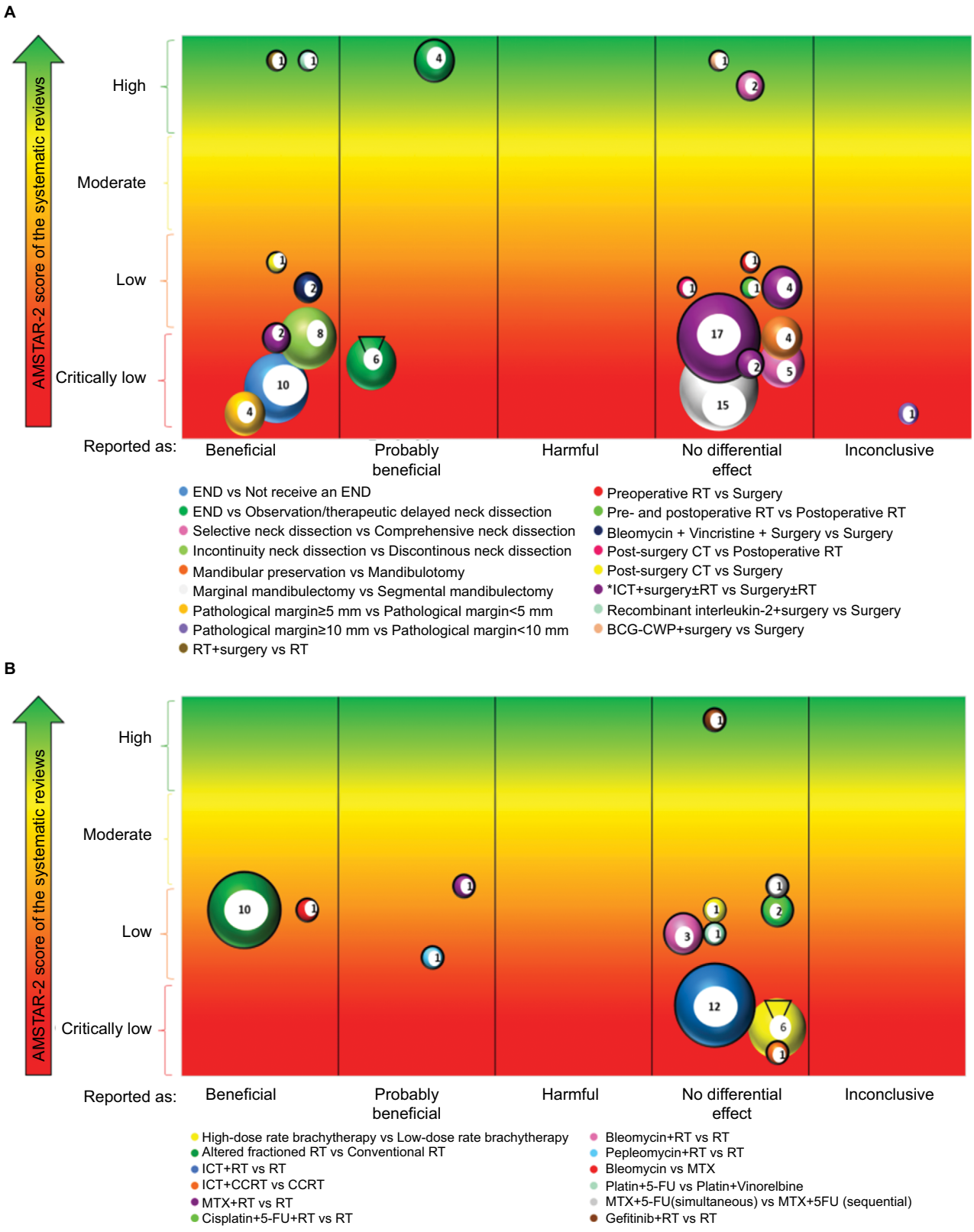


Figure 3 Evidence mapping of the therapeutic interventions for oral cancer.

Notes: (**A**) Interventions for resectable oral cancer. (**B**) Interventions for unresectable oral cancer. Bubble plots where each bubble represents one SR. The number of individual studies included in the SR is shown in each bubble and is represented by the bubble size. Each bubble also represents a pie showing the proportion of randomized controlled trials included with a black bold line. *Two PICOs included this comparison, but the intervention was reported as "beneficial" only in the PICO for patients with positive neck nodes level II. The number of individual studies included in the SR is shown in each bubble and is represented by the bubble size.

Abbreviations: 5-FU, 5-fluorouracil; BCG-CWP, Bacillus Calmette-Guérin-cell wall preparation; CCRT, concomitant chemo-radiotherapy; CT, chemotherapy; END, elective neck dissection; ICT, induction chemotherapy; MTX, methotrexate; PICO, Population–Intervention–Comparison–Outcome; RT, radiotherapy; SR, systematic review.

Table 2 Therapeutic interventions for resectable oral cancer by PICO framework

Systematic reviews	Population	Intervention	Comparison	Outcomes	Primary studies		Conclusion
					RCT	Observational	
Anderson et al, 2015[15]	Primary oral cavity cancers	Wider pathological margin (≥5 mm)	Narrow pathological margin (<5 mm)	Local recurrence		Sadeghi 1986, Loree 1990, Hicks 1997, Sieczka 2001	Beneficial
Anderson et al, 2015[15]	Primary oral cavity cancers	Wider pathological margin (≥10 mm)	Narrow pathological margin (<10 mm)	Local recurrence		Hicks 1998	Inconclusive
Bessell et al, 2011[17] Ding et al, 2018[19]	Primary oral cavity cancers, clinically negative neck nodes	Elective neck dissection	Observation/ therapeutic delayed neck dissection	Overall survival Disease-free survival Locoregional control Regional recurrences Death related to recurrences Occult lymph node metastasis Total number of recurrences	D Cruz 2015, Fakih 1989, Kligerman 1994, Vanderbrouck 1980, Yuen 2009	Mirea 2014	Probably beneficial
Bessell et al, 2011[17] Liang et al, 2015[24]	Primary oral cavity cancers, clinically positive neck nodes	Selective neck dissection	Comprehensive neck dissection	Regional recurrence Disease-specific death Overall death Overall survival Disease-free survival Disease recurrence	Bier 1994, BHNCSG 1998	Schiff 2005, Patel 2008, Yanai 2011, Shin 2013, Feng 2014	No differential effect
Bessell et al, 2011[17]	Head and neck cancers[a], stage T2–T4, N0–N2, M0	RT+surgery	RT alone	Total mortality	Robertson 1998		Beneficial
Chan et al, 2015[18]	Head and neck cancers[a]	Recombinant interleukin-2 + surgery	Surgery alone	Overall survival Disease-free survival Adverse effects	De Stefani 2002		Beneficial
Chan et al, 2015[18]	Head and neck cancers[a]	Pretreatment with BCG-CWP followed by surgery	Surgery alone	Overall survival Adverse effects	Bier 1981		No differential effect
Furness et al, 2011[20]	Primary oral cavity cancers	Bleomycin + vincristine + surgery	Surgery	Total mortality Disease-free survival Overall survival	Luboinski 1985, Richard 1991		Beneficial
Furness et al, 2011[20]	Primary oral cavity cancers	Post-surgery CT (MTX)	Postoperative RT	Total mortality Disease-free survival	Bitter 1979		No differential effect
Furness et al, 2011[20]	Primary oral cavity cancers	Post-surgery CT (MTX)	Surgery alone	Disease-free survival Disease recurrence Total mortality	Rao 1994		Beneficial

(*continued*)

Table 2 (*continued*)

Systematic reviews	Population	Intervention	Comparison	Outcomes	Primary studies		Conclusion
					RCT	Observational	
Furness et al, 2011[20] Lau et al, 2016[23] Marta et al, 2015[26]	Primary oral cavity cancers, stage T1–T4	ICT+surgery±RT	Surgery±RT	Total mortality Locoregional recurrence Disease-free survival Overall survival Distant metastasis	Szpirglas 1979, Holoye 1985, Luboinski 1985, Pearlman 1985, HNCProg 1987, Toohill 1987, Schuller 1988, Richard 1991, Depont 1993, Di Blasio 1994, Martin 1994, Paccagnella 1994, Volling 1994, Dalley 1995, Maipang 1995, Hasegawa 1996, Szabo 1999, Bossi 2014/Licitra 2003, Zhong 2015/Zhong 2013		No differential effect
Glenny et al, 2010[21]	Head and neck cancers[a]	Pre-operative RT	Surgery alone	Total mortality Locoregional control	Ketcham 1969		No differential effect
Glenny et al, 2010[21]	Primary oral cavity cancers, stage T2, N0–N2, M0	Preoperative and postoperative RT	Postoperative RT alone	Total mortality Locoregional control Disease-free survival	Bergermann 1992		No differential effect
Gou et al, 2018[22]	Primary oral cavity cancers	Marginal mandibulectomy	Segmental mandibulectomy	Disease-free survival Overall survival Local control		Ash 2000, Totsuka 1991, Ord 1997, Munoz Guerra 2003, O'Brien 2003, Patel 2008, Shaw 2004, Soo 1988, Wald 1983, Werning 2001, Pascoal 2007, Nie 2000, Barttelbort 1987, Dubner 1993, Overholt 1996	No differential effect
Marta et al, 2015[26]	Primary oral cavity cancers, positive neck nodes level II	ICT+surgery±RT	Surgery±RT	Overall survival Locoregional recurrence	Zhong 2013, Bossi 2014/Licitra 2003		Beneficial
Pang et al, 2016[27]	Primary oral cavity cancers	Mandibular preservation	Mandibulotomy	Surgical margins Survival rate Recurrence rate Fistula formation Functionality		Devine 2001, Song 2013, Li 2014, Li 2015	No differential effect
Tang and Leung, 2016[28]	Primary oral cavity cancers, stage T1–T4, with negative neck nodes	Elective neck dissection	Not receiving an elective neck dissection	Cervical metastasis rate Occult cervical metastasis Overall 5-year survival rate		Simental 2006, Montes 2008, Mourouzis 2010, Lubek 2011, Morris 2011, Poeschl 2012, Feng 2013, Brown 2013, Yang 2014, Philip 2014	Beneficial
Wang et al, 2018[29]	Primary oral cavity cancers	Incontinuity neck dissection	Discontinuous neck dissection	Local recurrence		Spiro 1973, Leemans 1991, Tesseroli 2006, Lim 2007, Feng 2015, Hu 2005, Zhang 2007, Guo 2009	Beneficial

Note: [a]At least 50% of the participants had oral cavity cancer.

Abbreviations: BCG-CWP, Bacillus Calmette-Guérin-cell wall preparation; CT, chemotherapy; ICT, induction chemotherapy; MTX, methotrexate; PICO, Population–Intervention–Comparison–Outcome; RCT, randomized controlled trial; RT, radiotherapy.

Discussion

Evidence mapping is a relatively new tool used to summarize available scientific evidence about a specific topic. However, although there is no standard definition of it or consensus about its components or the methods to be used, there are common characteristics for these types of review.[7] In general, it includes a systematic search covering a broad field to identify gaps in knowledge and/or future research needs. It also presents results in a user-friendly format, often a visual figure or graph, or a searchable database.[7] Evidence mapping can produce an extensive list of prioritized research questions in a topic area, even in the absence of study retrieval and data extraction. It is a potential springboard for research, policy development and research funding.[9]

This evidence mapping may be the first one about therapeutic interventions for oral cancer because we found no previous reports. We decided to use this methodology developed by GEM initiative since it is rational and systematic.[9] Recently, a report stated that most of the documents that met the common characteristics of evidence mapping referenced this methodology.[7] The referenced methodology includes three core tasks: setting the boundaries and context of the topic area in question, searching and selecting relevant studies and reporting on search results and study characteristics.[9] Moreover, we added two uncommon components in evidence mapping, which were previously reported: the methodological quality assessment of SRs and the classification of the conclusions as beneficial, probably beneficial, no differential effect, inconclusive or harmful according to the results reported by authors.[12] It has been suggested that this approach allows locating the results of one study in relation to other studies with the same comparison on a bubble plot, obtaining a broader outlook of the available evidence and its quality.[12]

The results of this evidence mapping show that in line with available evidence, there is a sprinkling of SRs about therapeutic interventions for oral cancer, since only 15 SRs focusing on different therapies met the criteria. Moreover, most SRs included a small number of primary studies; thus, it may suggest that the evidence of this issue is limited. However, we wish to highlight that most of the primary studies included in this evidence mapping were RCTs, which is an aspect with clinical relevance because experimental studies are the best design to evaluate the efficacy of new therapeutic options.[30] We also highlight that no comparison was reported as "harmful", which is probably because most RCTs with negative conclusions are seldom published.[31]

Table 3 Therapeutic interventions for unresectable oral cancer by PICO framework

Systematic reviews	Population	Intervention	Comparison	Outcomes	Primary studies		Conclusion
					RCT	Controlled trial	
Baujat et al, 2010[16]	Primary oral cavity cancers, M0	Altered fractionated RT	Conventional RT	Survival	Marcial 1987, Dische 1997, Horiot 1997, Jackson 1997, Dobrowsky 2000, Fu 2000, Skladowski 2000, Poulsen 2001, Overgaard 2003, Bourhis 2006		Beneficial
Chan et al, 2015[18]	Primary oral cavity cancers	Gefitinib+RT	RT alone	Disease-free survival Adverse effects	Singh 2013		No differential effect
Furness et al, 2011[20]	Primary oral cavity and oropharyngeal cancers[a]	MTX+RT	RT alone	Total mortality	Nervi 1978		Probably beneficial
Furness et al, 2011[20]	Primary oral cavity cancers	Cisplatin+5-FU+RT	RT alone	Total mortality Overall survival Disease-free survival Recurrent disease	Lewin 1997, Licitra 2003		No differential effect

(*continued*)

Table 3 (*continued*)

Systematic reviews	Population	Intervention	Comparison	Outcomes	Primary studies		Conclusion
					RCT	Controlled trial	
Furness et al, 2011[20]	Primary oral cavity and oropharynx cancers[a]	Bleomycin+RT	RT alone	Total mortality Locoregional control Disease-free survival	Shanta 1980, Morita 1980, Parvinen 1985		No differential effect
Furness et al, 2011[20]	Primary oral cavity and oropharynx cancers[a]	Pepleomycin+RT	RT alone	Locoregional control	Krishnamurthi 1990		Probably beneficial
Furness et al, 2011[20]	Primary oral cavity cancers	Bleomycin	MTX	Tumor regression	Molinari 1982		Beneficial
Furness et al, 2011[20]	Primary oral cavity cancers	Platin+5-FU	Platin + vinorelbine	Mortality Disease-free survival Toxicity	Segura 2002		No differential effect
Furness et al, 2011[20]	Primary oral cavity cancers, stage T2–T4	Induction simultaneous MTX+5-FU	Sequential MTX+5-FU	Total mortality	Browman 1986		No differential effect
Glenny et al, 2010[21] Liu et al, 2013[25]	Primary oral cavity cancers, stage T1–T3, negative neck nodes	High-dose rate brachytherapy	Low-dose rate brachytherapy	Local recurrence Complications Total mortality Cause-specific survival	Inoue 2001	Inoue 1998, Kakimoto 2003, Umeda 2005, Arrate 2010, Ghadja 2012	No differential effect
Lau et al, 2016[23]	Primary oral cavity cancers	ICT+RT	RT alone	Overall survival Disease-free survival Locoregional recurrence Distant metastasis	Richard 1974, Fazekas 1980, Pearlman 1985, Carugati 1988, Szpirglas 1988, Brunin 1992, Jaulerry 1992, Mazeron 1992, Salvajoli 1992, Martin 1994, Paccagnella 1994, Lewin 1997		No differential effect
Lau et al, 2016[23]	Primary oral cavity cancers	ICT+CCRT	CCRT	Overall survival Disease-free survival Locoregional recurrence Distant metastasis Adverse effects	Chhatui 2015		No differential effect

Note: [a]At least 50% of the participants had oral cavity cancer.

Abbreviations: 5-FU, 5-fluorouracil; CCRT, concomitant chemo-radiotherapy; ICT, induction chemotherapy; MTX, methotrexate; PICO, Population–Intervention–Comparison–Outcome; RCT, randomized controlled trial; RT, radiotherapy.

According to methodological quality assessment, most of the SRs scored "Critically low" methodology quality with the AMSTAR-2 tool. This indicates that there is room for a potential improvement of the quality of SRs in this field. Among the domains to improve are the inclusion of an explicit statement indicating that the SR methods were established prior to the conduct of the SR, as well as the inclusion of a report justifying any significant deviations from the protocol; the explanation of the selection of the study designs for inclusion in the SR; the provision of the list of excluded studies and justifying the exclusions; and the reporting of the conflicts of interests, indicating the source of funding or support for each of the included studies. Although the methodological quality assessment is not a core task of an evidence mapping, it has been suggested that any type of review should include this process in order to evaluate the consistency of its conclusions.[6,12]

In this evidence mapping, the main therapeutic interventions reported by the authors as beneficial for patients with resectable oral cancer are surgery alone or in combination with radiotherapy or chemotherapy, depending on the extent of the disease. These results were based on SRs[15,17,18,20,26,28,29] with "Critically low" to "High" methodological quality evaluated with AMSTAR-2 tool. However, these reports should be taken with caution because some SRs[15,28,29] only included observational studies. Moreover, despite the fact that some interventions reported by the authors as "beneficial" were based on RCTs,[32–39] the majority of these comparisons included just one RCT,[32,35,36] some of which had a small sample size.

There were fewer comparisons for patients with unresectable oral cancer than for those with resectable oral cancer. Only two interventions were reported by the authors as beneficial; these found altered fractionated radiotherapy to be superior to other forms of radiotherapy[16] and to the use of bleomycin as a chemotherapy drug.[20] We wish to emphasize that all comparisons for this population were based on SRs[16,18,20,21,23,25] including only RCTs and controlled clinical trials. Nevertheless, these results should be placed in context. Firstly, despite the fact that altered fractionated radiotherapy was reported as a beneficial treatment for oral cancer, there is a previous report[40] of the same SR[16] that shows the same outcomes, but there are some numeric inconsistencies in the results between these reports, even though the same authors included the same studies in the analysis. For these reasons, we contacted the authors and they clarified that the latest report had probably reclassified patients and provided the most accurate estimates. Secondly, recommending the use of bleomycin was based on only one single RCT[41] published long time ago. Thus, nowadays, it is likely that there are other options for chemotherapy. For example, 5-fluorouracil, cisplatin, carboplatin, paclitaxel and docetaxel are among the chemotherapy drugs most often used for oral and oropharyngeal cancers; these may be used alone or combined with other drugs.[42,43]

We were able to identify some research gaps on this topic such as targeted therapy, since just only one RCT[44] addressing this topic was included in one SR.[18] Moreover, despite a sharp increase in research into molecularly targeted therapies and a rapid expansion in the number of trials assessing new targeted therapies, their value for treating oral cancers remains unclear. The advantage that these therapies may have over conventional chemotherapy is that rather than affecting both healthy and cancerous cells, they target only cancer cells.[18] Recently, de Felice and Guerrero Urbano [45] reviewed the published clinical trials about a specific targeted therapy and suggested that it could become a "central player" in head and neck cancers as it offers a potential therapeutic opportunity. Likewise, the same authors claimed that despite the ongoing trials, clinical data are lacking.

This evidence mapping can be used to help with the interpretation of published research syntheses, such as SRs and meta-analyses, and it can also be used as a tool to engage stakeholders. Similarly, it can be used to address future research projects focused on knowledge gaps identified with this evidence mapping, as well as to conduct SRs and RCTs focused on new therapeutic interventions for oral cancer. It is useful to clarify that this evidence mapping does not intend to replace any clinical protocol or guideline. Its aim is to describe the available evidence on therapeutic interventions for oral cancers; thus, any recommendations and practice points should be considered in the context of clinical judgment for each patient, the available alternatives and their risk/benefit ratio, the available resources and other contextual factors.[46]

Among the strengths of this study, we highlight that a sensitive search strategy was performed, so it is unlikely that any relevant studies were missed. Likewise, two reviewers independently conducted the whole processes of selection, methodological quality assessment and data extraction from the included SRs. All these processes provide reasonable confidence in these results.

Certain limitations in this evidence mapping should be taken into account. Firstly, there were limited SRs comparing therapeutic interventions for oral cancer, and

some of them included only observational studies; thus, some bias due to confounding factor may exist in these studies. Secondly, since some SRs had methodological limitations, their conclusions can be subject to bias; therefore, their conclusions regarding the effectiveness of the different interventions could be invalid. However, this is thoroughly reported in our results, so each conclusion can be assessed by the reader including its limitation. Other limitation is the language barrier; all the included SRs were published in English, which eliminated the inclusion into this mapping of available evidence published in any other language.

Conclusion

There is limited available evidence about therapeutic interventions for oral cancer. The methodological quality of most included SRs in this mapping scored "Critically low" quality with AMSTAR-2 tool. The main beneficial therapeutic interventions reported by authors for patients with resectable oral cancer are surgery alone or in combination with radiotherapy or chemotherapy. Evidence for the benefits of treatments for unresectable oral cancer is lacking. These findings highlight the need to address future research focused on new therapeutic interventions and knowledge gaps in this field, as well as increased efforts are required to improve the methodology quality and reporting process of SRs on treatments for oral cancer. The evidence mapping is an adequate and reliable methodology to identify the current available evidence about therapeutic interventions.

Data sharing statement

All data generated or analyzed during this study are included in this published article and its Supplementary materials.

Acknowledgments

The authors thank Andrea Cervera Alepuz for proofreading this manuscript. This work was presented as a poster at the 95th General Session & Exhibition of the International Association for Dental Research-IADR 2017, San Francisco, USA.

Author contributions

XBC, GUC, MMA and MB conceived the study. MMA, MB, XBC, GUC, JVAF and IS designed the study. MMA and JVAF analyzed the data. MMA and JVAF wrote the first draft of the manuscript. MMA, JVAF, MB and XBC contributed to the writing of the manuscript. All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

MMA received financial support from the "Bolivar Gana con Ciencia" Fellowship Program. This author is a Ph.D candidate at the Methodology of Biomedical Research and Public Health program, Universitat Autònoma de Barcelona. The authors report no other conflicts of interest in this work.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67(1):7–30.
2. Johnson NW, Warnakulasuriya S, Gupta PC, et al. Global oral health inequalities in incidence and outcomes for oral cancer: causes and solutions. *Adv Dent Res*. 2011;23(2):237–246.
3. Weatherspoon DJ, Chattopadhyay A, Boroumand S, Garcia I. Oral cavity and oropharyngeal cancer incidence trends and disparities in the United States: 2000–2010. *Cancer Epidemiol*. 2015;39(4):497–504.
4. Wolff KD, Follmann M, Nast A. The diagnosis and treatment of oral cavity cancer. *Dtsch Arztebl Int*. 2012;109(48):829–835.
5. Grégoire V, Leroy R, Heus P. *Oral Cavity Cancer: Diagnosis, Treatment and Follow-up*. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE). KCE reports 227; 2014.
6. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 2011*. Available from: www.cochrane-handbook.org. 2011.
7. Miake-Lye IM, Hempel S, Shanman R, Shekelle PG. What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. *Syst Rev*. 2016;5:28.
8. Haddaway NR, Bernes C, Jonsson BG, Hedlund K. The benefits of systematic mapping to evidence-based environmental management. *Ambio*. 2016;45(5):613–620.
9. Bragge P, Clavisi O, Turner T, Tavender E, Collie A, Gruen RL. The global evidence mapping initiative: scoping research in broad topic areas. *BMC Med Res Methodol*. 2011;11:92.
10. Snilstveit B, Vojtkova M, Bhavsar A, Stevenson J, Gaarder M. Evidence & gap maps: a tool for promoting evidence informed policy and strategic research agendas. *J Clin Epidemiol*. 2016;79:120–129.
11. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018;169(7):467.
12. Ballesteros M, Montero N, López-Pousa A, et al. Evidence mapping based on systematic reviews of therapeutic interventions for gastrointestinal stromal tumors (GIST). *BMC Med Res Methodol*. 2017;17(1):135.
13. WHO. *International Classification of Diseases for Oncology*. 3rd ed, 1st revision. Geneva: WHO Library Cataloguing-in-Publication Data; 2013.
14. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008.
15. Anderson CR, Sisson K, Moncrieff M. A meta-analysis of margin size and local recurrence in oral squamous cell carcinoma. *Oral Oncol*. 2015;51(5):464–469.
16. Baujat B, Bourhis J, Blanchard P, et al. Hyperfractionated or accelerated radiotherapy for head and neck cancer. *Cochrane Database Syst Rev*. 2010;43(1):CD002026.
17. Bessell A, Glenny AM, Furness S, et al. Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. *Cochrane Database Syst Rev*. 2011;9(9):CD006205.
18. Chan KK, Glenny AM, Weldon JC, Furness S, Worthington HV, Wakeford H. Interventions for the treatment of oral and oropharyngeal cancers: targeted therapy and immunotherapy. *Cochrane Database Syst Rev*. 2015;12(12):CD010341.
19. Ding Z, Xiao T, Huang J, et al. Elective neck dissection versus observation in squamous cell carcinoma of oral cavity with clinically N0 neck: a systematic review and meta-analysis of prospective studies. *J Oral Maxillofac Surg*. 2018. Epub August 22,2018.

20. Furness S, Glenny AM, Worthington HV, et al. Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy. *Cochrane Database Syst Rev*. 2011;4(4):CD006386.
21. Glenny A-M, Furness S, Worthington HV, et al. Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy. *Cochrane Database Syst Rev*. 2010;51(3):CD006387.
22. Gou L, Yang W, Qiao X, et al. Marginal or segmental mandibulectomy: treatment modality selection for oral cancer: a systematic review and meta-analysis. *Int J Oral Maxillofac Surg*. 2018;47(1):1–10.
23. Lau A, Li KY, Yang WF, Su YX. Induction chemotherapy for squamous cell carcinomas of the oral cavity: a cumulative meta-analysis. *Oral Oncol*. 2016;61:104–114.
24. Liang L, Zhang T, Kong Q, Liang J, Liao G. A meta-analysis on selective versus comprehensive neck dissection in oral squamous cell carcinoma patients with clinically node-positive neck. *Oral Oncol*. 2015;51(12):1076–1081.
25. Liu Z, Huang S, Zhang D. High dose rate versus low dose rate brachytherapy for oral cancer – a meta-analysis of clinical trials. *PLoS One*. 2013;8(6):e65423.
26. Marta GN, Riera R, Bossi P, et al. Induction chemotherapy prior to surgery with or without postoperative radiotherapy for oral cavity cancer patients: systematic review and meta-analysis. *Eur J Cancer*. 2015;51(17):2596–2603.
27. Pang P, Li RW, Shi JP, et al. A comparison of mandible preservation method and mandibulotomy approach in oral and oropharyngeal cancer: a meta-analysis. *Oral Oncol*. 2016;63:52–60.
28. Tang L, Leung YY. When should elective neck dissection be performed in maxillary gingival and alveolar squamous cell carcinoma with a cN0 neck? A systematic review. *Int J Oral Maxillofac Surg*. 2016;45(11):1358–1365.
29. Wang HC, Zheng Y, Pang P, Li RW, Qi ZZ, Sun CF. Discontinuous versus in-continuity neck dissection in squamous cell carcinoma of the tongue and floor of the mouth: comparing the rates of locoregional recurrence. *J Oral Maxillofac Surg*. 2018;76(5):1123–1132.
30. Sylvester RJ, Canfield SE, Lam TB, et al. Conflict of evidence: resolving discrepancies when findings from randomized controlled trials and meta-analyses disagree. *Eur Urol*. 2017;71(5):811–819.
31. Jones CW, Handler L, Crowell KE, Keil LG, Weaver MA, Platts-Mills TF. Non-publication of large randomized clinical trials: cross sectional analysis. *BMJ*. 2013;347:f6104.
32. Robertson AG, Soutar DS, Paul J, et al. Early closure of a randomized trial: surgery and postoperative radiotherapy versus radiotherapy in the management of intra-oral tumours. *Clin Oncol*. 1998;10(3):155–160.
33. Richard JM, Kramar A, Molinari R, et al. Randomised EORTC head and neck cooperative group trial of preoperative intra-arterial chemotherapy in oral cavity and oropharynx carcinoma. *Eur J Cancer*. 1991;27(7):821–827.
34. Luboinski B. Preliminary results of a randomized study on preoperative intra-arterial chemotherapy combined with surgery and irradiation for carcinomas of the floor of the mouth. *Prog Clin Biol Res*. 1985;201:199–203.
35. de Stefani A, Forni G, Ragona R, et al. Improved survival with perilymphatic interleukin 2 in patients with resectable squamous cell carcinoma of the oral cavity and oropharynx. *Cancer*. 2002;95(1):90–97.
36. Rao RS, Parikh DM, Parikh HK, Bhansali MB, Deshmane VH, Fakih AR. Perioperative chemotherapy in patients with oral cancer. *Am J Surg*. 1994;168(3):262–267.
37. Zhong LP, Zhang CP, Ren GX, et al. Randomized Phase III trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by surgery versus up-front surgery in locally advanced resectable oral squamous cell carcinoma. *J Clin Oncol*. 2013;31(6):744–751.
38. Bossi P, Lo Vullo S, Guzzo M, et al. Preoperative chemotherapy in advanced resectable OCSCC: long-term results of a randomized Phase III trial. *Ann Oncol*. 2014;25(2):462–466.
39. Licitra L, Grandi C, Guzzo M, et al. Primary chemotherapy in resectable oral cavity squamous cell cancer: a randomized controlled trial. *J Clin Oncol*. 2003;21(2):327–333.
40. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet*. 2006;368(9538):843–854.
41. Molinari R, Jortay A, Sancho-Garnier H, et al. A randomized EORTC trial comparing intra-arterial infusion with methotrexate vs bleomycin as initial therapy in carcinoma of the oral cavity. *Eur J Cancer Clin Oncol*. 1982;18(9):807–812.
42. Srivastava S, Mohammad S, Pant AB, et al. Co-delivery of 5-fluorouracil and curcumin nanohybrid formulations for improved chemotherapy against oral squamous cell carcinoma. *J Maxillofac Oral Surg*. 2018;17(4):597–610.
43. Noronha V, Joshi A, Patil V, et al. Cisplatin based adjuvant chemoradiation following neoadjuvant chemotherapy and surgery in advanced oral cavity cancers: a deliverable regimen? *Indian J Cancer*. 2016;53(1):141–142.
44. Singh P, Dixit AK, Prashad SN, Saxena T, Shahoo DP, Sharma D. A randomized trial comparing radiotherapy alone versus radiotherapy with Geftinib in locally advance oral cavity cancer. *Clin Cancer Investig J*. 2013;2(1):29–33.
45. de Felice F, Guerrero Urbano T. New drug development in head and neck squamous cell carcinoma: the PI3-K inhibitors. *Oral Oncol*. 2017;67:119–123.
46. Alonso-Coello P, Schünemann HJ, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: introduction. *BMJ*. 2016;353:i2016.

5.2 PUBLICATION 2. QUALITY OF CLINICAL PRACTICE GUIDELINES ON TREATMENTS FOR ORAL CAVITY CANCER

5.2.1 SUMMARY OF RESULTS

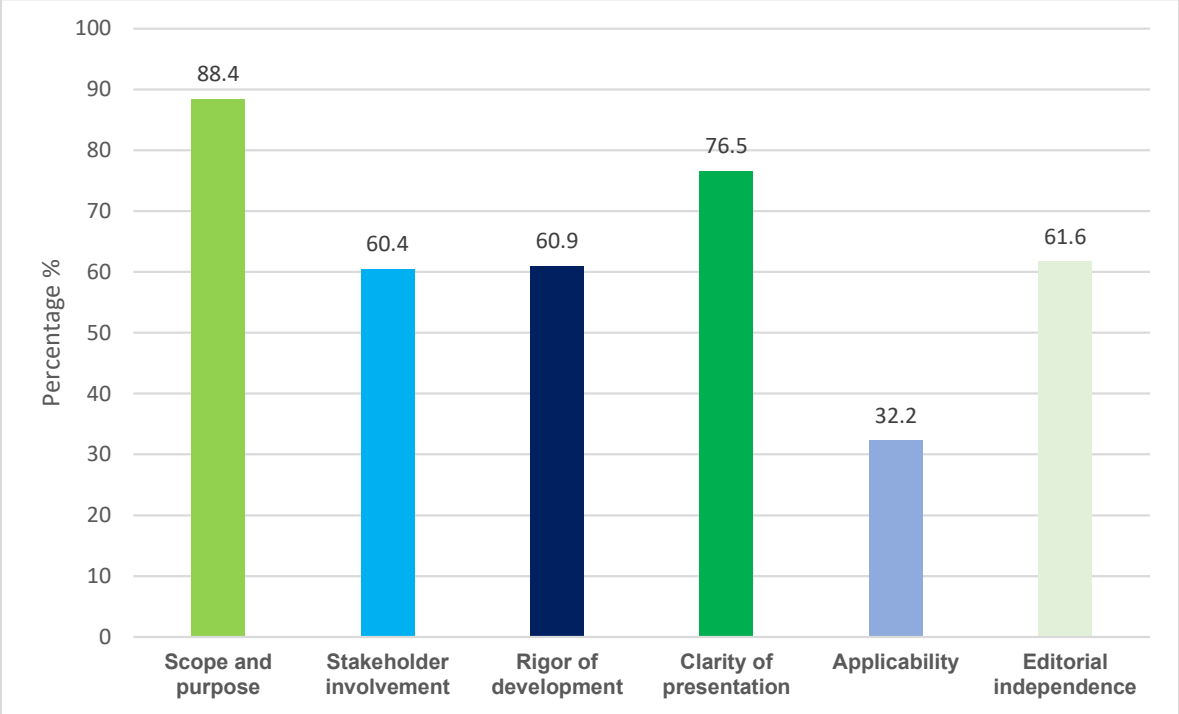
Characteristics of the included clinical practice guidelines

All clinical practice guidelines (82-93) were published in English language between 2005 and 2017. Six guidelines (84-86, 90, 92, 93) only included recommendations for treatments, whereas six guidelines (82, 83, 87-89, 91) also included recommendations related to processes such as diagnosis and follow-up of oral cancer. Three guidelines (88, 92, 93) were from Canada, while the others were one from each of the following: United States (87), United Kingdom (82), Scotland (83), Belgium (89), Germany (91), Taiwan (85), Japan (86), Denmark (90) and European society (84).

Quality assessment of clinical practice guidelines

The overall agreement among appraisers on the clinical practice guidelines assessment with the AGREE II instrument was very good (overall ICC: 0.865; 95% CI: 0.835 - 0.889). The mean scores for each AGREE domain were the following: “scope and purpose” 88.4% ± 12.4%; “stakeholder involvement” 60.4% ± 25%; “rigor of development” 60.9% ± 25.3%; “clarity of presentation” 76.5% ± 19.8%; “applicability” 32.2% ± 30.7%; and “editorial independence” 61.6% ± 35.5% (Figure 6).

Figure 6. *Mean quality score by each AGREE II domain*



Overall clinical practice guideline assessment

Among all guidelines assessed, three guidelines (82, 83, 89) (25%) were "recommended" by the appraisers, six guidelines (86-88, 91-93) (50%) were "recommended with modifications", and three guidelines (84, 85, 90) (25%) were "not recommended". Those guidelines rated as "recommended" scored over 60% in all domains. Moreover, there was no improvement in the overall score or by domains in the development of CPGs over time (published in 2005-2009 versus 2010-2017; p-value: 0.571).

PUBLICATION 2

Madera Anaya MV, Franco JV, Merchan-Galvis AM, Gallardo CR, Bonfill Cosp X. Quality assessment of clinical practice guidelines on treatments for oral cancer. *Cancer Treat Rev*. 2018; 65:47-53.

Cancer Treatment Review. 2018.

Impact factor: 8.885. Q1(18/368). Oncology

Cancer Treatment Reviews 65 (2018) 47–53

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

General and Supportive Care

Quality assessment of clinical practice guidelines on treatments for oral cancer

Meisser Vidal Madera Anaya[a,b,c,*], Juan Victor Franco[d], Ángela María Merchán-Galvis[a,c], Carmen R. Gallardo[e], Xavier Bonfill Cosp[a,c,f]

[a] Iberoamerican Cochrane Centre, Institute of Biomedical Research Sant Pau (IIB Sant Pau), Barcelona, Spain
[b] Department of Research, Faculty of Dentistry, University of Cartagena, Cartagena, Colombia
[c] Public Health and Clinical Epidemiology Service, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain
[d] Cochrane Argentina, Instituto Universitario Hospital Italiano, Buenos Aires, Argentina
[e] Unit of Preventive Medicine, Hospital Vega Baja de Orihuela, Alicante, Spain
[f] CIBER de Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain

ARTICLE INFO

Keywords:
Oral cancer
Neoplasm mouth
Treatments
Guidelines
AGREE II

ABSTRACT

Background: The applicability of clinical practice guidelines (CPGs) on treatments for oral cancer remains unknown since there are no systematic assessments of their quality. Thus, the objective of this study is to identify and assess the quality of them.

Methods: We conducted a systematic search to identify CPGs that provided recommendations on treatments for oral cancer. The quality of each included CPG was determined using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, by four appraisers independently. The inter-appraisers agreement was assessed.

Results: Twelve CPGs met the eligibility criteria. Overall agreement among appraisers was very good (ICC: 0.865; 95% CI: 0.835–0.889). The mean scores for each AGREE domain were the following: "scope and purpose" 88.4% ± 12.4%; "stakeholder involvement" 60.4% ± 25%; "rigor of development" 60.9% ± 25.3%; "clarity of presentation" 76.5% ± 19.8%; "applicability" 32.2% ± 30.7%; and "editorial independence" 61.6% ± 35.5%. Three CPGs were rated as "recommended"; six as "recommended with modifications"; and three as "not recommended".

Conclusions: Overall, the quality of CPGs on treatments for oral cancer is suboptimal. These findings highlight the need to improve CPG development processes and their applicability in this field. Thus, increased efforts are required to enable the development of high-quality evidence-based CPGs for oral cancer.

Introduction

Oral cancer is diagnosed worldwide in approximately 350,000 patients every year. Its incidence varies widely among different geographical areas, accounting under 5% of all cancer diagnoses in Europe and the United States, whereas in developing countries its incidence is higher, due to smoking and drinking habits associated with poor socioeconomic status [1]. The impact of oral cancer and its treatment on speech, swallowing function, and self-image can have a devastating psychological and physical impact on afflicted people, and can be a considerable economic burden on the public healthcare system [2].

The standard management of oral cavity cancers is mainly based on anatomic considerations and TNM (tumor, lymph nodes, metastasis) stage [3]. Early stages are treated with a single modality, surgery or radiotherapy, depending on tumor location, tumor extent, anticipated cure rate, and functional and esthetic outcome [3–5]. The aggressive nature of advanced oral cancer usually indicates a poor prognosis, requiring a multimodal treatment approach of surgery, radiotherapy, and chemotherapy [6,7]. The sequencing and combination of these therapies are based on stage, tumor location, expertise of the treating physicians, and patient preferences [8]. Despite the advances in treatment modalities, long-term survival and cure rates remain low, whereas locoregional recurrence and distant metastasis rates remain high, primarily in advanced cancers [6].

In general, most beneficial treatment modalities are included in clinical practice guidelines (CPGs), which are useful tools systematically developed to assist practitioner's and patient's decisions on appropriate healthcare in specific clinical circumstances [9]. The

* Corresponding author at: Faculty of Dentistry, University of Cartagena, Campus de la Salud, Zaragocilla Cra. 50 No. 29 - 11, CP: 130014 Cartagena, Colombia.
E-mail address: mmaderaa@unicartagena.edu.co (M.V. Madera Anaya).

https://doi.org/10.1016/j.ctrv.2018.03.001
Received 23 January 2018; Received in revised form 22 February 2018; Accepted 8 March 2018

objectives of CPGs are to provide explicit recommendations for healthcare professionals involved in clinical practice, and to diminish inappropriate clinical discrepancies in order to improve results, reduce risks, and support a cost-effective practice [10].

The advantages of using CPGs include the fact that they guide healthcare professionals in decision-making, reducing inadequate variability in clinical practice, and that their development involve a multidisciplinary team using the most relevant up-to-date available evidence [11,12]. Likewise, it has been reported that the implementation of an evidence-based CPG may have a positive impact on patients suffering from oral squamous cancer [13]. Despite these benefits, low-quality CPGs may also harmfully influence patient care or be of questionable applicability [14,15]. Previous quality assessments of CPGs conducted in the dental field have concluded that their reporting and quality is lacking and inadequate [16–18].

The applicability of any CPG depends on several factors such as rigorous development, clarity of presentation, editorial independence, adequate dissemination, and implementation strategy [10]. There are multiple tools that evaluate these characteristics [19]; however the most comprehensively validated appraisal tool is the Appraisal of Guidelines Research and Evaluation (AGREE) instrument, which was developed to address the variability issue in CPG quality [20]. The original AGREE instrument was first published in 2003 by the AGREE Collaboration, a group of international CPG developers and researchers [21]. This instrument was refined later, resulting in the new AGREE II published in 2010 [22,23]. The new AGREE II replaced the original one as the preferred valid reliable international tool to assess the quality of CPGs, and can be used as part of an overall quality strategy aimed to improve healthcare [20].

Currently, there are many GPCs on treatments for oral cancer; however, their quality and applicability remain unknown since there are no systematic assessments of their quality. Thus, the aim of this study is to identify and assess the quality of CPGs on treatments for oral cancer using the AGREE II instrument.

Materials and methods

Study design

We performed a systematic assessment of the quality of CPGs on treatments for oral cancer with the AGREE II instrument, following a previously published methodology [24]. All methods were specified a priori in a protocol.

Eligibility criteria

We included CPGs defined as documents developed by a nationally recognized committee, a publicly funded institution, a medical society, or particular authors, providing recommendations for the treatment of primary oral cancer in adult population. CPGs about other cancers such as head and neck cancers were considered if they contained at least two explicit recommendations for oral cancer. We only selected CPGs published between 2005 and 2017, with an explicit description of their methodology—either within the CPG or in supporting documents (for example, definition of search strategy, methods used to create recommendations, and evidence quality assessment). When more than one publication from the same organization or authors group was identified, we only included the most recent version. Conversely, documents without recommendations or CPGs only focused on screening or diagnosis were excluded.

Search strategy

We searched for systematic literature in MEDLINE (via PubMed), EMBASE (via Ovid), TRIP (Turning Research Into Practice), CPG clearinghouses, prominent CPG developer groups, and scientific societies in this field in order to identify eligible CPGs. We used specific terms for oral cavity cancer such as “mouth neoplasms”, “oral carcinoma”, “oral cancer”, “oral tumor”, “buccal carcinoma”; with no language restrictions. The last search was conducted on October 27, 2017 (Appendix A).

CPGs selection

We managed all retrieved titles and abstracts with the reference manager software EndNote® (Version X7, Thomson Reuters). After removing duplicates, two reviewers (MM, AM) independently screened all titles/abstracts to exclude irrelevant documents. Then, full texts were obtained for a final decision. Disagreements were resolved by consensus, if needed, a third reviewer (JF) participated in the discussion until an agreement was reached. Detailed reasons for exclusion of any document considered relevant were clearly stated.

Data extraction and quality assessment

Two reviewers (MM, AM) independently extracted general characteristics of each CPG such as authoring organization, title, year of publication, period of publication (published in 2005–2009 versus 2010–2017), country or region, and language, using a standardized pilot-test form.

Four appraisers (MM, AM, JF, CG) independently evaluated the quality of each CPG. We used the AGREE II instrument to assess the quality of the included CPGs [20,22]. This tool includes 23 items on a seven-point Likert scale across six domains. Each domain captures a unique dimension of the CPG quality: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence (Appendix B). In addition, this instrument included two overall quality assessments for each CPG: a final score of 1–7, and whether the appraiser would recommend using the CPG, rating it as “recommended”, “recommended with modifications” or “not recommended”.

Data analysis

We calculated the domain scores by adding up all the scores of the individual items in a domain, and by scaling the total as a percentage of the maximum possible score for that domain [20]. Consequently, standardization was calculated as follows: (obtained score − minimum possible score)/(maximum possible score − minimum possible score). The maximum possible score for each domain was the number of items multiplied by the number of appraisers, and multiplied by seven (highest possible score; strongly agree). The minimum possible score was the number of items multiplied by the number of appraisers multiplied by one (lowest possible score; strongly disagree). The range of standardized score for each domain was 0–100%. We considered 60% as a threshold of acceptable quality. Descriptive statistics (mean, median, standard deviation, range) were calculated for each domain score for each CPG. Moreover, Student's *t*-test ($p < 0.05$) was used to compare the AGREE II scores of all CPGs by publication period.

In addition, we calculated the intraclass coefficient (ICC) with its 95% confidence interval (95% CI) as an indicator of overall agreement between appraisers. The degree of agreement between 0.01 and 0.20 is slight; from 0.21 to 0.40 is fair; from 0.41 to 0.60 is moderate; from 0.61 to 0.80 is substantial; and from 0.81 to 1.00 is very good [25]. Statistical analyses were performed using SPSS® version 20.0 (SPSS Inc, Chicago, IL).

Results

Selected CPGs

The research yielded 464 records after removing duplicates. After

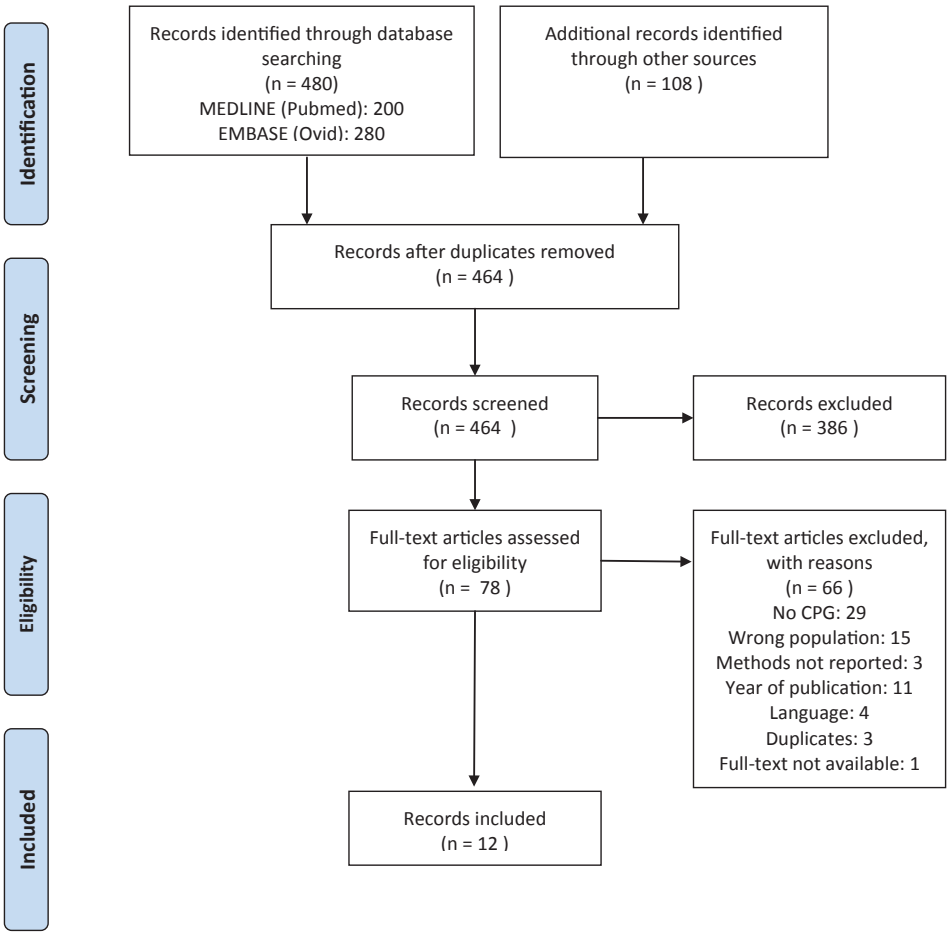


Fig. 1. Flow chart detailing the selection process.

title and abstract screening, 78 documents were obtained for final full-text review; 12 CPGs [26–37] met the eligibility criteria (Fig. 1). The list of excluded documents along with exclusion rationale is available in an additional file (Appendix C).

Characteristics of the included CPGs

All CPGs were published in English language between 2005 and 2017. Five CPGs [29,32–35] focused on recommendations for oral cancer exclusively, and the other seven CPGs [26–28,30,31,36,37] focused on head and neck cancers. Six CPGs [28–30,34,36,37] only included recommendations for treatments, whereas six CPGs [26,27,31–33,35] also included recommendations related to processes such as diagnosis and follow-up of oral cancer. Three CPGs [32,36,37] were from Canada, while the others were one from each of the following: United States [31], United Kingdom [26], Scotland [27], Belgium [33], Germany [35], Taiwan [29], Japan [30], Denmark [34] and European society [28] (Table 1).

Quality assessment of CPGs

The overall agreement among appraisers on the CPGs assessment with the AGREE II instrument was very good (overall ICC: 0.865; 95% CI: 0.835–0.889). The mean quality scores for each domain of the AGREE II instrument for all the included CPGs are represented in Fig. 2. Table 2 shows the standardized score of each CPG by domain and the overall recommendation.

Scope and purpose

This domain includes the main objectives of the CPGs, the health questions, and the target population [20]. The mean score for this domain was 88.4% ± 12.4% (range 65.3–100%), all CPGs [26–37] (100%) scored over 60%.

Stakeholder involvement

This domain focuses on the extent to which the CPG was developed by the appropriate stakeholders and represents the views of its intended users [20]. The mean score for this domain was 60.4% ± 25.0% (range 30.6–95.8%). Six CPGs [26,27,31,33,35,36] (50%) scored over 60%.

Rigor of development

This domain focuses on the process for synthesizing and gathering evidence and the methods used to formulate and update the recommendations [20]. The mean score for this domain was 60.9% ± 25.3% (range 22.4–98.4%). Seven CPGs [27,31–33,35–37] (58.3%) scored over 60%.

Clarity of presentation

This domain assesses whether recommendations are specific and unambiguous, different options for managing the condition or health issue are clearly presented, and key recommendations are easily identifiable [20]. The mean score for this domain was 76.5% ± 19.8% (range 25–98.6%). Ten CPGs [26,27,30–37] (83.3%) scored over 60%.

Table 1
Characteristics of the included CPGs.

Guideline	Year	Organization or author	Country
Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over [26]	2016	National Institute for Health and Care Excellence	United Kingdom
Diagnosis and management of head and neck cancer [27]	2006	The Scottish Intercollegiate Guidelines Network	Scotland
GEC-ESTRO ACROP recommendations for brachytherapy for head and neck squamous cell carcinomas [28]	2016	European Brachytherapy Group-European Society for Therapeutic Radiology and Oncology	Europe
Guideline and preliminary clinical practice results for dose specification and target delineation for postoperative radiotherapy for oral cavity cancer [29]	2015	Liu	Taiwan
Japanese Clinical Practice Guideline for Head and Neck Cancer [30]	2017	Japan Society for Head and Neck Cancer	Japan
NCCN – head and neck cancers [31]	2017	National Comprehensive Cancer Network	United States
Oral cavity cancer [32]	2014	Alberta Provincial Head and Neck Tumor Team	Canada
Oral cavity cancer: diagnosis, treatment and follow-up [33]	2014	Belgian Health Care Knowledge Centre-KCE	Belgium
The Danish national guidelines for treatment of oral squamous cell carcinoma [34]	2006	The Danish Society for Head and Neck Oncology	Denmark
The Diagnosis and Treatment of Oral Cavity Cancer [35]	2012	Klaus-Dietrich Wolff	Germany
The Management of Head and Neck Cancer in Ontario [36]	2009	Cancer Care Ontario	Canada
The Role of Postoperative Chemoradiotherapy for Advanced Squamous Cell Carcinoma of the Head and Neck [37]	2013	Cancer Care Ontario	Canada

Applicability

This domain focuses on processes related to CPG implementation such as organizational facilitators and barriers, additional materials provided, cost implications, and monitoring or audit criteria [20]. The mean score in this domain was 32.2% ± 30.7% (range 0–88.5%). Only three CPGs [26,27,33] (25%) scored over 60%.

Editorial independence

This domain is about whether the views or interests of the funding body have influenced the final recommendations, and whether the competing interests of all the CPG development group have been recorded and reported [20]. The mean score in this domain was 61.6% ± 35.5% (range 0–93.8%). Eight CPGs [26–28,31–33,36,37] (66.7%) scored over 60%.

Overall CPG assessment

Among all CPGs evaluated, three CPGs [26,27,33] (25%) were "recommended" by the reviewers; six CPGs [30–32,35–37] (50%) were "recommended with modifications"; and three CPGs [28,29,34] (25%) were "not recommended". Those CPGs rated as "recommended" scored over 60% in all domains.

In addition, there was no improvement in the overall score or by domains in the development of CPGs over time (published in 2005–2009 versus 2010–2017; p-value: 0.571) (Table 3).

Discussion

CPGs are one of several tools available for healthcare providers to improve quality of care [38]; therefore, performing quality assessments on them is essential to improve their trustworthiness and applicability. This study may be the first one to evaluate the methodological quality of published CPGs on treatments for oral cancer, since we found no previous reports.

Our results show that overall quality of CPGs in this field is suboptimal with only three out of 12 CPGs being rated as "recommended" [26,27,33]. The highest quality CPGs were developed by the Belgian Health Care Knowledge Centre-KCE [33], the British National Institute for Health and Care Excellence [26], and the Scottish Intercollegiate Guidelines Network [27], scoring over 60% in all domains. This threshold of acceptable quality has been suggested to be an appropriate figure to reflect that a valid and transparent process was adopted in the development of recommendations [24,39]. In addition, some authors have suggested classifying CPGs as high quality when at least three of

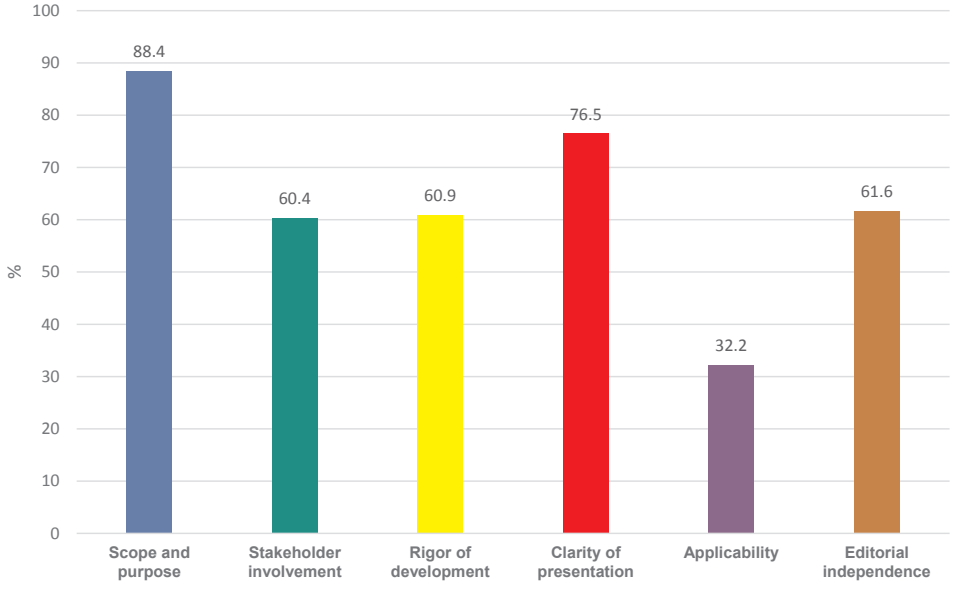


Fig. 2. Mean quality score by each AGREE II domain.

Table 2
Standardized scores across CPGs by domain (AGREE II).

Domains Guideline	Scope and purpose %	Stakeholder involvement %	Rigor of development %	Clarity of presentation %	Applicability %	Editorial independence %	Overall recommendation
Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over [26]	100.0	91.7	93.8	98.6	88.5	89.6	Recommended
Diagnosis and management of head and neck cancer [27]	95.8	87.5	78.1	93.1	64.6	64.6	Recommended
GEC-ESTRO ACROP recommendations for brachytherapy for head and neck squamous cell carcinomas [28]	70.8	31.9	26.0	59.7	0.0	62.5	Not recommended
Guideline and preliminary clinical practice results for dose specification and target delineation for postoperative radiotherapy for oral cavity cancer [29]	75.0	30.6	22.4	25.0	0.0	0.0	Not recommended
Japanese Clinical Practice Guideline for Head and Neck Cancer [30]	79.2	34.7	48.4	87.5	0.0	18.8	Recommended with modifications
NCCN – Head and Neck Cancers [31]	91.7	73.6	56.8	79.2	19.8	93.8	Recommended with modifications
Oral cavity cancer [32]	100.0	47.2	66.1	80.6	27.1	75.0	Recommended with modifications
Oral cavity cancer: diagnosis, treatment and follow-up [33]	100.0	95.8	98.4	90.3	79.2	93.8	Recommended
The Danish national guidelines for treatment of oral squamous cell carcinoma [34]	65.3	34.7	29.7	65.3	29.2	4.2	Not recommended
The Diagnosis and Treatment of Oral Cavity Cancer [35]	94.4	68.1	60.9	72.2	16.7	54.2	Recommended with modifications
The Management of Head and Neck Cancer in Ontario [36]	97.2	79.2	78.1	88.9	44.8	89.6	Recommended with modifications
The Role of Postoperative Chemoradiotherapy for Advanced Squamous Cell Carcinoma of the Head and Neck [37]	91.7	50.0	71.4	77.8	16.7	93.8	Recommended with modifications
Mean	88.4	60.4	60.9	76.5	32.2	61.6	
SD	12.4	25.0	25.3	19.8	30.7	35.5	
Median	93.1	59.0	63.5	79.9	23.4	69.8	
Range	65.3–100	30.6–95.8	22.4–98.4	25–98.6	0–88.5	0–93.8	

Table 3
Comparison of the AGREE II scores by publication period.

Domains	Not recent CPGs[a] (n = 3)		Recent CPGs[b] (n = 9)		p-value
	Mean (%)	SD (%)	Mean (%)	SD (%)	
Scope and purpose	86.1	18.1	89.2	11.3	0.363
Stakeholder involvement	67.1	28.4	58.2	25.2	0.693
Rigor of development	62.0	28.0	60.5	26.2	0.533
Clarity of presentation	65.3	0.0	64.0	16.9	0.548
Applicability	46.2	17.7	27.5	33.5	0.806
Editorial independence	52.8	43.9	34.8	34.8	0.320
Overall mean	63.2	21.8	60.6	20.8	0.571

[a] CPGs published between 2005 and 2009.
[b] CPGs published between 2010 and 2017.

the domain scores were higher than or equal to this cutoff, including the domain of "rigor of development" [24,40]. However, this last approach should be taken with caution since we considered that all domains included in the AGREE II are essential to develop a good CPG. Thus, all domains should score over this threshold; as in the case of the three CPGs classified as recommended in this study [26,27,33]. Likewise, recommendations from these CPGs should also be considered with caution because the AGREE II instrument only evaluates the methodological quality for their development, without judging the validity of the recommendations themselves. Other instruments can be used to assess the quality of the evidence underlying each recommendation, such as the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework [41], which has been endorsed by over 90 health organizations worldwide.

Most of the included CPGs [30–32,35–37] were rated as "recommended with modifications". These define well specific and focused clinical questions and target populations, but poorly report other aspects, such as strategies of implementation of the GPC, conflict-of-interest statements, etc. This suggests that there is room for a potential improvement of their quality if their deficiencies are addressed in future updates. Consistently, Mubeen [16], who assessed the quality of dental CPGs, concluded that it is suboptimal, and that there is variation in the overall quality, reporting of individual items, and domains of the AGREE II instrument between different dental specialty CPGs. Moreover, the latest studies limited to specific subspecialties such as orthodontic [18], pediatric dentistry [42], dental radiology [43] and common dental procedures [44] have concluded that the reporting of CPGs varies considerably. Likewise, others reports have shown that the methodological quality of CPGs published in diverse clinical areas such as oncology [45], rheumatology [46], nutrition [24] and neurology [47] is extremely variable and that there is a considerable opportunity for improvement. It has been suggested that for a CPG to be effective, it needs to be disseminated and implemented with additional materials such as a summary document, a book section, or a quick reference guide [38].

The domains with the highest scores were "scope and purpose" and "clarity of presentation", whereas the domain with the lowest score was "applicability". These results are similar to those reported in oncology by Jiang [38], who evaluated CPGs focused on treatment, screening, imaging, nursing, complications, and follow-up of carcinoma of the head and neck. Similarly, Chen [45] assessed CPGs for nasopharyngeal carcinoma concluding that the "applicability" domain scored consistently low across CPGs, whereas the "scope and purpose" and the "editorial independence" domains scored the highest. Regarding a quality assessment of dental GPGs, Mubeen [16] also concluded that the domain with the lowest score was "applicability". Likewise, our findings are consistent with previous CPG evaluations in other medical areas [24,39,48,49]. Some have reported that certain factors may influence the domain scores, such as the type of developer; for example, CPGs developed by professional organizations score significantly higher than those of individuals groups in four domains (stakeholder involvement, rigor of development, clarity of presentation, and editorial independence) [38]. Likewise, the scores in these four domains in evidence-based CPGs are significantly higher than those in the non–evidence-based CPGs [16,38]. This suggests that all CPGs should be based on the best available evidence and designed by groups experienced in CPG development.

We found that overall quality of CPGs in this field has not improved over time. This result is consistent compared with some of the previous CPG assessments [24,49,50]. Conversely, other studies reported improvement in quality over time [16,48,49]. This approach is based on the assumption that after the AGREE II instrument was published in 2010 [17,18], all CPGs developed since then could follow the AGREE II statements, reaching an acceptable quality of development. However, these results suggest that no standardized methodology for CPG development has been implemented in this field. Hence, developers should adapt their methodology to include the AGREE II considerations, which can be used as part of an overall quality strategy aimed at improving healthcare [24]. Moreover, establishing an expert organization to promote the development and implementation of high-quality evidence-based CPGs in this field would be useful, as well as using the GRADE system to formulate recommendations.

We wish to highlight that we excluded some documents [51–53] containing recommendations because they lacked a written methodology section. Thus, this study did not evaluate all available recommendations in the field that may influence the beliefs and actions of the public and health care practitioners. However, some have reported the fact that a comprehensive understanding of the methods used to develop a CPG is essential to assess the quality of the development and of the evidence for recommendations [39].

The main practical applications of this study are related to the improvement the development process of future CPGs in this field or their updates, as well as their methodological quality and applicability. Clinicians need to have access to recommendations based on the best available evidence for the adequate treatment of patients with oral cancer. Thus, greater efforts are needed to provide high-quality CPGs that serve as a useful and reliable tool for clinical decision-making. Moreover, in an effort to reduce publication bias and promote transparency, a publicly accessible database is essential; a place where CPG protocols can be registered before being developed, published, and disseminated.

This study has several strengths such as the fact that all priori eligibility criteria, objectives, and planned methods of analysis were documented in a protocol. Moreover, four appraisers independently assessed the quality of CPG development with very good agreement, by using a validated instrument. This ensures that our conclusions are valid and reliable.

One of the limitations of this study is that we might have not identified some CPGs since they are often not indexed or easily accessible. However, it is reasonable to assume that the quality of un-indexed CPGs is probably lower than that of those indexed [24]. Other limitations are related to language barrier. Firstly, all selected CPGs were published in English, which eliminated CPGs published in any other language. Secondly, due to the limitation of provided pages, the English version of the Japanese CPG for Head and Neck Cancer [30] only presented the six most relevant clinical questions. Thus, this CPG could potentially score higher in some domains but we were unable to read the supplementary materials in Japanese. In general, we believe that these limitations do not substantially change the main results of this study.

In conclusion, the overall quality of CPGs on treatments for oral cancer is suboptimal, with only three CPGs rated as recommended for clinical use. These findings highlight the need to improve CPG development processes in this field. Thus, increased efforts are required to

enable the development of high-quality evidence-based CPGs. In this context, the quality of CPGs on treatments for oral cancer can be improved with an evaluation of the quality of the available evidence using a unified framework to present recommendations, and using a clear implementation strategy.

Conflict of interest statement

The authors declared that there is no conflict of interest.

Acknowledgments

The financial support for MM covered by *Bolívar Gana con Ciencia* Fellowship Program. This author is a Ph.D candidate at the Methodology of Biomedical Research and Public Health program, Universitat Autònoma de Barcelona. Thank you to Andrea Cervera Alepuz for proofreading this manuscript.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ctrv.2018.03.001.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin 2017;67:7–30.
[2] Kyrgias G, Hajiioannou J, Tolia M, Kouloulias V, Lachanas V, Skoulakis C, et al. Intraoperative radiation therapy (IORT) in head and neck cancer: a systematic review. Medicine (Baltimore) 2016;95:e5035.
[3] Anderson CR, Sisson K, Moncrieff M. A meta-analysis of margin size and local recurrence in oral squamous cell carcinoma. Oral Oncol 2015;51:464–9.
[4] Bessell A, Glenny AM, Furness S, Clarkson JE, Oliver R, Conway DI, et al. Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. Cochrane Database Syst Rev 2011:CD006205.
[5] Glenny AM, Furness S, Worthington HV, Conway DI, Oliver R, Clarkson JE, et al. Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy. Cochrane Database Syst Rev 2010:CD006387.
[6] Lau A, Li KY, Yang WF, Su YX. Induction chemotherapy for squamous cell carcinomas of the oral cavity: a cumulative meta-analysis. Oral Oncol 2016;61:104–14.
[7] Furness S, Glenny AM, Worthington HV, Pavitt S, Oliver R, Clarkson JE, et al. Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy. Cochrane Database Syst Rev 2011:CD006386.
[8] Cohen EE, LaMonte SJ, Erb NL, Beckman KL, Sadeghi N, Hutcheson KA, et al. American cancer society head and neck cancer survivorship care guideline. CA Cancer J Clin 2016;66:203–39.
[9] Eslava-Schmalbach J, Sandoval-Vargas G, Mosquera P. Incorporating equity into developing and implementing for evidence-based clinical practice guidelines. Rev Salud Publica (Bogota) 2011;13:339–51.
[10] Grimshaw J, Freemantle N, Wallace S, Russell I, Hurwitz B, Watt I, et al. Developing and implementing clinical practice guidelines. Qual Health Care 1995;4:55–64.
[11] Graham ID, Beardall S, Carter AO, Glennie J, Hebert PC, Tetroe JM, et al. What is the quality of drug therapy clinical practice guidelines in Canada? CMAJ 2001;165:157–63.
[12] Grilli R, Magrini N, Penna A, Mura G, Liberati A. Practice guidelines developed by specialty societies: the need for a critical appraisal. Lancet 2000;355:103–6.
[13] Wolff KD, Rau A, Ferencz J, Langer T, Kesting M, Nieberler M, et al. Effect of an evidence-based guideline on the treatment of maxillofacial cancer: a prospective analysis. J Craniomaxillofac Surg 2017;45:427–31.
[14] Bateman GJ, Saha S. A brief guide to clinical guidelines. Br Dent J 2007;203:581–3.
[15] Geleris P, Boudoulas H. Problems related to the application of guidelines in clinical practice: a critical analysis. Hellenic J Cardiol 2011;52:97–102.
[16] Mubeen S, Patel K, Cunningham Z, O'Rourke N, Pandis N, Cobourne MT, et al. Assessing the quality of dental clinical practice guidelines. J Dent 2017;67:102–6.
[17] Glenny AM, Worthington HV, Clarkson JE, Esposito M. The appraisal of clinical guidelines in dentistry. Eur J Oral Implantol 2009;2:135–43.
[18] Tejani T, Mubeen S, Seehra J, Cobourne MT. An exploratory quality assessment of orthodontic clinical guidelines using the AGREE II instrument. Eur J Orthod 2017;39:654–9.
[19] Siering U, Eikermann M, Hausner E, Hoffmann-Esser W, Neugebauer EA. Appraisal tools for clinical practice guidelines: a systematic review. PLoS ONE 2013;8:e82915.
[20] AGREE. The appraisal of guidelines for research & evaluation. AGREE. Ontario, Canada: The AGREE Next Steps Consortium. < http://www.agreetrust.org > ; 2009 [Update: 2013].
[21] Collaboration A. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003;12:18–23.
[22] Brouwers M, Kho M, Browman G, Burgers J, Cluzeau F, Feder G. For the AGREE next steps consortium. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. CMAJ 2010;182:E472–8.
[23] Brouwers M, Kho M, Browman G, Burgers J, Cluzeau F, Feder G. AGREE next steps consortium. AGREE II: advancing guideline development, reporting, and evaluation in health care. CMAJ 2010;182:E839–42.
[24] Fuentes Padilla P, Martinez G, Vernooij RW, Cosp XB, Alonso-Coello P. Nutrition in critically ill adults: a systematic quality assessment of clinical practice guidelines. Clin Nutr 2016;35:1219–25.
[25] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.
[26] NICE. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. NICE guideline 36; 2016.
[27] SIGN. Diagnosis and management of head and neck cancer; 2006.
[28] Kovacs G, Martinez-Monge R, Budrukkar A, Guinot JL, Johansson B, Strnad V, et al. GEC-ESTRO ACROP recommendations for head & neck brachytherapy in squamous cell carcinomas: 1st update – improvement by cross sectional imaging based treatment planning and stepping source technology. Radiother Oncol 2017;122:248–54.
[29] Liu SH, Chao KS, Leu YS, Lee JC, Liu CJ, Huang YC, et al. Guideline and preliminary clinical practice results for dose specification and target delineation for post-operative radiotherapy for oral cavity cancer. Head Neck 2015;37:933–9.
[30] Nibu KI, Hayashi R, Asakage T, Ojiri H, Kimata Y, Kodaira T, et al. Japanese clinical practice guideline for head and neck cancer. Auris Nasus Larynx 2017;44:375–80.
[31] Adelstein D, Gillison ML, Pfister DG, Spencer S, Adkins D, Brizel DM, et al. NCCN guidelines insights: head and neck cancers, version 2.2017. J Natl Compr Canc Netw 2017;15:761–70.
[32] AHS. Oral cavity cancer. Clinical practice guideline HN-002; 2014.
[33] Grégoire V, Leroy R, Heus P, Van de Wetering F, Hooft L, Scholten R, et al. Oral cavity cancer: diagnosis, treatment and follow-up. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). KCE Reports 227; 2014.
[34] Bilde A, von Buchwald C, Johansen J, Bastholt L, Sorensen JA, Marker P, et al. The Danish national guidelines for treatment of oral squamous cell carcinoma. Acta Oncol 2006;45:294–9.
[35] Wolff KD, Follmann M, Nast A. The diagnosis and treatment of oral cavity cancer. Dtsch Arztebl Int 2012;109:829–35.
[36] Gilbert R, Devries-Aboud M, Winquist E, Waldron J, McQuestion M, Group. HaNDS. The management of head and neck cancer in Ontario. Program in evidence-based care evidence-based series no:5–3; 2009.
[37] Winquist E, Oliver T, Gilbert R, Group. HaNDS. The role of postoperative chemoradiotherapy for advanced squamous cell carcinoma of the head and neck. Cancer care Ontario 2004 program in evidence-based care evidence-based series no: 5–10; 2013.
[38] Jiang Y, Zhu XD, Qu S, Li L, Zhou Z. Guidelines for squamous cell carcinoma of the head and neck: a systematic assessment of quality. Ear Nose Throat J 2015;94:E14–24.
[39] Erickson J, Sadeghirad B, Lytvyn L, Slavin J, Johnston BC. The scientific basis of guideline recommendations on sugar intake: a systematic review. Ann Intern Med 2017;166:257–67.
[40] Yaman ME, Gudeloglu A, Senturk S, Yaman ND, Tolunay T, Ozturk Y, et al. A critical appraisal of the North American Spine Society guidelines with the Appraisal of Guidelines for Research and Evaluation II instrument. Spine J 2015;15:777–81.
[41] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
[42] Shah P, Moles DR, Parekh S, Ashley P, Siddik D. Evaluation of pediatric dentistry guidelines using the AGREE instrument. Pediatr Dent 2011;33:120–9.
[43] Horner K, O'Malley L, Taylor K, Glenny AM. Guidelines for clinical use of CBCT: a review. Dentomaxillofac Radiol 2015;44:20140225.
[44] Faggion Jr. CM. Clinician assessment of guidelines that support common dental procedures. J Evid Based Dent Pract 2008;8:1–7.
[45] Chen YP, Wang YQ, Li WF, Chen L, Xu C, Lu TX, et al. Critical evaluation of the quality and recommendations of clinical practice guidelines for nasopharyngeal carcinoma. J Natl Compr Canc Netw 2017;15:336–44.
[46] Brosseau L, Rahman P, Poitras S, Toupin-April K, Paterson G, Smith C, et al. A systematic critical appraisal of non-pharmacological management of rheumatoid arthritis with Appraisal of Guidelines for Research and Evaluation II. PLoS ONE 2014;9:e95369.
[47] Zhang Z, Guo J, Su G, Li J, Wu H, Xie X. Evaluation of the quality of guidelines for myasthenia gravis with the AGREE II instrument. PLoS ONE 2014;9:e111796.
[48] Acuna-Izcaray A, Sanchez-Angarita E, Plaza V, Rodrigo G, de Oca MM, Gich I, et al. Quality assessment of asthma clinical practice guidelines: a systematic appraisal. Chest 2013;144:390–7.
[49] Alonso-Coello P, Irfan A, Sola I, Gich I, Delgado-Noguera M, Rigau D, et al. The quality of clinical practice guidelines over the last two decades: a systematic review of guideline appraisal studies. Qual Saf Health Care 2010;19:e58.
[50] Barajas-Nava L, Sola I, Delgado-Noguera M, Gich I, Villagran CO, Bonfill X, et al. Quality assessment of clinical practice guidelines in perioperative care: a systematic appraisal. Qual Saf Health Care 2010;19:e50.
[51] ENTUK. Head and neck cancer: multidisciplinary management guidelines. In: British Association of Otorhinolaryngology HaNS, editor. 4th ed.; 2011.
[52] Kerawala C, Roques T, Jeannon JP, Bisase B. Oral cavity and lip cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol 2016;130:S83–9.
[53] HNCWG. South Australian head and neck cancer pathway: optimising outcomes for all South Australians diagnosed with Head and Neck Cancer. Head and neck cancer working group; 2013. p. 1–146.

5.3 PUBLICATION 3. QUALITY OF CLINICAL PRACTICE GUIDELINES ON DIAGNOSIS OF ORAL CAVITY CANCER

5.3.1 SUMMARY OF RESULTS

Characteristics of the selected clinical practice guidelines

All included guidelines (83, 88, 89, 91, 94-97) were published in the English language. Four guidelines (83, 88, 89, 91) included recommendations for diagnosis, two guidelines (94, 95) focused on screening and two guidelines (96, 97) focused on suspected oral cancer. Moreover, four guidelines (83, 88, 89, 91) also included recommendations related to processes such as the treatment and management of oral cancer. Six guidelines (83, 88, 89, 94, 96, 97) were developed by a government agency, three guidelines (94-96) were an update, and only three guidelines (89, 95, 96) used GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework to develop their recommendations.

Quality appraisal of clinical practice guidelines

The overall agreement among reviewers was considered very good (ICC: 0.823; 95% CI: 0.777 - 0.861). The median scores of the six AGREE II domains were as follows: “scope and purpose” 97.9% (IQR: 96.2%-100.0%); “stakeholder involvement” 86.1% (IQR: 69.8%-93.1%); “rigor of development” 75.3% (IQR: 64.2%-94.3%); “clarity of presentation” 91.7% (IQR: 82.6%-94.4%); “applicability” 53.1% (IQR: 19.3%-74.2%); and “editorial independence” 83.3% (IQR: 67.2%-93.8%).

Overall clinical practice guideline assessment

Among all guidelines assessed, four guidelines (83, 89, 95, 96) (50%) were "recommended" by the reviewers; four guidelines (88, 91, 94, 97) (50%) were "recommended with modifications"; and no guidelines (0%) was "not recommended". Almost all guidelines rated as "recommended" scored over 60% for all domains. The median of overall rate was 6.0 (Q1-Q3: 4.6 – 6.4), the highest score was 7.0 (89) and the lowest one was 4.0 (91).

Characteristics of recommendations included in the clinical practice guidelines

One clinical practice guideline (94) did not provide recommendation because the authors concluded that the current evidence was insufficient to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults, whereas the other seven guidelines (83, 88, 89, 91, 95-97) provided a total of 23 recommendations, most of them having a low or very low level of evidence. Moreover, four clinical practice guidelines (83, 91, 95, 97) provided 10 Good Practice Points (Table 6).

Table 6. *Good Practice Points included in the guidelines*

Guideline	Good Practice Point
Diagnosis and management of head and neck cancer (83)	All healthcare practitioners —including dental and medical practitioners— should be aware of the presenting features of head and neck cancer, and the local referral pathways for suspected cancers
	Dental practitioners should include a full examination of the oral mucosa as part of routine dental checkup
	Patients should be seen within two weeks of urgent referral
	Patients should be seen by an experienced clinician with access to the necessary diagnostic tools
	General or dental practitioners should be aware of symptoms suggestive of head and neck cancer
Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity (95)	Clinicians should obtain an updated medical, social, and dental history and perform an intraoral and extraoral conventional visual and tactile examination in all adult patients
The Diagnosis and Treatment of Oral Cavity Cancer (91)	All patients with mucosal lesions of unknown origin and more than two weeks' duration should immediately be referred to a specialist
Suspected cancer in primary care (97)	A person presenting with unexplained persistent sore or painful throat or mouth, (particularly unilateral pain) for more than four weeks, should be referred urgently to a specialist
	A person presenting with unilateral unexplained pain in the head and neck area for more than four weeks, or with paresthesia or dysesthesia in an area of nerve distribution should be referred urgently to a specialist
	A person presenting with hoarseness persisting for more than three weeks (particularly if a smoker aged 50 years or older, or a heavy drinker) should be referred to an ear, nose and throat specialist, and for a chest x-ray.

PUBLICATION 3

Madera, M., Franco, J., Solà, I. Bonfill J., Alonso-Coello, P. Screening and diagnosis of oral cancer: a critical quality appraisal of clinical guidelines. Clin Oral Invest. 2019; 23:2215-2226.

Clinical Oral Investigations. 2019

Impact factor: 2.812. Q1(15/143). Dentistry (miscellaneous)

Clinical Oral Investigations (2019) 23:2215–2226
https://doi.org/10.1007/s00784-018-2668-7

ORIGINAL ARTICLE

Screening and diagnosis of oral cancer: a critical quality appraisal of clinical guidelines

Meisser Madera[1,2,3] · Juan Franco[4] · Ivan Solà[1,3] · Xavier Bonfill[1,3,5] · Pablo Alonso-Coello[1,3,5]

Received: 29 June 2018 / Accepted: 25 September 2018 / Published online: 3 October 2018

Abstract

Objectives To assess the quality of clinical practice guidelines (CPGs) on screening and diagnosis of oral cancer and to describe the characteristics of their recommendations.

Materials and methods We systematically searched EMBASE, MEDLINE, CPG' websites, and dentistry and oncology scientific societies to identify CPGs that were related to screening and diagnosis of oral cancer. The quality of selected CPGs was independently assessed by four appraisers using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument. The inter-appraiser agreement was assessed. We performed a descriptive analysis of the recommendations included in the selected CPGs.

Results Eight CPGs were selected. The overall agreement among reviewers was considered very good (ICC: 0.823; 95% CI: 0.777–0.861). The median scores of the six AGREE II domains were as follows: "scope and purpose" 97.9% (IQR: 96.2–100.0%); "stakeholder involvement" 86.1% (IQR: 69.8–93.1%); "rigor of development" 75.3% (IQR: 64.2–94.3%); "clarity of presentation" 91.7% (IQR: 82.6–94.4%); "applicability" 53.1% (IQR: 19.3–74.2%); and "editorial independence" 83.3% (IQR: 67.2–93.8%). Four CPGs were assessed as "recommended", four "recommended with modifications", and none "not recommended". Twenty-three recommendations were provided, mostly with a low or very low level of evidence.

Conclusion The methodological quality of CPGs on screening and diagnosis of oral cancer is moderate. The "applicability" domain scored the lowest. Most recommendations were based on a low o very low level of evidence.

Clinical relevance Greater efforts are needed to provide healthcare based on high-quality evidence-based CPGs in this field.

Keywords Oral cancer · Guidelines · Evidence-based medicine · Screening · Diagnosis

Introduction

Due to increasing pressure to provide evidence-based medical care, the use of clinical practice guidelines (CPGs) has been increasing worldwide over the last decade [1, 2]. CPGs are a summary of evidence-based recommendations that were developed using systematic methods of literature review. These are a very useful tool for the translation of research evidence into practice [3]. By using CPGs based on the best available evidence, healthcare professionals can be assisted in minimizing inappropriate variation in clinical practice, improving decision-making processes on the most suitable

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00784-018-2668-7) contains supplementary material, which is available to authorized users.

✉ Meisser Madera
mmaderaa@unicartagena.edu.co

[1] Iberoamerican Cochrane Centre, Institute of Biomedical Research Sant Pau, Barcelona, Spain

[2] Department of Research, Faculty of Dentistry, University of Cartagena, Campus de la Salud, Zaragocilla Cra. 50 # 29-11, CP 130014 Cartagena, Colombia

[3] Public Health and Clinical Epidemiology Service, Sant Pau Hospital, Barcelona, Spain

[4] Cochrane Argentina, Instituto Universitario Hospital Italiano, Buenos Aires, Argentina

[5] CIBER of Epidemiology and Public Health, Barcelona, Spain

healthcare for explicit clinical circumstances, and promoting effective and safe patient outcomes [4]. However, some have reported that many CPGs are lacking quality and that there is a wide vast of heterogeneity among their recommendations [5, 6]. Thus, systematically developed CPGs using the best available evidence to provide transparent recommendations are required.

The appraisal of Guidelines for Research and Evaluation (AGREE) instrument is a validated, generic tool to systematically appraise CPG methodological development and quality [7]. In 1988, the AGREE initiative was established by an international group of researchers and CPG developers; the original AGREE instrument was published in 2003, and its update—AGREE II—was released in 2010 [7]. This instrument has become the standard tool for CPG evaluation and development, with the purpose of improving CPG quality and the likelihood of broad endorsement [8].

Currently, oral cavity cancer is considered a public health issue worldwide. Around 600,000 new cases are expected per annum. Oral squamous cell carcinoma (OSCC) is the most common type of oral cancer [9]. While it represents just over 2% of the global cancer incidence, its 50% fatality rate is a major cause of concern [10]. The high mortality rate of oral cancer may be associated with many factors, one the main ones being the diagnostic delay. Commonly, oral suspicious lesions are easy to assess and should be diagnosed early for the therapeutic intervention to be effective [11]. Nonetheless, patients are often diagnosed in advanced stages of disease; this might be due to the lack of consultation, or the barriers in adequate healthcare accessibility [12]. Moreover, the value of screening healthy adults with no symptoms and using several tools for diagnosing oral cancer is uncertain [13]; thus, these issues need to be addressed clearly using reliable and high-quality CPGs.

There are many CPGs on screening and diagnosis of oral cancer; nevertheless, little is known about the quality, applicability, and potential impact of those CPGs, since their quality has not been systematically evaluated. This study belongs to a project that aims to assess the quality of CPGs on oral cancer; the quality of CPGs on therapeutic interventions for oral cancer has been previously reported [14]. This report focuses on quality methodological assessment of CPGs on screening and diagnosis of oral cancer and describes the characteristics of their recommendations.

Materials and methods

We conducted a systematic critical appraisal of the quality and recommendations of CPGs on screening and diagnosis of oral cancer using the AGREE II instrument. The methods used were previously published [14].

Data sources and strategy search

Using search strategies developed by an expert, we systematically searched EMBASE (via Ovid), MEDLINE (via PubMed), CPG' websites, and dentistry and oncology scientific societies to identify CPGs published between 2006 and 2018. We used key words and terms related to oral cavity tumor and CPGs such as "oral cancer", "oral tumor", "oral carcinoma", "mouth neoplasms", "buccal carcinoma", "guideline", "practice guideline", "guidance", and "recommendation". The last search was conducted on 22 May 2018 (Additional file 1).

CPG identification

Our eligibility criteria were: (i) CPGs providing recommendations for screening, suspicion, or diagnosis of primary oral cavity cancer (all histopathological types of malignancies) in adults; (ii) CPGs about other cancers were selected if they provided at least two clear recommendations for oral cancer; (iii) inclusion of an explicit methods section; and (iv) the most recent version from a CPG developer.

Two authors independently reviewed titles/abstracts and full texts to identify eligible CPGs. Any discrepancies were resolved by consensus, if needed, a third author was included in the discussion until a consensus was obtained.

Quality appraisal of CPG

The quality of CPGs was independently assessed by four appraisers using the AGREE II instrument [8, 15], which includes a 23-item checklist rated on a seven-point Likert scale and categorized into the following six domains:

Domain 1: Scope and purpose; including the main objectives of the CPGs, the health questions, and the target population.
Domain 2: Stakeholder involvement; this focuses on the extent to which the CPG was developed by the appropriate stakeholders and represents the views of its intended users.
Domain 3: Rigor of development; describing the process used to synthesize and gather evidence, and the methodology used to formulate and update the recommendations.
Domain 4: Clarity and presentation; assessing whether recommendations are explicit and unambiguous, different options for managing the condition or health issue are clearly presented, and key recommendations are easily identifiable.
Domain 5: Applicability; dealing with implementation issues, such as the assessment of organizational facilitators and barriers, the development of educational sources, economic implications, and monitoring or audit criteria.

Domain 6: Editorial independence; assessing whether the views or interests of the funding sources have influenced the recommendations, and if the conflicts of interest statement reports all information about the CPG developer team.

The AGREE II instrument also includes two overall quality appraisals for each CPG: an overall score of 1 to 7, and whether the reviewer would recommend using the CPG, assessing it as "recommended", "recommended with modifications", or "not recommended".

CPG data extraction

Two authors independently extracted data from each CPG such as: title, country, year of publication, authoring organization, language, level of development, funding source, whether or not it is an update, recommendations, methods used to determine the recommendations, level of evidence, grading of the recommendations, and histological type of oral cancer.

Statistical analysis

Inter-appraiser agreement was assessed using the intraclass correlation coefficient (ICC) with a 95% confidence interval (95% CI) [16]. We calculated the domain scores by adding up all the scores of the individual items within a domain and calculated the percentage of the maximum possible score for that domain [15]. Standardized scores (range, 0 to 100%) for each domain were calculated as follows: [(obtained score − minimum possible score) / (maximum possible score − minimum possible score)] × 100%. We used 60% as a cut-off point for adequate quality. Median and the interquartile range (IQR: Q1-Q3) were calculated for each domain score for each CPG. Moreover, we performed a descriptive analysis of recommendation included in the selected CPGs. Statistical analyses were performed with SPSS® version 20.0 software (SPSS Inc., Chicago, IL).

Results

Selection of CPGs

The selection process is presented in Fig. 1. We initially identified 496 records and excluded 433 references after screening titles and abstracts. We reviewed 63 full-text documents and excluded 55 of them (Additional file 2). Finally, we selected eight CPGs [17–24].

Characteristics of the selected CPGs

All included CPGs [17–24] were published in English language. Five CPGs [18–22] included recommendations for oral cancer exclusively, whereas the other three CPGs [17, 23, 24] also included recommendations for other cancers. Four CPGs [17, 19, 20, 22] included recommendations for diagnosis, two CPGs [18, 21] focused on screening and two CPGs [23, 24] focused on suspected oral cancer. Moreover, four CPGs [17, 19, 20, 22] also included recommendations related to processes such as the treatment and management of oral cancer. Five CPGs [17, 19–22] included recommendations for OSCC, one [17] of them also included recommendations for other histological types of mouth neoplasms, whereas three CPGs [18, 23, 24] did not specify that information. Two CPGs [18, 21] were from USA, two CPGs [17, 23] were from United Kingdom, while the others were one from each of the following: Canada [19], Belgium [20], Germany [22], and New Zealand [24]. Six CPGs [17–20, 23, 24] were developed by a government agency, three CPGs [18, 21, 23] were an update, only three CPGs [20, 21, 23] used GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework to develop their recommendations, and one CPG [19] did not report the level of evidence nor grading of its recommendations (Table 1).

Quality appraisal of CPGs

The overall agreement among reviewers was considered very good (ICC: 0.823; 95% CI: 0.777–0.861). Table 2 represents standardized scores across CPGs by domain, and the overall recommendation for clinical use of the included CPGs.

Scope and purpose

The median score for this domain was 97.4% (IQR: 96.2–100.0%), demonstrating that most CPGs were considered to have an adequate report of this domain. All CPGs [17–24] (100.0%) scored over 60%.

Stakeholder involvement

The median score for this domain was 86.1% (IQR: 69.8–93.1%). Seven CPGs [17, 18, 20–24] (87.5%) scored over 60%. The main limitation across some CPGs was that, although patients were included in the CPG process, the way the panel included their values and preferences remained unclear.

Rigor of development

The median score for this domain was 75.3% (IQR: 64.2–94.3%). Although all CPGs [17–24] (100.0%) scored over

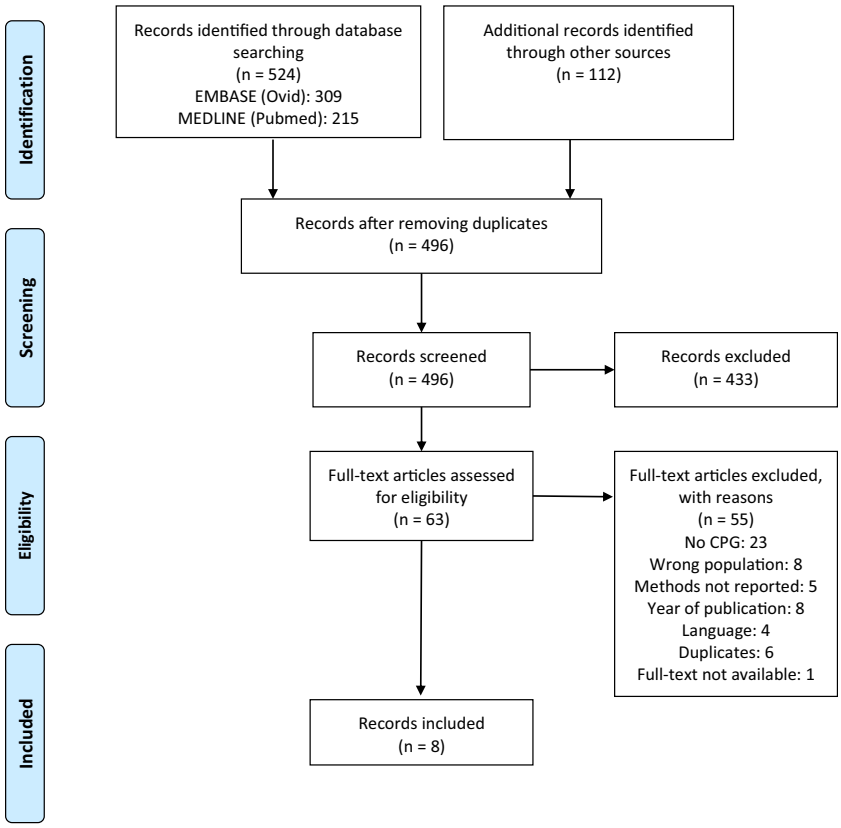


Fig. 1 Flow chart detailing the selection process

60%, three of them [18, 19, 22] (37.5%) scored just above this threshold. Limitations included that it was unclear how some CPGs had assessed the potential harms of the screening and diagnostic recommendations. Moreover, one CPG [19] showed no direct link between the recommendation and the evidence, and there was no formal assessment of the strengths and limitations of the supporting evidence.

Clarity of presentation

The median score for this domain was 91.7% (IQR: 82.6–94.4%), indicating that recommendations were clearly presented. All CPGs [17–24] (100.0%) scored over 60%.

Applicability

The median score in this domain was 53.1% (IQR: 19.3–88.5%). Only four CPGs [17, 20, 23, 24] (50.0%) scored over 60%. The main limitations were that most CPGs lacked a discussion on their facilitators, and application barriers, and that they failed to assess the implications of use of resources or the auditing criteria.

Editorial independence

The median score in this domain was 83.3% (IQR: 67.2–93.8%). Seven CPGs [17–21, 23, 24] (87.5%) scored over 60%. Some CPGs did not fully describe a declaration about their funding sources and their possible influence on CPG development process or failed to clearly report the potential conflicts of interest of authors or CPG developer.

Overall CPG assessment

Among all CPGs evaluated, four CPGs [17, 20, 21, 23] (50%) were "recommended" by the reviewers; four CPGs [18, 19, 22, 24] (50%) were "recommended with modifications"; and no CPG (0%) was "not recommended". Almost all CPGs assessed as "recommended" scored over 60% for all domains. The median of overall rate was 6.0 (IQR: 4.6–6.4), the highest score was 7.0 [20], and the lowest one was 4.0 [22].

Recommendation characteristics

Among the selected CPGs [17–24], one CPG [18] did not provide recommendation because the authors concluded that the current evidence was insufficient to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults, whereas the other seven CPGs [17, 19–24] provided a total of 23 recommendations, most of them having a low or very low level of evidence. Regarding grade of recommendation, three recommendations were reported as strong [20], 16 recommendations were reported as weak [17, 21, 22, 24] (conditional, B, C, D), and four recommendations did not

Table 1 Characteristics of the included guidelines

Guideline	Year	Organization	Country	Level of development	Funding source	CPG is an update	Methods	Level of evidence	Grading the recommendation
Diagnosis and management of head and neck cancer [17]	2006	The Scottish Intercollegiate Guidelines Network	United Kingdom	Governmental agency	Government	No	SR and critical appraisal of the scientific literature	$1^{++}/1^{+}/1^{-}/2^{++}/2^{+}/2^{-}/3/4$	A/B/C/D/ GPP
Screening for Oral Cancer: U.S. Preventive Services Task Force Recommendation Statement [18]	2014	The U.S. Preventive Services Task Force	United States of America	Governmental agency	Government	Yes	Evaluation of available evidence	High/moderate/low	A/B/C/D/I statement
Oral cavity cancer [19]	2014	Alberta Provincial Head and Neck Tumor Team	Canada	Governmental agency	Government	No	Review of relevant scientific literature	Not given	Not given
Oral cavity cancer: diagnosis, treatment and follow-up [20]	2014	Belgian Health Care Knowledge Centre	Belgium	Governmental agency	Government	No	GRADE	High/moderate/low/very low	Strong/weak
Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity [21]	2017	The American Dental Association	United States of America	Professional organization	Specialty society	Yes	GRADE	High/moderate/low/very low	Strong/conditional
The Diagnosis and Treatment of Oral Cavity Cancer [22]	2012	German Cancer Society	Germany	Professional organization	Specialty society	No	SR, grading of evidence, consensus	$1^{++}/1^{+}/1^{-}/2^{++}/2^{+}/2^{-}/3/4$	Must/should/can
Suspected cancer [23]	2015	National Institute for Health and Care Excellence	United Kingdom	Governmental agency	Government	Yes	GRADE	High/moderate/low/very low	Must/should/consider
Suspected cancer in primary care [24]	2009	New Zealand Guideline Group	New Zealand	Governmental agency	Government	No	Literature review, grading of evidence	+/~/x	A/B/C/GPP

CPG Clinical Practice Guideline, *SR* systematic review, *GPP* good practice points, *GRADE* Grading of Recommendations Assessment, Development and Evaluation

Table 2 Standardized scores across guidelines by domain (AGREE II)

Domains	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence	Overall rate	Overall recommendation
Guideline	%	%	%	%	%	%		
Diagnosis and management of head and neck cancer [17]	95.8	87.5	78.1	93.1	64.6	64.6	6.0	Recommended
Screening for Oral Cancer: U.S. Preventive Services Task Force Recommendation Statement [18]	97.2	75.0	63.5	88.9	6.3	95.8	4.5	Recommended with modifications
Oral cavity cancer [19]	100.0	47.2	66.1	80.6	27.1	75.0	5.0	Recommended with modifications
Oral cavity cancer: diagnosis, treatment and follow-up [20]	100.0	95.8	98.4	90.3	79.2	93.8	7.0	Recommended
Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity [21]	97.2	88.9	92.7	94.4	41.7	91.7	6.0	Recommended
The Diagnosis and Treatment of Oral Cavity Cancer [22]	94.4	68.1	60.9	72.2	16.7	54.2	4.0	Recommended with modifications
Suspected cancer [23]	100.0	94.4	94.8	94.4	77.1	93.8	6.5	Recommended
Suspected cancer in primary care [24]	98.6	84.7	72.4	95.8	65.6	75.0	6.0	Recommended with modifications
Median	97.9	86.1	75.3	91.7	53.1	83.3	6.0	
Interquartile range (IQR: Q1-Q3)	96.2–100.0	69.8–93.1	64.2–94.3	82.6–94.4	19.3–74.2	67.2–93.8	4.6–6.4	

report level of evidence or the grade of recommendation [19, 23] (Table 3). In addition, four CPGs [17, 21, 22, 24] provided 10 good practice points (Table 4).

Discussion

CPGs can be used to optimize clinical practice; however, their assimilation and use will depend on how they are developed. Hence, this study sought to assess the quality of CPGs involving screening and diagnosis oral cancer recommendations, to assist clinicians when selecting appropriate CPGs.

Overall, quality of CPGs on screening and diagnosis of oral cancer is moderate with only 50% of CPGs being assessed as "recommended". The highest quality CPGs were developed by the Belgian Health Care Knowledge Centre (KCE) [20], the Scottish Intercollegiate Guidelines Network (SIGN) [17], The American Dental Association (ADA) [21], and the National Institute for Health and Care Excellence (NICE) [23], scoring over 60% in most domains. However, despite that some of these CPGs were rated as "recommended", there are aspects that should be considered. For example, although the NICE CPG [23] was developed through a rigorous process, its recommendations neither report the level of evidence nor the strength of recommendations; the ADA CPG [21] scored below the threshold in the applicability domain, because it discussed the implications but there was no assessment of the use of resources nor auditing criteria. Likewise, the SIGN CPG [17] was published 12 years ago; thus, its recommendations are likely to be based on outdated evidence. It has been suggested that CPGs should be updated at 3-year intervals, because new evidence may result in substantial changes to the recommendations [25]. Moreover, we wish to highlight that the recommendations included in these CPGs should be considered with caution, since the AGREE II instrument only assesses the reporting of methodological quality aspects for their development, not judging the rationality of their recommendations.

Half of the included CPGs [18, 19, 22, 24] were assessed as "recommended with modifications", indicating that there is room for improving their quality if their deficiencies are addressed. Some of the aspects that need to be addressed are: the lack of patient involvement in the CPG development process, the insufficient inclusion of patients' values and preferences, the lack of direct link between the recommendation and the evidence, and the inadequate assessment of the strengths and limitations of the supporting evidence. Consistently, the methodological quality of CPGs in diverse clinical areas has been

Table 3 Recommendations included in the guidelines

Guideline	Recommendation	LE/gradeR
Diagnosis and management of head and neck cancer [17]	Rapid access or "one stop" clinics should be available for patients who fulfill appropriate referral criteria	D
	Fine needle aspiration cytology should be used in the investigation of head and neck masses	D
Oral cavity cancer [19]	The following investigations are recommended at diagnosis for all patients with suspected or confirmed oral cavity cancer: complete head and neck examination, biopsy, chest imaging, nutrition, speech and swallowing evaluation, computed tomography (CT) with contrast and/or magnetic resonance imaging (MRI) with contrast of primary site and neck, as indicated, positron emission tomography-computed tomography, as indicated, chest CT scan, if not included with other imaging, examination under anesthesia with endoscopy, as indicated, preanesthetic studies, and dental/prosthodontic evaluation, including jaw imaging, as indicated	Not provided
Oral cavity cancer: diagnosis, treatment and follow-up [20]	A biopsy should be taken from the most suspect part of the tumor. The pathologist should be provided with any clinically relevant information. If the result is inconclusive, or negative but the tumor is suspect, the biopsy should be repeated	Very low/strong
	When a patient with a diagnosis of OSCC is referred to another centre for work-up completion and treatment, and if no additional biopsies need to be performed in the reference centre, pathology specimens (slices and/or blocks) should be sent for revision to the reference laboratory for diagnosis confirmation upon request from the reference centre. Every uncommon tumor diagnosis beside classical SCC should be reviewed by an expert from a reference laboratory	Very low/strong
	The biopsy report should include: tumor localization, tumor histology, tumor grade, depth of invasion (if assessable), lymphatic, vascular and perineural invasion. Some other prognostic factors, such as growing pattern (infiltrative vs. pushing border), can be considered	Very low/strong
Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity [21]	Adult patients with a clinically evident oral mucosal lesion with an unknown clinical diagnosis considered to be seemingly innocuous or nonsuspicious of malignancy, or other symptoms, clinicians should follow up periodically with the patient to determine the need for further evaluation. If the lesion has not resolved and the clinical diagnosis of a potentially malignant disorder cannot be ruled out, then clinicians should perform a biopsy of the lesion or refer the patient to a specialist	Low/conditional
	Adult patients with a clinically evident oral mucosal lesion considered to be suspicious of a potentially malignant or malignant disorder, or other symptoms, clinicians should perform a biopsy of the lesion or provide immediate referral to a specialist	Low/conditional
	The panel does not recommend cytologic adjuncts for the evaluation of potentially malignant disorders among adult patients with clinically evident, seemingly innocuous, or suspicious lesions. Should a patient decline the clinician's recommendation for performing a biopsy of the lesion or referral to a specialist, the clinician can use a cytologic adjunct to provide additional lesion assessment. A positive or atypical cytologic test result reinforces the need for a biopsy or referral. A negative cytologic test result indicates the need for periodic follow-up of the patient. If the clinician detects persistence or progression of the lesion, immediately performing a biopsy of the lesion or referral to a specialist is indicated	Low/conditional
	The panel does not recommend autofluorescence, tissue reflectance, or vital staining adjuncts for the evaluation of potentially malignant disorders among adult patients with clinically evident, seemingly innocuous, or suspicious lesions	Low to very low/conditional
	Adult patients with no clinically evident lesions or symptoms, no further action is necessary at that time	Low/conditional
	The panel does not recommend commercially available salivary adjuncts for the evaluation of potentially malignant disorders among adult patients with or without clinically evident, seemingly innocuous, or suspicious lesions, and their use should be considered only in the context of research	Low/conditional
The Diagnosis and Treatment of Oral Cavity Cancer [22]	Computed tomography (CT) or magnetic resonance imaging (MRI) should be performed	3/B

Table 3 (continued)

Guideline	Recommendation	LE/gradeR
Suspected cancer [23]	Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for oral cancer in people with either: unexplained ulceration in the oral cavity lasting for more than 3 weeks or a persistent and unexplained lump in the neck	Not provided
	Consider an urgent referral (for an appointment within 2 weeks) for assessment for possible oral cancer by a dentist in people who have either: a lump on the lip or in the oral cavity or a red or red and white patch in the oral cavity consistent with erythroplakia or erythroleukoplakia	Not provided
	Consider a suspected cancer pathway referral by the dentist (for an appointment within 2 weeks) for oral cancer in people when assessed by a dentist as having either: a lump on the lip or in the oral cavity consistent with oral cancer or a red or red and white patch in the oral cavity consistent with erythroplakia or erythroleukoplakia	Not provided
Suspected cancer in primary care [24]	A person with persistent symptoms and signs related to the oral cavity where a definitive diagnosis of a benign lesion cannot be made should be referred to a dentist or specialist or followed-up until the symptoms and signs disappear. An urgent referral to a specialist should be made if the symptoms and signs have not disappeared after 6 weeks	C
	A person presenting with unexplained ulceration of the oral mucosa or a mass persisting for more than 3 weeks should be referred urgently to a dentist or specialist	C
	A person presenting with unexplained tooth mobility persisting for more than 3 weeks should be referred urgently to a dentist	C
	A person should be referred urgently to a specialist if they have unexplained red and white patches of the oral mucosa (including suspected lichen planus) with one or more of the following features: painful, swollen and bleeding. A non-urgent referral to a specialist should be made in the absence of these features. If oral lichen planus is confirmed, the person should be monitored for oral cancer as part of routine dental examination	C
	A person presenting with an unexplained, painless new lump in the neck, or a pre-existing lump that has recently changed over a period of 3 to 6 weeks, should be referred urgently to a specialist	C
	A person with an unexplained persistent swelling in the parotid or submandibular gland should be referred urgently to a specialist	C
	A person presenting with symptoms and/or signs suggestive of head and neck cancer (with the exception of persistent hoarseness where a chest x-ray is indicated), no investigations in primary care are recommended as they can delay referral	C

LE level of evidence, *GradeR* grade of recommendation

reported to be extremely variable, showing a substantial opportunity for improvement [6, 26].

The domain with the highest scores was "scope and purpose", and the domain with the lowest scores was "applicability". These results are in accordance with our previous report [14] that assessed the quality of CPGs on therapeutic interventions for oral cancer. However, we would like to highlight that both studies evaluated the same four CPGs [17, 19, 20, 22], which included recommendations for both screening/diagnosis and treatment for oral cavity cancer. Likewise, these findings are similar to some reports in oncology area, specifically in carcinoma of the head and neck [2, 27], as well as dentistry area [28, 29]. These findings are also similar to CPG quality appraisals in other clinical fields [6, 30–32]. The fact that most CPGs do not consider economic analysis for the implementation of their recommendations or that the cost implications are usually not fully described have been reported as some of the reasons for lower scores in the applicability domain [28, 33]. These results suggest that nowadays, most CPGs report their main objectives, the health questions, and the target population, but they have a lack guidance on their applicability; therefore, a major effort is required to address this issue, which reflects on factors such as implementation, organizational facilitators and barriers, additional materials provided, and economical implications. Similarly, it is important to disseminate the quality of available CPGs. This could improve clinicians' adherence to CPGs, since it has been reported that healthcare professionals' lack of adherence may be a result of distrust in CPG development processes and recommendations [34].

Regarding quality of CPGs and their recommendations, the following main recommendations were included in CPGs

Table 4 Good practice points included in the guidelines

Guideline	Good practice point
Diagnosis and management of head and neck cancer [17]	All healthcare practitioners—including dental and medical practitioners—should be aware of the presenting features of head and neck cancer, and the local referral pathways for suspected cancers
	Dental practitioners should include a full examination of the oral mucosa as part of routine dental checkup
	Patients should be seen within 2 weeks of urgent referral
	Patients should be seen by an experienced clinician with access to the necessary diagnostic tools
	General or dental practitioners should be aware of symptoms suggestive of head and neck cancer
Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity [21]	Clinicians should obtain an updated medical, social, and dental history and perform an intraoral and extraoral conventional visual and tactile examination in all adult patients
The Diagnosis and Treatment of Oral Cavity Cancer [22]	All patients with mucosal lesions of unknown origin and more than 2-week duration should immediately be referred to a specialist
Suspected cancer in primary care [24]	A person presenting with unexplained persistent sore or painful throat or mouth, (particularly unilateral pain) for more than 4 weeks, should be referred urgently to a specialist
	A person presenting with unilateral unexplained pain in the head and neck area for more than 4 weeks, or with paresthesia or dysesthesia in an area of nerve distribution should be referred urgently to a specialist
	A person presenting with hoarseness persisting for more than 3 weeks (particularly if a smoker aged 50 years or older, or a heavy drinker) should be referred to an ear, nose and throat specialist, and for a chest x-ray

rated as "recommended" and including grading of evidence; thus, these may be key recommendations for clinical practice: (i) rapid access to clinics should be available for patients who have a suspicious lesion of oral cancer [17]; (ii) if the lesion has not resolved, clinicians should perform a biopsy of the lesion and/or refer the patient to a specialist [21]; (iii) a biopsy should be taken from the most suspicious part of the tumor and its report should be clearly described [20]; (iv) fine needle aspiration cytology should be used in the investigation of head and neck masses [17]; (v) every uncommon tumor diagnosis besides classical OSCC should be reviewed by an expert from a reference laboratory [20]; (vi) the autofluorescence, tissue reflectance, or vital staining adjuncts for the evaluation of potentially malignant disorders are not recommended [21]; (vii) cytologic adjuncts are not recommended for the evaluation of potentially malignant disorders, it should be an alternative if the patient declines a biopsy [21]; (viii) the use of commercially available salivary adjuncts for the evaluation of potentially malignant disorders should only be considered in the context of research [21]; (ix) for adult patients with no clinically evident lesions or symptoms, no further action is necessary at that time [21]. This approach is based on the fact that high-quality CPGs are likely to provide helpful recommendations [33]. However, we wish to highlight that all these recommendations should be considered with caution because we only performed a descriptive analysis with no assessment of the quality of the evidence underlying each recommendation. For this purpose, it is necessary to use other tools such as the GRADE framework [35]. Moreover, most of these recommendations were based on low or very low level of evidence. Likewise, some CPGs did not take in account key risk factors to define their target population for oral cancer screening. It has been reported that oral cancer screening in general population is considered unnecessary, whereas that screening has a value in reducing the oral cancer mortality in high-risk group of population [36]. Therefore, any recommendations and practice points should be considered in the context of clinical judgment for each patient, his/her values and preferences, the available alternatives and their risk/benefit ratio, the available resources, and other contextual aspects [37].

Some CPGs developed by important healthcare organizations, such as the British Dental Association [38], the College of Dental Surgeons of British Columbia [39], Royal Australian College of General Practitioners [40], Australian

Head and Neck Cancer Working Group [41], and individual authors as Kerawala [42], were excluded since they did not provide a written methods section. Therefore, we did not assess all existing recommendations on screening and diagnosis of oral cancer that may impact the clinical practice of healthcare professionals. However, a thorough review of the methodology used to develop a CPG is mandatory to evaluate its quality and the reliability of its recommendations [32].

We wish to highlight that the AGREE II instrument lacked clear instructions regarding the weight of the different domain scores when determining the optimal CPG [31, 43]. It did not set minimum domain scores or score patterns across different domains that would allow establishing a difference between high- and low-quality CPGs [8, 44]. These decisions are left to the user's discretion [45]. Therefore, to improve the selection of optimal CPGs for clinical use, instead of assigning different weights across domains, we based on inter-appraiser agreement.

Among the main implications of our study is evidencing the need to improve CPG-development processes in this area, considering methodological aspects and applicability. The variability across the included CPGs shows the importance of identifying high-quality CPGs before implementing recommendations. For instance, the use of recommendations from low-quality CPGs may not meet effective health outcomes or might not contemplate the risk of their use in specific scenarios [28]. To standardize high-quality care, CPGs must be developed to minimize the use of unnecessary—and sometimes even harmful—medical interventions [44]. Therefore, it is essential to make available high-quality CPGs on screening and diagnosis of oral cancer that could serve as a useful and reliable tool for clinical decision-making. Authors have reported that CPGs must be based on the best available evidence and need to use validated recommendation-rating systems, to provide an explicit connection with the evidence [28].

This study has several strengths, such as the use of a protocol describing aims, selection criteria, planned methodology, and data analysis. The access to the included CPGs had no barrier, since they were available in full-text with no charges. Moreover, all information regarding the methodological quality of CPGs was obtained through a systematic search and was assessed independently by four appraisers using a standardized instrument. Currently, the AGREE II instrument is the only reliable and validated tool that allows a quantitative comparison of CPGs, providing also a methodological strategy for the development of CPGs, and the type of information that should be reported [7].

A limitation of this study might be our inability to retrieve CPGs that are not indexed or easily accessible. Nevertheless, some authors have reported that the methodology quality of non-indexed CPGs is likely lower than that of those indexed [6]. Likewise, the AGREE II tool was only used to evaluate the methods used to formulate and present recommendations, and not to appraise their validity; consequently, we only performed a description of recommendations. Another limitation is the restriction of CPGs in English, thus limiting the external validity of these findings to non-English CPGs. Likewise, although the English version of the German CPG [22] for the Diagnosis and Treatment of Oral Cavity Cancer was fully described, we were unable to read the full version in German. Hence, this CPG could possibly score higher in some domains.

Conclusion

The overall methodological quality of CPGs providing recommendations on screening and diagnosis of oral cancer is moderate, with only half of the included CPGs being assessed as recommended for clinical practice. The lowest domain scored was "applicability". Most recommendations were based on a low or very low level of evidence. One of the most common recommendations across all CPGs is that clinicians should perform a biopsy of the lesion and/or refer the patient to a specialist for the evaluation of potentially malignant disorders. Thus, it is essential that all CPGs provide a clear implementation strategy. This could facilitate clinicians' adherence to CPGs, contributing to evidence-based health care.

Acknowledgments Thank you to Ángela Merchán and Carmen Gallardo for participating in the guidelines assessment process, and to Andrea Cervera for proofreading this manuscript.

Funding information The *Bolívar Gana con Ciencia* grant financially supported Meisser Madera. This author is a Ph.D candidate at the Methodology and Biomedical Research and Public Health program, Universitat Autònoma de Barcelona.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

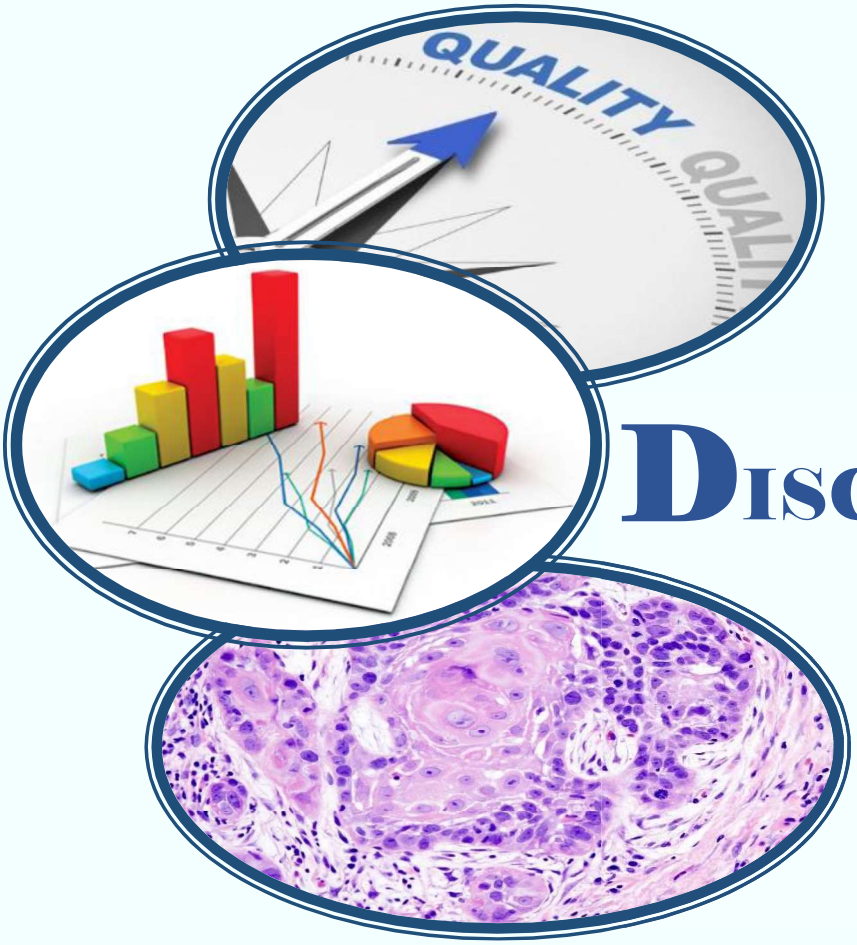
Informed consent For this type of study, formal consent is not required.

References

1. Grilli R, Magrini N, Penna A, Mura G, Liberati A (2000) Practice guidelines developed by specialty societies: the need for a critical appraisal. Lancet 355(9198):103–106. https://doi.org/10.1016/S0140-6736(99)02171-6
2. Chen YP, Wang YQ, Li WF, Chen L, Xu C, Lu TX, Lin AH, Yao JJ, Li YC, Sun Y, Mao YP, Ma J (2017) Critical evaluation of the quality and recommendations of clinical practice guidelines for nasopharyngeal carcinoma. J Natl Compr Cancer Netw 15(3):336–344
3. Eslava-Schmalbach J, Sandoval-Vargas G, Mosquera P (2011) Incorporating equity into developing and implementing for

evidence-based clinical practice guidelines. Rev Salud Publica (Bogota) 13(2):339–351
4. Lee GH, McGrath C, Yiu CK (2016) Developing clinical practice guidelines for caries prevention and management for pre-school children through the ADAPTE process and Delphi consensus. Health Res Policy Syst 14(1):44. https://doi.org/10.1186/s12961-016-0117-0
5. Graham ID, Beardall S, Carter AO, Glennie J, Hebert PC, Tetroe JM, McAlister FA, Visentin S, Anderson GM (2001) What is the quality of drug therapy clinical practice guidelines in Canada? CMAJ 165(2):157–163
6. Fuentes Padilla P, Martinez G, Vernooij RW, Cosp XB, Alonso-Coello P (2016) Nutrition in critically ill adults: a systematic quality assessment of clinical practice guidelines. Clin Nutr 35(6):1219–1225. https://doi.org/10.1016/j.clnu.2016.03.005
7. Brouwers M, Kho M, Browman G, Burgers J, Cluzeau F, Feder G (2010) AGREE next steps consortium. AGREE II: advancing guideline development, reporting, and evaluation in health care. CMAJ 182(18):E839–E842. https://doi.org/10.1503/cmaj.090449
8. Brouwers M, Kho M, Browman G, Burgers J, Cluzeau F, Feder G (2010) For the AGREE next steps consortium. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. CMAJ 182(10):E472–E478. https://doi.org/10.1503/cmaj.091716
9. Warnakulasuriya S (2009) Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 45(4–5):309–316. https://doi.org/10.1016/j.oraloncology.2008.06.002
10. Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017. CA Cancer J Clin 67(1):7–30. https://doi.org/10.3322/caac.21387
11. Moreira MA, Lessa LS, Bortoli FR, Lopes A, Xavier EP, Ceretta RA, Sonego FGF, Tomasi CD, Pires PDS, Ceretta LB, Perry IDS, Waleska Simoes P (2017) Meta-analysis of magnetic resonance imaging accuracy for diagnosis of oral cancer. PLoS One 12(5): e0177462. https://doi.org/10.1371/journal.pone.0177462
12. Costa K, Cunha K, Rodrigues F, Silva L, Dias E (2013) Concordance between cytopathology and incisional biopsy in the diagnosis of oral squamous cell carcinoma. Braz Oral Res 27(2):122–127
13. Macey R, Walsh T, Brocklehurst P, Kerr AR, Liu JL, Lingen MW, Ogden GR, Warnakulasuriya S, Scully C (2015) Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions. Cochrane Database Syst Rev 5:CD010276. https://doi.org/10.1002/14651858.CD010276.pub2
14. Madera Anaya MV, Franco JV, Merchan-Galvis AM, Gallardo CR, Bonfill Cosp X (2018) Quality assessment of clinical practice guidelines on treatments for oral cancer. Cancer Treat Rev 65:47–53. https://doi.org/10.1016/j.ctrv.2018.03.001
15. AGREE (2009) (Update: 2013) The Appraisal of Guidelines for Research & Evaluation. AGREE. Ontario, Canada:The AGREE Next Steps Consortium. (http://www.agreetrust.org)
16. Landis JR, Koch GG (1977) The measurement of observer agreement for categorical data. Biometrics 33(1):159–174
17. SIGN (2006) SIGN (2006) The Scottish Intercollegiate Guidelines Network. Diagnosis and management of head and neck cancer. A national clinical guideline: 1–96. https://www.uhb.nhs.uk/Downloads/pdf/CancerPbDiagnosisHeadAndNeckCancer.pdf. Accessed 28 Jan 2018
18. Moyer VA, Force USPST (2014) Screening for oral cancer: U.S. preventive services task force recommendation statement. Ann Intern Med 160(1):55–60. https://doi.org/10.7326/M13-2568
19. AHS (2014) Alberta Health Services. Oral cavity cancer. Clinical Practice Guideline HN-002. Version 1: 1–22. https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-hn002-oral-cavity.pdf. Accessed 28 Jan 2018
20. Grégoire V, Leroy R, Heus P, Van de Wetering F, Hooft L, Scholten R, Verleye L, Carp L, Clement P, Deron P, Goffin K, Hamoir M, Hauben E, Hendrickx K, Hermans R, Kunz S, Lenssen O, Nuyts S, Van Laer C, Vermorken J, Appermont E, De Prins A, Hebbelinck E, Hommez G, Vandenbruaene C, Vanhalewyck E, Vlayen J (2014) Oral cavity cancer: diagnosis, treatment and follow-up. Good Clinical Practice (GCP). Belgian Health Care Knowledge Centre (KCE), Brussels KCE Reports 227
21. Lingen MW, Abt E, Agrawal N, Chaturvedi AK, Cohen E, D'Souza G, Gurenlian J, Kalmar JR, Kerr AR, Lambert PM, Patton LL, Sollecito TP, Truelove E, Tampi MP, Urquhart O, Banfield L, Carrasco-Labra A (2017) Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity: a report of the American dental association. J Am Dent Assoc 148(10):712–727 e710. https://doi.org/10.1016/j.adaj.2017.07.032
22. Wolff KD, Follmann M, Nast A (2012) The diagnosis and treatment of oral cavity cancer. Dtsch Arztebl Int 109(48):829–835. https://doi.org/10.3238/arztebl.2012.0829
23. NICE (2015) NICE Guideline. In: Suspected Cancer: Recognition and Referral. National Institute for Health and Care Excellence: Clinical Guidelines, London, pp 1–378
24. NZGG (2009) New Zealand Guidelines Group. Suspected Cancer in primary care. Guidelines for investigation, referral and reducing ethnic disparities. Wellington: 1–190. https://www.health.govt.nz/system/files/documents/publications/suspected-cancer-guideline-sep09.pdf. Accessed 28 Jan 2018
25. Shekelle PG, Ortiz E, Rhodes S, Morton SC, Eccles MP, Grimshaw JM, Woolf SH (2001) Validity of the Agency for Healthcare Research and Quality clinical practice guidelines: how quickly do guidelines become outdated? Jama 286(12):1461–1467
26. Yaman ME, Gudeloglu A, Senturk S, Yaman ND, Tolunay T, Ozturk Y, Arslan AK (2015) A critical appraisal of the North American Spine Society guidelines with the appraisal of guidelines for research and evaluation II instrument. Spine J 15(4):777–781. https://doi.org/10.1016/j.spinee.2015.01.012
27. Jiang Y, Zhu XD, Qu S, Li L, Zhou Z (2015) Guidelines for squamous cell carcinoma of the head and neck: a systematic assessment of quality. Ear Nose Throat J 94(4–5):E14–E24
28. Seiffert A, Zaror C, Atala-Acevedo C, Ormeno A, Martinez-Zapata MJ, Alonso-Coello P (2018) Dental caries prevention in children and adolescents: a systematic quality assessment of clinical practice guidelines. Clin Oral Investig. https://doi.org/10.1007/s00784-018-2405-2
29. Mubeen S, Patel K, Cunningham Z, O'Rourke N, Pandis N, Cobourne MT, Seehra J (2017) Assessing the quality of dental clinical practice guidelines. J Dent 67:102–106. https://doi.org/10.1016/j.jdent.2017.10.003
30. Acuna-Izcaray A, Sanchez-Angarita E, Plaza V, Rodrigo G, de Oca MM, Gich I, Bonfill X, Alonso-Coello P (2013) Quality assessment of asthma clinical practice guidelines: a systematic appraisal. Chest 144(2):390–397. https://doi.org/10.1378/chest.12-2005
31. Alonso-Coello P, Irfan A, Sola I, Gich I, Delgado-Noguera M, Rigau D, Tort S, Bonfill X, Burgers J, Schunemann H (2010) The quality of clinical practice guidelines over the last two decades: a systematic review of guideline appraisal studies. Qual Saf Health Care 19(6):e58. https://doi.org/10.1136/qshc.2010.042077
32. Erickson J, Sadeghirad B, Lytvyn L, Slavin J, Johnston BC (2017) The scientific basis of guideline recommendations on sugar intake: a systematic review. Ann Intern Med 166(4):257–267. https://doi.org/10.7326/M16-2020
33. Wang Y, Ye ZK, Li JF, Cui XL, Liu LH (2018) Heparin-induced thrombocytopenia: a critical appraisal of clinical practice guidelines with the AGREE II instrument. Thromb Res 166:10–18. https://doi.org/10.1016/j.thromres.2018.03.017
34. Sox HC (2014) Assessing the trustworthiness of the guideline for management of high blood pressure in adults. Jama 311(5):472–474. https://doi.org/10.1001/jama.2013.284429
35. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336(7650):924–926. https://doi.org/10.1136/bmj.39489.470347.AD

36. Iyer S, Thankappan K, Balasubramanian D (2016) Early detection of oral cancers: current status and future prospects. Curr Opin Otolaryngol Head Neck Surg 24(2):110–114. https://doi.org/10.1097/MOO.0000000000000237
37. Alonso-Coello P, Schunemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Treweek S, Mustafa RA, Rada G, Rosenbaum S, Morelli A, Guyatt GH, Oxman AD (2016) GRADE evidence to decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: introduction. BMJ 353:i2016. https://doi.org/10.1136/bmj.i2016
38. BDA (2010) Early detection and prevention of oral cancer: a management strategy for dental practice. The British Dental Association-Occasional paper, pp 1–37
39. CDSBC (2008) College of Dental Surgeons of British Columbia. Guideline for the early detection of Oral Cancer in British Columbia 2008: 1–8. https://www.cdsbc.org/CDSBCPublicLibrary/Oral-Cancer-Clinical-Practice-Guideline.pdf. Accessed 28 Jan 2018
40. RACGP (2012) The Royal Australian College of General Practitioner. Early detection of cancers. Guidelines for preventive activities in general practice ('the red book') 8th edition: 68. https://www.racgp.org.au. Accessed 28 Jan 2018
41. AHNCWG (2013) Australian Head and Neck Cancer Working Group. South Australian Head and Neck Cancer Pathway: Optimising outcomes for all South Australians diagnosed: 1–146. http://www.sahealth.sa.gov.au. Accessed 28 Jan 2018
42. Kerawala C, Roques T, Jeannon JP, Bisase B (2016) Oral cavity and lip cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol 130(S2):S83–S89. https://doi.org/10.1017/S0022215116000499
43. Vlayen J, Aertgeerts B, Hannes K, Sermeus W, Ramaekers D (2005) A systematic review of appraisal tools for clinical practice guidelines: multiple similarities and one common deficit. Int J Qual Health Care 17(3):235–242. https://doi.org/10.1093/intqhc/mzi027
44. Jiang M, Liao LY, Liu XQ, He WQ, Guan WJ, Chen H, Li YM (2015) Quality assessment of clinical practice guidelines for respiratory diseases in China: a systematic appraisal. Chest 148(3):759–766. https://doi.org/10.1378/chest.14-3201
45. Lytras T, Bonovas S, Chronis C, Konstantinidis AK, Kopsachilis F, Papamichail DP, Dounias G (2014) Occupational asthma guidelines: a systematic quality appraisal using the AGREE II instrument. Occup Environ Med 71(2):81–86. https://doi.org/10.1136/oemed-2013-101656



Discussion

6. DISCUSSION

The joint discussion of this doctoral thesis is structured around the quality assessment of scientific evidence about oral cancer. About this topic, we have evaluated two key aspects related to oral cavity cancer such as diagnosis and treatment. To describe and appraisal the evidence about therapeutic interventions for oral cancer, two studies have been conducted, one of them was an evidence mapping and another study was a systematic assessment of clinical practice guidelines. Regarding oral cancer diagnosis, one study has been conducted, which corresponds to a critical appraisal of clinical practice guidelines and describing their recommendations.

6.1 QUALITY OF EVIDENCE ON THERAPEUTIC INTERVENTIONS FOR ORAL CANCER

There is a rising pressure to provide evidence-based medical care, so the use the scientific evidence to support the dental practice has been increasing globally over recent decades. By using the best available evidence, practitioners can be assisted in minimizing inappropriate variation in clinical practice, improving decision-making processes, and promote effective and safe patient outcomes (98). Moreover, given there is a huge of published scientific literature advising a range of therapeutic interventions for oral cancer, knowing the effectiveness of those treatments and their indications may be difficult.

Therefore, the conducting of an evidence mapping and a systematic assessment of clinical practice guidelines on therapeutic interventions for oral cavity cancer into this doctoral thesis allow to us provide relevant information about the scientific evidence on treatments for oral cancer along with its quality.

The main findings of these two studies (99, 100) suggest that there is limited evidence about treatments for oral cancer and its quality is suboptimal. These results can be considered relevant since their implications on the future improvement of quality and reporting of research in this field.

Regarding the first study (99), scientific evidence on treatments for oral cancer is limited since only 15 systematic reviews met the eligibility criteria. This number could be considered small since it is widely known the increase of systematic reviews being published worldwide. To illustrate, Ioannidis (101) concluded that more than 265000 records were identified as systematic reviews in PubMed between 1986 and 2015 after applying the corresponding filter. Moreover, it has been reported that more than 20 systematic reviews of biomedical research are published daily (102). Likewise, it has been suggested that in dentistry, the same tendency exists (103), publishing around 1200 systematic reviews between 1991 and 2012, which had diverse characteristics across dental specialties (104). Similarly, Bassani (103) concluded that many systematic reviews in dentistry were published in 2017. The limited evidence on treatments for oral cancer also was confirmed for our second study (100), where only 12 clinical practice guidelines on this topic were included. One possible explanation of the limited evidence available in systematic reviews on treatments for cancer may be that oral oncology could be among dental specialties with a smaller number of systematic reviews being conducted. In this sense, it has been reported that implantology, periodontology, oral and maxillofacial surgery, and stomatology stand among dental specialties that more frequent are covered by systematic reviews (103). Moreover, it is useful to clarify that the risen volume of evidence being published in dentistry, may not necessarily indicate an improvement in its quality. Thus, some actions are needed in order to increase the quality

of evidence focused on oral diseases, which will allow dental care professionals to provide better dental care based on high-quality evidence.

Concerning the quality of evidence about treatments for oral cancer, both studies (99, 100) concluded that it is critically low. In the evidence mapping (99), most systematic reviews were rated as "critically low" using the AMSTAR-2 instrument. Among the main aspects to improve were: i) reporting the existing of a protocol before to conduct of the systematic review and indicate any significant deviations from the protocol; ii) the explanation of the selection of the study designs for inclusion in the systematic review; iii) the provision of the list of excluded studies along with their reasons; and iv) the inclusion of a conflict-of-interest statement, demonstrating the source of financial support for each primary study included in the systematic review. Likewise, the study (100) of quality assessment of clinical practice guidelines on treatments for oral cancer, showed that their quality is suboptimal since that only three (82, 83, 89) out of 12 guidelines were rated as recommended for clinical use. The domains with the highest scores were "scope and purpose" and "clarity of presentation", whereas the domain with the lowest score was "applicability". Overall, the clinical practice guidelines defined well specific and focused clinical questions and target populations, whereas lacked on reporting other aspects such as explicit plans of implementation and conflict-of-interest statements. These results suggest that there is room for potential improvement in the quality of scientific evidence in this field.

Given we could not identify previous reports assessing the quality of systematic reviews and clinical practice guidelines on treatments for oral cancer, we do not have similar reports to compare our results

with. However, some reports in dentistry have suggested that there is a mandatory need to improve the quality of reporting and conduct of systematic reviews in this field (103). In this sense, El-Rabbany (105) conducted a study aimed to assess the quality of therapeutic meta-analyses of RCTs on dental-related topics and to analyze how quality has changed over time, concluding that there is a room for improvement in the all aspect of systematic reviews reporting and their methodology. Similarly, Nagendrababu (106) concluded that systematic reviews in endodontics had high variability in both methodologic and reporting quality. Regarding the quality of clinical practice guidelines in dentistry, Mubeen (107) concluded that it is suboptimal and that there is variation in the overall quality, reporting of individual items, and AGREE II instrument domains across different dental specialties guidelines. Moreover, others reports assessing the quality of clinical practice guidelines on specific dental specialties such as orthodontic (108), pediatric dentistry (109), dental radiology (110), and common dental procedures (111) have concluded that their reporting changes considerably. Therefore, clinicians must take caution when reading available evidence in systematic reviews and/or clinical practice guidelines, ensuring that the principals of a critical appraisal are applied when interpreting them.

Regarding the treatments for oral cancer, our evidence mapping (99) showed that among the main therapeutic interventions reported by the authors as beneficial for patients with resectable oral cancer are surgery alone or in combination with radiotherapy or chemotherapy, depending on the extent of the tumor. These results were based on systematic reviews (33, 68, 70, 71, 78, 80, 81) ranging from "critically low" to "high" methodological quality using the AMSTAR-2 tool. However, these reports should be taken with caution since some systematic reviews (68, 80, 81) only included observational

studies. Moreover, despite some interventions reported by the authors as "beneficial" were based on RCTs (112-119) the majority of those comparisons included just one RCT (112, 115, 116), some of which had a small sample size.

Overall, there were fewer comparisons for patients with unresectable oral cancer than for those with resectable oral cancer. Only two interventions were reported by the authors as beneficial; these found altered fractionated radiotherapy to be superior to other forms of radiotherapy (69) and the use of bleomycin as a chemotherapy drug (33). Although all comparisons for this population were based on systematic reviews (33, 69, 71, 73, 75, 77) including only RCTs and controlled clinical trials, these results should be placed in context. To illustrate, the use of bleomycin was based on only one single RCT (120) published a long time ago. Therefore, nowadays it is likely that there are other options for chemotherapy such as Cisplatin, 5-Fluorouracil Carboplatin, Paclitaxel, and Docetaxel; which may be used alone or combined with other drugs (121, 122).

In order to verify whether the therapeutic interventions reported as beneficial in the evidence mapping (99) are listed into the recommendations of the clinical practice guidelines assessed in our second study (100), we have revised the recommendations of the highest quality clinical practice guidelines. These were developed by the Belgian Health Care Knowledge Centre-KCE (89), the British National Institute for Health and Care Excellence (82), and the Scottish Intercollegiate Guidelines Network (83), scoring over 60% in all AGREE II domains. We can now confirm that only some treatments for oral cancer identified as beneficial in our evidence mapping are included in the recommendations for clinical

practice. Likewise, we highlight that recommendations from these clinical practice guidelines should also be considered with caution because the AGREE II instrument only evaluates the methodological quality for their development, without judging the validity of the recommendations themselves.

Overall, the evidence about treatments for oral cancer is limited and its methodology quality is low. However, it useful to highlight that this issue is not exclusive of oral oncology, instead of it is a common problem across dental specialties. Hence, some measures are required to solve this issue and to improve the evidence-based dental practice. In this sense, it has been suggested that among those actions is undoubtedly the validation and implementation of novel didactic and practical methods to teach evidence-based dentistry—both research and practice—to the future researchers and clinicians in the dentistry field and to optimize the integration of evidence-based dentistry in the dental curriculum. Likewise, it is crucial to open and expand new research opportunities in subdomains critical to successful evidence-based dental practice, such as stakeholder engagement, patient-centered care, teledentistry, individual patient data analysis, and health literacy of the patients and caregivers (123, 124). This approach assumes that whether all health care professionals are taught and trained in evidence-based medicine, they will be able to conduct better research, critical appraisal it, and to include it into practice, so there will be improvement of patients' outcomes.

6.2 QUALITY OF EVIDENCE ABOUT DIAGNOSIS OF ORAL CAVITY CANCER

It is widely known that one of the major concerns about oral cavity cancer is its high mortality rate, which in most cases is associated with delayed diagnosis, and has a huge burden disease in the healthcare public system. Consequently, providing evidence-based dental care may help to decrease

the lethality of this oral disease and its burden. In this doctoral thesis, we have conducted a study (125) that aimed to assess the quality of clinical practice guidelines on the diagnosis of oral cancer and describe their recommendations, concluding that greater efforts are needed to provide healthcare based on high-quality evidence-based in this field.

Since only eight (83, 88, 89, 91, 94-97) clinical practice guidelines met the eligibility criteria, we may assume that available scientific evidence on the diagnosis of oral cancer that supports the dental clinic practice is very limited. Moreover, it is likely that some clinical practice guidelines including recommendations on diagnosis of oral cancer and impacting the clinical practice of some dentists are not evidence-based. To illustrate, we excluded some clinical practice guidelines developed by prominent healthcare associations because they did not provide a written methods section, such as the British Dental Association (126), the College of Dental Surgeons of British Columbia (127), Royal Australian College of General Practitioners (128), and Australian Head and Neck Cancer Working Group (129). It is useful to highlight that in order to assess the quality of a clinical practice guideline and the reliability of its recommendations, a comprehensive assessment of its methodology is essential (130). These findings suggest that it is indispensable to incorporate the available scientific evidence into the development process of clinical practice guidelines to assist clinicians in the decision-making process.

Overall, quality of clinical practice guidelines on the diagnosis of oral cancer can be considered as moderate because half (4 out of 8) of the assessed guidelines were rated as “recommended”, the other half was rated as “recommended with modifications”, and there was none rated as “not recommended”.

The highest quality clinical practice guidelines were developed by the Belgian Health Care Knowledge Centre (89), the Scottish Intercollegiate Guidelines Network (83), the National Institute for Health and Care Excellence (96), and The American Dental Association (95); apart from the latter one, others scored over 60% in all AGREE II domains. However, some factors could be improved such as the reporting of the level of evidence of recommendations (96), applicability statement (95), and the use the outdated evidence (83). Moreover, we wish to highlight that since only a small number of clinical practice guidelines were rated as "recommended" in our study, it may suggest that evidence being used to support the dental practice in this field is limited and there is a room for improvement.

As in our second study (100) of guidelines on treatments for oral cancer, in this study (125), the "scope and purpose" domain had the highest scores, whereas the "applicability" domain had the lowest scores. Similarly, these findings are in concordance with some previous reports in dentistry (107, 131), oncology (46, 132, 133), and other medical specialties (52, 130, 134-137). These results suggest that although most clinical practice guidelines are developed considering a clear aim, specific health questions, and the target population, they are lacking a statement on their applicability. Among the reasons that have been stated to explain the poorly report of the "applicability" domain in some clinical practice guidelines are the absence of the economic analysis for the implementation of recommendations and that the cost implications are commonly not fully explained (131, 138). Hence, a major effort is required to address this issue, which reflects on factors such as implementation, organizational facilitators and barriers, and economical implications.

Regarding the recommendations included in the selected clinical practice guidelines, we considered that those recommendations included in the guidelines (83, 89, 95, 96) with the highest scores in

AGREE II domains and rated as “recommended” could be useful for diagnosis of oral cancer in the clinical practice. This approach is based on the fact that high-quality clinical practice guidelines are likely to provide helpful recommendations (138). However, we wish to highlight that most recommendations on the diagnosis of oral cancer were based on low or very low level of evidence. Thus, improving the quality of research on this field is mandatory to achieve a good level of evidence-based dentistry.

Among the recommendations included in the recommended clinical practice guidelines, we can mention that: i) for patients with a suspicious lesion of oral cancer, rapid access to clinics should be available (83); ii) a biopsy of suspicious lesion should be performed and/or refer the patient to a specialist whether the lesion has not resolved (95); iii) the biopsy should be taken from the most suspicious part of the tumor and its report should be clearly described (89); iv) fine needle aspiration cytology should be used in the investigation of head and neck masses (83); and v) no further action is necessary at that time, for adult patients with no symptoms or clinically evident lesions (47). However, we wish to highlight that all these recommendations should be considered with caution because we only performed a descriptive analysis with not an assessment of the quality of the evidence underlying each recommendation. Moreover, the AGREE II instrument only assesses the reporting of methodological quality aspects for their development, not judging the rationality of their recommendations. For this purpose, it is necessary to use other tools such as the GRADE framework (139). Overall, any recommendations and practice points should be considered in the context of clinical judgment for each patient, their values and preferences, the available alternatives and their risk/benefit ratio, the available resources, and other contextual aspects (140).

Finally, it is useful to clarify that just a study is not enough to evaluate the evidence on diagnosis for oral cavity cancer. Consequently, we have conducted other studies (141-143) into this promising line of research, which are available in the Appendix 2. These are focused on the evaluation on the scientific evidence on salivary biomarkers for early diagnosis of oral cancer and potential malignant disorders. Overall, greater efforts are required to improve the opportune diagnosis of oral cavity cancer, which is fundamental to provide adequate treatment and increase the survival rate of this oral disease. Likewise, other factors could have a positive impact if delayed diagnosis of oral cancer is avoided, such as prognosis, quality of life, prompt recovery, and less after-effects.

6.3 POTENTIAL LIMITATIONS AND STRENGTHS

Potential limitations

The main limitations of this doctoral thesis are those related to the methodology designs of each study that comprise it. Some limitations are common across all studies such as the language barrier, due to all evidence found was published in English, which eliminated the inclusion of available evidence published in any other language. However, it is useful to highlight that no restrictions about languages were performed; moreover, since most evidence is published in English, it more likely that evidence meeting the eligibility criteria is published in this language.

Likewise, due to language barriers, we were not able to read the supplementary materials in Japanese nor the full version in German of two (86, 91) clinical practice guidelines included in our studies; thus, it likely that these clinical practice guidelines could potentially score higher in some domains.

In the evidence mapping, some limitations should be considered. To illustrate, limited systematic reviews are comparing therapeutic interventions for oral cancer and some of them only included observational studies. Therefore, some bias due to confounding factors may exist in these studies.

Similarly, given some systematic reviews had methodological limitations, their conclusions can be subject to bias; therefore, their conclusions regarding the effectiveness of the different interventions could be invalid. However, this is thoroughly reported in our results, so each conclusion can be assessed by the reader including its limitation.

Finally, regarding the two studies assessing the quality of clinical practice guidelines, one of the limitations is that we might have not identified some guidelines because they are often not indexed or easily accessible. However, it is reasonable to assume that the quality of the un-indexed guideline is probably lower than that of those indexed (52). Likewise, the AGREE II tool was only used to evaluate the methods used to formulate and present recommendations, and not to appraise their validity; consequently, we only performed description of recommendations in the third study.

Overall, we believe that these limitations do not substantially change the main results of this doctoral thesis.

Strengths

The findings of this doctoral thesis are novel and relevant for the diagnosis and treatments for oral cancer, which allow improving the reporting of the evidence about this topic, helping to provide a better evidence-based dental care. Thus, it will contribute to the health status of patients suffer from this oral disease. Moreover, we did not find any previous report using an evidence mapping methodology to assess the evidence on therapeutic interventions for oral cancer nor quality assessments of clinical practice guidelines including recommendations about diagnosis and treatments for oral cancer.

This doctoral thesis has several strengths such as the fact that a comprehensive analysis of available scientific evidence on diagnosis and treatments for oral cancer was conducted using different validated tools of synthesis of evidence, critical appraisal, and presentation of evidence. Moreover, it is consistent with the lines of investigation that are carried out in our research group, in which some doctoral theses have been developed to contribute with evidence-based clinical practice through the evaluation, implementation and dissemination of evidence. Thus, the results of those research have been published in different clinical areas, such as oncology (66, 144, 145), nutrition (146), cardiovascular (147, 148), traumatology (149, 150), and others (151).

Similarly, among the strengths of this doctoral thesis is that all three studies (99, 100, 125) were conducted in concordance with protocols designed in advance, where all eligibility criteria, objectives, and planned methods of analysis were documented. Moreover, we highlight that a sensitive search strategy was performed in each study, so it is unlikely that any relevant evidence was missed.

In the evidence mapping (99), two reviewers independently conducted the whole processes of selection, methodological quality assessment and data extraction from the included systematic reviews. Similarly, in the two studies (100, 125) of systematic appraisal of clinical practice guidelines, four evaluators independently assessed the quality of clinical practice guidelines development with very good agreement by using a validated instrument. Currently, the AGREE II instrument is the only reliable and validated tool that allows a quantitative comparison of clinical practice guidelines, providing also a methodological strategy for the development of guidelines, and the type of information that should be reported (59). All these processes provide reasonable confidence in our findings.

6.4 IMPLICATIONS TO DENTAL CLINICAL PRACTICE

According to our three studies, we can conclude that available scientific evidence on diagnosis and treatments for oral cancer is limited and that there is room for improving its quality and reporting. Given knowing the available evidence is so important to provide evidence-based healthcare, the findings of this doctoral thesis can be useful to improve the diagnosis and management of oral cavity cancer.

Regarding the evidence mapping results, the therapeutic interventions identified and reported as beneficial or probably beneficial could be considered into dental clinical practice to provide evidence-based dentistry, especially during the decision-making process. Similarly, those treatments that have been using for decades without evidence' support, and that according to our evidence mapping, they have no differential effect or any advantage on the standard treatment, should not be considered as options to treat mouth cancers. However, we wish to emphasize that this doctoral thesis does not pretend to replace any clinical practice guideline or protocol. Its main goal is to describe the available

evidence on diagnosis and treatments for oral cancers; thus, any practice point or clinical decision must be based on the context of clinical judgment for each patient, considering all available alternatives along with their risks and benefits, patient' preferences and other factors.

Likewise, other implications to the dental clinical practice of this doctoral thesis are related to identifying and disseminating of the quality of clinical practice guidelines on diagnosis and treatments for oral cancer. This implication is based on several reasons. Firstly, due to variability across the clinical practice guidelines assessed in this doctoral thesis, the identifying of those with high-quality is mandatory before implementing recommendations. Secondly, since healthcare professionals' lack of adherence to clinical practice guidelines because they may be distrust in their development processes and recommendations (152), knowing the quality of clinical practice guidelines in this field, could improve clinicians' adherence to high-quality guidelines. Finally, given that the use of recommendations from low-quality guidelines may not meet effective health outcomes or might not contemplate the risk of their use in specific scenarios (131), the identifying of high-quality clinical practice guidelines is essential to provide high-quality health care. In this sense, those guidelines identified as recommended in this doctoral thesis could be useful for clinical practice, whereas that those identified as not recommended or recommended with modifications should not be considered or at least considered with caution.

Similarly, another implication of this doctoral thesis is associated with the improvement of the development process of clinical practice guidelines in this field, taking account of both methodological

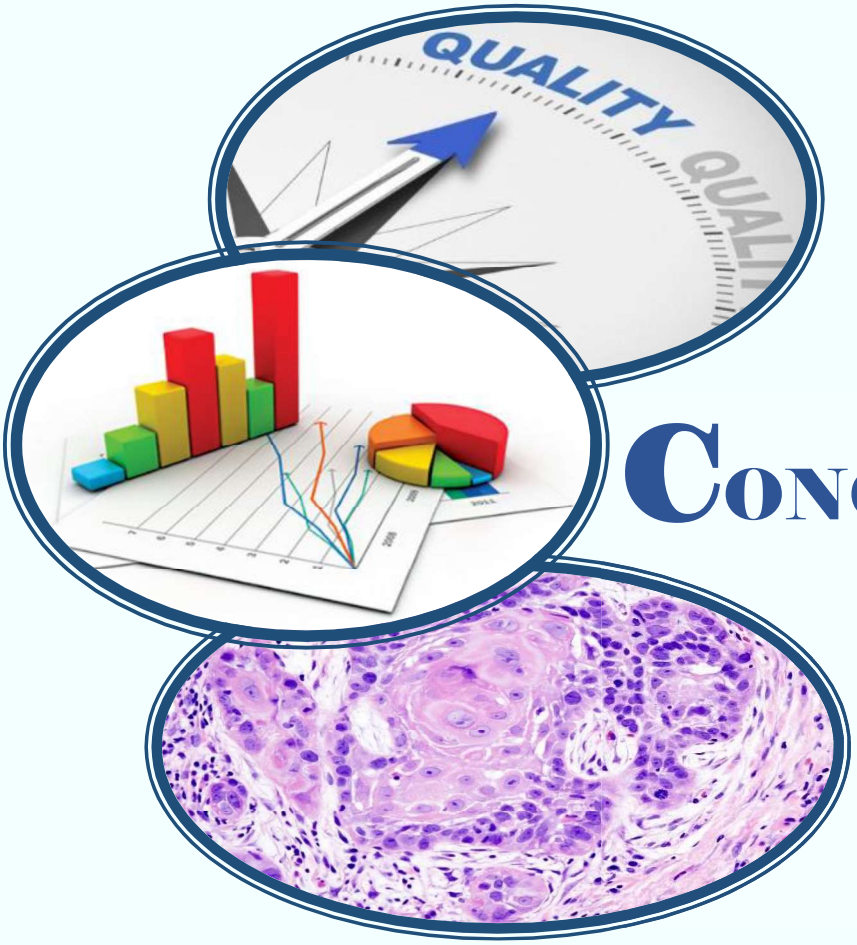
and applicability features. In this sense, given that many clinical practice guidelines were rated as not recommended or recommended with modifications, the improvement of them is needed, so in order to standardize high-quality care, and make available high-quality clinical practice guidelines on diagnosis and treatments for oral cancer that could serve as a useful and reliable tool for clinical decision-making, some aspects should be considered such as the inclusion of the best available evidence into clinical practice guidelines, and the use of validated recommendation-rating systems to provide an explicit connection with the evidence.

6.5 IMPLICATIONS TO RESEARCH ON THIS FIELD

The results of this doctoral thesis are a key piece to planning, design and conducting future research on the dentistry area, especially in oral oncology. We were able to identify some knowledge gaps in our evidence mapping, so it can be used to address future research projects focused on them. Likewise, it could be useful to conduct RCTs and/or systematic reviews on those treatments with limited evidence. Moreover, given the latest advances in technology proposing innovative therapeutic interventions in oncology, it is likely that new therapeutic options for oral cancer are being introduced constantly into clinical practice, so the assessment of the quality of evidence on those new therapies is a need and should be ongoing.

Likewise, since that we only assessed the quality methodology of clinical practice guidelines including recommendations on diagnosis and treatments for oral cancer using the AGREE II instrument, more research is needed to evaluate the reliability of recommendation included in the clinical practice guidelines being used into the dental clinical practice.

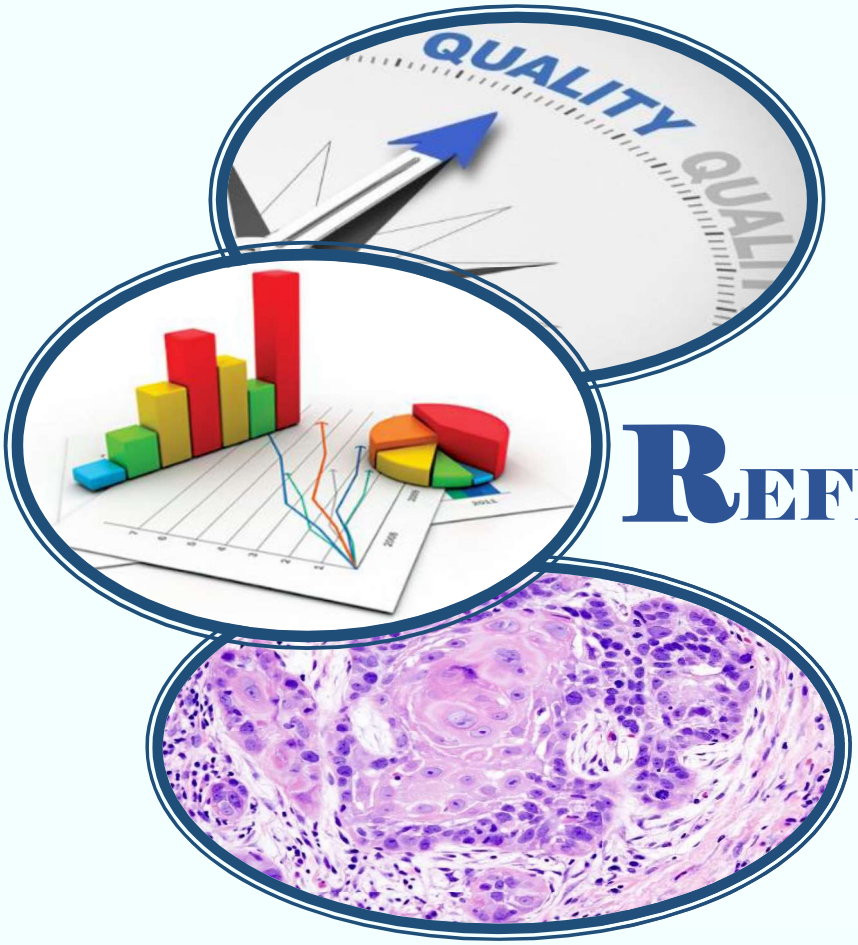
Finally, the methodology used in each study comprising this doctoral thesis could be useful to describe and evaluate the evidence on diagnosis and treatments for other diseases, especially for oral conditions. This could help to increase and improve the health care provided in the dentistry area, which must be based on high-quality evidence.



Conclusions

CONCLUSIONS

- Although there is a vast scientific literature focused on mouth cancers; in general, the scientific evidence about diagnosis and treatments for oral cancer is limited and their quality is mainly low.
- The methodological quality of clinical practice guidelines including recommendations on diagnosis and treatments for oral cancer was rated from suboptimal to moderate. Moreover, most recommendations on the diagnosis of oral cancer are based on a low level of evidence. Therefore, there is room for improvement in this area.
- Increased efforts are required to enable the development of high-quality evidence-based clinical practice guidelines on diagnosis and treatments for oral cancer.
- Our findings highlight the need to address future research focused on new therapeutic interventions and knowledge gaps in this field. Likewise, the reliability of recommendations included in the selected clinical practice guidelines should be evaluated.
- Overall, the scientific evidence about diagnosis and treatments for oral cancer is limited and their quality is critically low. Consequently, in order to improve the clinical dental practice provided and to increase the use of scientific evidence in the dentistry area, some actions should be taken such as improving the reporting of research focused on oral diseases, design and development of high-quality clinical practice guidelines along with their dissemination plan, considering the main barriers and costs related to the implementation process. Likewise, dental care professionals should be able to critical appraisal of the available scientific evidence and use it for decision-making, which could increase survival rates, prognosis and improve the quality of life of people suffer from mouth diseases such as oral cancer.



REFERENCES

REFERENCES

1. Daly B, Batchelor P, Treasure E. Introduction to the principles of public health In: Press OU, editor. Essential dental public health. 2: Oxford; 2013. p. 1-48.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67:7-30.
3. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral oncology. 2009;45:309-16.
4. Kyrgias G, Hajiioannou J, Tolia M, Kouloulias V, Lachanas V, Skoulakis C, et al. Intraoperative radiation therapy (IORT) in head and neck cancer: A systematic review. Medicine (Baltimore). 2016;95:e5035.
5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
6. Moreira MA, Lessa LS, Bortoli FR, Lopes A, Xavier EP, Ceretta RA, et al. Meta-analysis of magnetic resonance imaging accuracy for diagnosis of oral cancer. PLoS One. 2017;12:e0177462.
7. Costa K, Cunha K, Rodrigues F, Silva L, Dias E. Concordance between cytopathology and incisional biopsy in the diagnosis of oral squamous cell carcinoma. Brazilian Oral Research. 2013;27:122-7.
8. Ghani WMN, Ramanathan A, Prime SS, Yang Y-H, Razak IA, Abdul Rahman ZA, et al. Survival of Oral Cancer Patients in Different Ethnicities. Cancer Investigation. 2019;37:275-87.
9. Howlader N, Noone A, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review, 1975-2017. National Cancer Institute; 2020.
10. Gupta B, Johnson NW. Systematic review and meta-analysis of association of smokeless tobacco and of betel quid without tobacco with incidence of oral cancer in South Asia and the Pacific. PLoS One. 2014;9:e113385.
11. Mello FW, Melo G, Pasetto JJ, Silva CAB, Warnakulasuriya S, Rivero ERC. The synergistic effect of tobacco and alcohol consumption on oral squamous cell carcinoma: a systematic review and meta-analysis. Clinical oral investigations. 2019;23:2849-59.
12. Dhanuthai K, Rojanawatsirivej S, Thosaporn W, Kintarak S, Subarnbhesaj A, Darling M, et al. Oral cancer: A multicenter study. Med Oral Patol Oral Cir Bucal. 2018;23:e23-e9.
13. Perry BJ, Zammit AP, Lewandowski AW, Bashford JJ, Dragovic AS, Perry EJ, et al. Sites of origin of oral cavity cancer in nonsmokers vs smokers: possible evidence of dental trauma carcinogenesis and its importance compared with human papillomavirus. JAMA otolaryngology-- head & neck surgery. 2015;141:5-11.
14. Warnakulasuriya S. Causes of oral cancer--an appraisal of controversies. Br Dent J. 2009;207:471-5.
15. Sankaranarayanan R, Ramadas K, Thara S, Muwonge R, Thomas G, Anju G, et al. Long term effect of visual screening on oral cancer incidence and mortality in a randomized trial in Kerala, India. Oral oncology. 2013;49:314-21.
16. Pagano A, Gubner NR, Le T, Yip D, Williams D, Delucchi K, et al. Differences in tobacco use prevalence, behaviors, and cessation services by race/ethnicity: A survey of persons in addiction treatment. Journal of substance abuse treatment. 2018;94:9-17.

17. Asthana S, Labani S, Kailash U, Sinha DN, Mehrotra R. Association of Smokeless Tobacco Use and Oral Cancer: A Systematic Global Review and Meta-Analysis. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2019;21:1162-71.
18. Sadri G, Mahjub H. Tobacco smoking and oral cancer: a meta-analysis. Journal of research in health sciences. 2007;7:18-23.
19. Warnakulasuriya S, Dietrich T, Bornstein MM, Casals Peidró E, Preshaw PM, Walter C, et al. Oral health risks of tobacco use and effects of cessation. International dental journal. 2010;60:7-30.
20. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, et al. A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. The Lancet Oncology. 2009;10:1033-4.
21. Khariwala SS, Hatsukami D, Hecht SS. Tobacco carcinogen metabolites and DNA adducts as biomarkers in head and neck cancer: potential screening tools and prognostic indicators. Head & neck. 2012;34:441-7.
22. Hecht SS. Progress and challenges in selected areas of tobacco carcinogenesis. Chem Res Toxicol. 2008;21:160-71.
23. Varela-Rey M, Woodhoo A, Martinez-Chantar ML, Mato JM, Lu SC. Alcohol, DNA methylation, and cancer. Alcohol Res. 2013;35:25-35.
24. Feller L, Chandran R, Khammissa RA, Meyerov R, Lemmer J. Alcohol and oral squamous cell carcinoma. SADJ : journal of the South African Dental Association = tydskrif van die Suid-Afrikaanse Tandheelkundige Vereniging. 2013;68:176-80.
25. Montero PH, Patel SG. Cancer of the oral cavity. Surg Oncol Clin N Am. 2015;24:491-508.
26. Warnakulasuriya S. Diagnostic adjuncts on oral cancer and precancer: an update for practitioners. British Dental Journal. 2017;223:663-6.
27. Sobin L, Gospodarowicz M, Wittekind C. TNM Classification of Malignant Tumours. 7th ed2009.
28. Koch L, Jansen L, Brenner H, Arndt V. Fear of recurrence and disease progression in long-term (≥ 5 years) cancer survivors--a systematic review of quantitative studies. Psycho-oncology. 2013;22:1-11.
29. Dzioba A, Aalto D, Papadopoulos-Nydam G, Seikaly H, Rieger J, Wolfaardt J, et al. Functional and quality of life outcomes after partial glossectomy: a multi-institutional longitudinal study of the head and neck research network. Journal of Otolaryngology - Head & Neck Surgery. 2017;46:56.
30. Bulsara VM, Worthington HV, Glenny A-M, Clarkson JE, Conway DI, Macluskey M. Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. The Cochrane database of systematic reviews. 2018;12:CD006205-CD.
31. Huang SH, O'Sullivan B. Oral cancer: Current role of radiotherapy and chemotherapy. Med Oral Patol Oral Cir Bucal. 2013;18:e233-40.
32. Chan AK, Huang SH, Le LW, Yu E, Dawson LA, Kim JJ, et al. Postoperative intensity-modulated radiotherapy following surgery for oral cavity squamous cell carcinoma: patterns of failure. Oral oncology. 2013;49:255-60.
33. Furness S, Glenny AM, Worthington HV, Pavitt S, Oliver R, Clarkson JE, et al. Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy. The Cochrane database of systematic reviews. 2011:CD006386.
34. Hartner L. Chemotherapy for Oral Cancer. Dental clinics of North America. 2018;62:87-97.

35. Patil VM, Noronha V, Joshi A, Abhyankar A, Menon N, Dhumal S, et al. Beyond conventional chemotherapy, targeted therapy and immunotherapy in squamous cell cancer of the oral cavity. Oral oncology. 2020;105:104673.
36. Ohnishi Y, Yasui H, Nozaki M, Nakajima M. Molecularly-targeted therapy for the oral cancer stem cells. The Japanese dental science review. 2018;54:88-103.
37. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 2011. Available from: www.cochrane-handbook.org. 2011.
38. Miake-Lye IM, Hempel S, Shanman R, Shekelle PG. What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. Systematic reviews. 2016;5:28.
39. Haddaway NR, Bernes C, Jonsson BG, Hedlund K. The benefits of systematic mapping to evidence-based environmental management. Ambio. 2016;45:613-20.
40. Pai M, McCulloch M, Gorman JD, Pai N, Enanoria W, Kennedy G, et al. Systematic reviews and meta-analyses: an illustrated, step-by-step guide. The National medical journal of India. 2004;17:86-95.
41. Robinson P, Lowe J. Literature reviews vs systematic reviews. Australian and New Zealand journal of public health. 2015;39:103.
42. Bragge P, Clavisi O, Turner T, Tavender E, Collie A, Gruen RL. The Global Evidence Mapping Initiative: scoping research in broad topic areas. BMC Med Res Methodol. 2011;11:92.
43. Snilstveit B, Vojtkova M, Bhavsar A, Stevenson J, Gaarder M. Evidence & Gap Maps: A tool for promoting evidence informed policy and strategic research agendas. Journal of clinical epidemiology. 2016;79:120-9.
44. Buchberger B, Krabbe L, Lux B, Mattivi JT. Evidence mapping for decision making: feasibility versus accuracy - when to abandon high sensitivity in electronic searches. Ger Med Sci. 2016;14:Doc09.
45. Grilli R, Magrini N, Penna A, Mura G, Liberati A. Practice guidelines developed by specialty societies: the need for a critical appraisal. Lancet. 2000;355:103-6.
46. Chen YP, Wang YQ, Li WF, Chen L, Xu C, Lu TX, et al. Critical Evaluation of the Quality and Recommendations of Clinical Practice Guidelines for Nasopharyngeal Carcinoma. J Natl Compr Canc Netw. 2017;15:336-44.
47. Eslava-Schmalbach J, Sandoval-Vargas G, Mosquera P. Incorporating equity into developing and implementing for evidence-based clinical practice guidelines. Rev Salud Publica (Bogota). 2011;13:339-51.
48. Grimshaw J, Freemantle N, Wallace S, Russell I, Hurwitz B, Watt I, et al. Developing and implementing clinical practice guidelines. Qual Health Care. 1995;4:55-64.
49. Graham ID, Beardall S, Carter AO, Glennie J, Hebert PC, Tetroe JM, et al. What is the quality of drug therapy clinical practice guidelines in Canada? CMAJ. 2001;165:157-63.
50. Bateman GJ, Saha S. A brief guide to clinical guidelines. Br Dent J. 2007;203:581-3.
51. Geleris P, Boudoulas H. Problems related to the application of guidelines in clinical practice: a critical analysis. Hellenic J Cardiol. 2011;52:97-102.
52. Fuentes Padilla P, Martinez G, Vernooij RW, Cosp XB, Alonso-Coello P. Nutrition in critically ill adults: A systematic quality assessment of clinical practice guidelines. Clin Nutr. 2016;35:1219-25.
53. Kredo T, Bernhardsson S, Machingaidze S, Young T, Louw Q, Ochodo E, et al. Guide to clinical practice guidelines: the current state of play. International journal for quality in health care : journal of the International Society for Quality in Health Care. 2016;28:122-8.

54. Román A. Clinical guidelines, clinical pathways and protocols of care. Medwave. 2012;12:e5436.
55. Siering U, Eikermann M, Hausner E, Hoffmann-Esser W, Neugebauer EA. Appraisal tools for clinical practice guidelines: a systematic review. PLoS One. 2013;8:e82915.
56. AGREE. The Appraisal of Guidelines for Research & Evaluation. AGREE. Ontario, Canada:The AGREE Next Steps Consortium. (http://www.agreetrust.org). 2009 (Update: 2013)
57. Collaboration A. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care. 2003 12:18-23.
58. Brouwers M, Kho M, Browman G, Burgers J, Cluzeau F, Feder G. For the AGREE Next Steps Consortium. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. CMAJ 2010;182:E472-8.
59. Brouwers M, Kho M, Browman G, Burgers J, Cluzeau F, Feder G. AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting, and evaluation in health care. CMAJ. 2010;182:E839-42.
60. Jafari A, Najafi S, Moradi F, Kharazifard M, Khami M. Delay in the diagnosis and treatment of oral cancer. J Dent (Shiraz). 2013;14:146-50.
61. Güneri P, Epstein JB. Late stage diagnosis of oral cancer: components and possible solutions. Oral oncology. 2014;50:1131-6.
62. Wong T, Wiesenfeld D. Oral Cancer. Australian dental journal. 2018;63 Suppl 1:S91-s9.
63. Alobaidi F, Doss J, Abmurat N. Multi-Disciplinary Team (MDT) Approach in Oral Cancer Management: An Exploratory Study. Journal of Global Oncology. 2018;4:96s-s.
64. WHO. International Classification of Diseases for Oncology. WHO Library Cataloguing-in-Publication Data2013.
65. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
66. Ballesteros M, Montero N, López-Pousa A, Urrútia G, Solà I, Rada G, et al. Evidence mapping based on systematic reviews of therapeutic interventions for gastrointestinal stromal tumors (GIST). BMC Medical Research Methodology. 2017;17:135.
67. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33:159-74.
68. Anderson CR, Sisson K, Moncrieff M. A meta-analysis of margin size and local recurrence in oral squamous cell carcinoma. Oral oncology. 2015;51:464-9.
69. Baujat B, Bourhis J, Blanchard P, Overgaard J, Ang KK, Saunders M, et al. Hyperfractionated or accelerated radiotherapy for head and neck cancer. The Cochrane database of systematic reviews. 2010:CD002026.
70. Bessell A, Glenny AM, Furness S, Clarkson JE, Oliver R, Conway DI, et al. Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. The Cochrane database of systematic reviews. 2011:CD006205.
71. Chan KK, Glenny AM, Weldon JC, Furness S, Worthington HV, Wakeford H. Interventions for the treatment of oral and oropharyngeal cancers: targeted therapy and immunotherapy. The Cochrane database of systematic reviews. 2015;12:CD010341.
72. Ding Z, Xiao T, Huang J, Yuan Y, Ye Q, Xuan M, et al. Elective Neck Dissection Versus Observation in Squamous Cell Carcinoma of Oral Cavity With Clinically N0 Neck: A Systematic Review

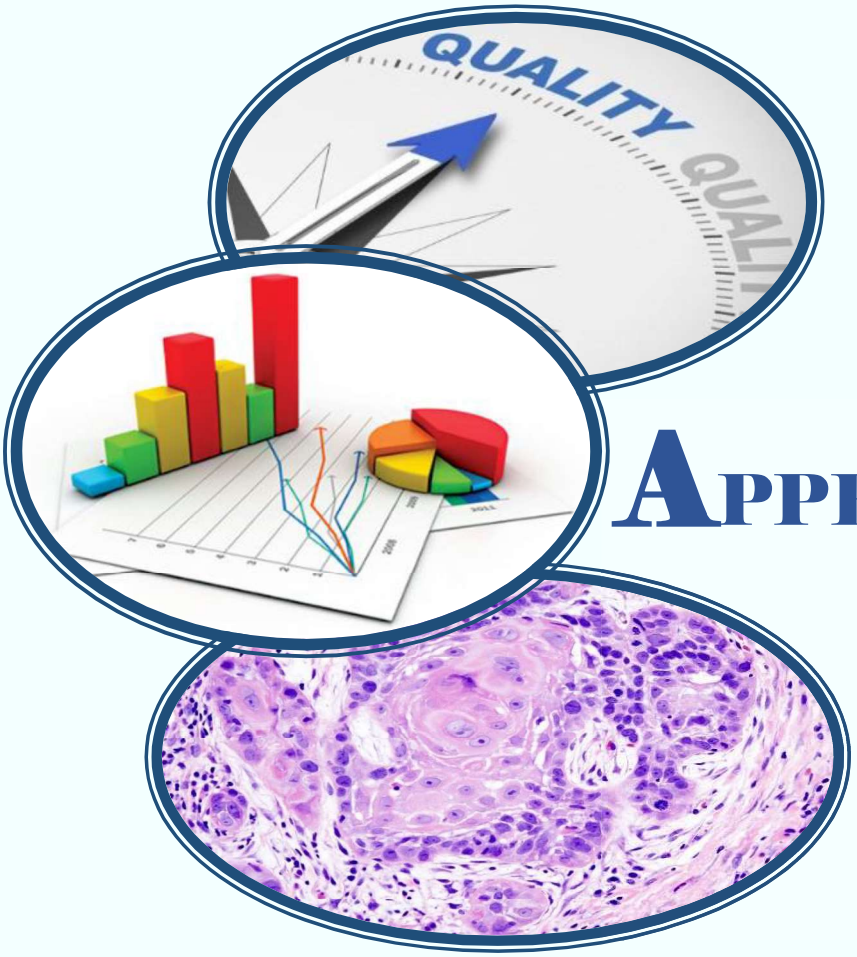
and Meta-Analysis of Prospective Studies. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons. 2018.
73. Glenny AM, Furness S, Worthington HV, Conway DI, Oliver R, Clarkson JE, et al. Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy. The Cochrane database of systematic reviews. 2010:CD006387.
74. Gou L, Yang W, Qiao X, Ye L, Yan K, Li L, et al. Marginal or segmental mandibulectomy: treatment modality selection for oral cancer: a systematic review and meta-analysis. International journal of oral and maxillofacial surgery. 2018;47:1-10.
75. Lau A, Li KY, Yang WF, Su YX. Induction chemotherapy for squamous cell carcinomas of the oral cavity: A cumulative meta-analysis. Oral oncology. 2016;61:104-14.
76. Liang L, Zhang T, Kong Q, Liang J, Liao G. A meta-analysis on selective versus comprehensive neck dissection in oral squamous cell carcinoma patients with clinically node-positive neck. Oral oncology. 2015;51:1076-81.
77. Liu Z, Huang S, Zhang D. High dose rate versus low dose rate brachytherapy for oral cancer--a meta-analysis of clinical trials. PLoS One. 2013;8:e65423.
78. Marta GN, Riera R, Bossi P, Zhong LP, Licitra L, Macedo CR, et al. Induction chemotherapy prior to surgery with or without postoperative radiotherapy for oral cavity cancer patients: Systematic review and meta-analysis. Eur J Cancer. 2015;51:2596-603.
79. Pang P, Li RW, Shi JP, Xu ZF, Duan WY, Liu FY, et al. A comparison of mandible preservation method and mandibulotomy approach in oral and oropharyngeal cancer: A meta-analysis. Oral oncology. 2016;63:52-60.
80. Tang L, Leung YY. When should elective neck dissection be performed in maxillary gingival and alveolar squamous cell carcinoma with a cN0 neck? A systematic review. Int J Oral Maxillofac Surg. 2016;45:1358-65.
81. Wang HC, Zheng Y, Pang P, Li RW, Qi ZZ, Sun CF. Discontinuous Versus In-Continuity Neck Dissection in Squamous Cell Carcinoma of the Tongue and Floor of the Mouth: Comparing the Rates of Locoregional Recurrence. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons. 2018;76:1123-32.
82. NICE. Cancer of the Upper Aerodigestive Tract: Assessment and Management in People Aged 16 and Over. NICE Guideline 36. 2016.
83. SIGN. Diagnosis and management of head and neck cancer. 2006.
84. Kovacs G, Martinez-Monge R, Budrukkar A, Guinot JL, Johansson B, Strnad V, et al. GEC-ESTRO ACROP recommendations for head & neck brachytherapy in squamous cell carcinomas: 1st update - Improvement by cross sectional imaging based treatment planning and stepping source technology. Radiother Oncol. 2017;122:248-54.
85. Liu SH, Chao KS, Leu YS, Lee JC, Liu CJ, Huang YC, et al. Guideline and preliminary clinical practice results for dose specification and target delineation for postoperative radiotherapy for oral cavity cancer. Head & neck. 2015;37:933-9.
86. Nibu KI, Hayashi R, Asakage T, Ojiri H, Kimata Y, Kodaira T, et al. Japanese Clinical Practice Guideline for Head and Neck Cancer. Auris Nasus Larynx. 2017;44:375-80.
87. Adelstein D, Gillison ML, Pfister DG, Spencer S, Adkins D, Brizel DM, et al. NCCN Guidelines Insights: Head and Neck Cancers, Version 2.2017. J Natl Compr Canc Netw. 2017;15:761-70.
88. AHS. Oral cavity cancer. Clinical Practice Guideline HN-002. 2014.

89. Grégoire V, Leroy R, Heus P, Van de Wetering F, Hooft L, Scholten R, et al. Oral cavity cancer: diagnosis, treatment and follow-up. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). KCE Reports 227. 2014.
90. Bilde A, von Buchwald C, Johansen J, Bastholt L, Sorensen JA, Marker P, et al. The Danish national guidelines for treatment of oral squamous cell carcinoma. Acta Oncol. 2006;45:294-9.
91. Wolff KD, Follmann M, Nast A. The diagnosis and treatment of oral cavity cancer. Dtsch Arztebl Int. 2012;109:829-35.
92. Gilbert R, Devries-Aboud M, Winquist E, Waldron J, McQuestion M, Group. HaNDS. The management of head and neck cancer in Ontario. Program in Evidence-based Care Evidence-Based Series No:5-3. 2009.
93. Winquist E, Oliver T, Gilbert R, Group. HaNDS. The role of postoperative chemoradiotherapy for advanced squamous cell carcinoma of the head and neck, Cancer Care Ontario 2004 Program in Evidence-based Care Evidence-Based Series No: 5-10. 2013.
94. Moyer VA, Force USPST. Screening for oral cancer: U.S. Preventive Services Task Force recommendation statement. Annals of internal medicine. 2014;160:55-60.
95. Lingen MW, Abt E, Agrawal N, Chaturvedi AK, Cohen E, D'Souza G, et al. Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity: A report of the American Dental Association. J Am Dent Assoc. 2017;148:712-27 e10.
96. NICE. NICE Guideline. Suspected Cancer: Recognition and Referral. National Institute for Health and Care Excellence: Clinical Guidelines. London2015. p. 1-378.
97. NZGG. Suspected Cancer in Primary Care. Guidelines for investigation, referral and reducing ethnic disparities. New Zealand Guidelines Group. 2009:1-190.
98. Lee GH, McGrath C, Yiu CK. Developing clinical practice guidelines for caries prevention and management for pre-school children through the ADAPTE process and Delphi consensus. Health research policy and systems. 2016;14:44.
99. Madera M, Franco J, Ballesteros M, Solà I, Urrútia G, Bonfill X. Evidence mapping and quality assessment of systematic reviews on therapeutic interventions for oral cancer. Cancer Manag Res. 2019;11:117-30.
100. Madera Anaya MV, Franco JV, Merchan-Galvis AM, Gallardo CR, Bonfill Cosp X. Quality assessment of clinical practice guidelines on treatments for oral cancer. Cancer treatment reviews. 2018;65:47-53.
101. Ioannidis JP. The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. The Milbank quarterly. 2016;94:485-514.
102. Page MJ, Shamseer L, Altman DG, Tetzlaff J, Sampson M, Tricco AC, et al. Epidemiology and Reporting Characteristics of Systematic Reviews of Biomedical Research: A Cross-Sectional Study. PLoS medicine. 2016;13:e1002028.
103. Bassani R, Pereira GKR, Page MJ, Tricco AC, Moher D, Sarkis-Onofre R. Systematic reviews in dentistry: Current status, epidemiological and reporting characteristics. J Dent. 2019;82:71-84.
104. Saltaji H, Cummings GG, Armijo-Olivo S, Major MP, Amin M, Major PW, et al. A descriptive analysis of oral health systematic reviews published 1991-2012: cross sectional study. PLoS One. 2013;8:e74545.
105. El-Rabbany M, Li S, Bui S, Muir JM, Bhandari M, Azarpazhooh A. A Quality Analysis of Systematic Reviews in Dentistry, Part 1: Meta-Analyses of Randomized Controlled Trials. J Evid Based Dent Pract. 2017;17:389-98.

106. Nagendrababu V, Pulikkotil SJ, Sultan OS, Jayaraman J, Peters OA. Methodological and Reporting Quality of Systematic Reviews and Meta-analyses in Endodontics. J Endod. 2018;44:903-13.
107. Mubeen S, Patel K, Cunningham Z, O'Rourke N, Pandis N, Cobourne MT, et al. Assessing the quality of dental clinical practice guidelines. J Dent. 2017;67:102-6.
108. Tejani T, Mubeen S, Seehra J, Cobourne MT. An exploratory quality assessment of orthodontic clinical guidelines using the AGREE II instrument. Eur J Orthod. 2017;39:654-9.
109. Shah P, Moles DR, Parekh S, Ashley P, Siddik D. Evaluation of pediatric dentistry guidelines using the AGREE instrument. Pediatr Dent. 2011;33:120-9.
110. Horner K, O'Malley L, Taylor K, Glenny AM. Guidelines for clinical use of CBCT: a review. Dentomaxillofac Radiol. 2015;44:20140225.
111. Faggion CM, Jr. Clinician assessment of guidelines that support common dental procedures. J Evid Based Dent Pract. 2008;8:1-7.
112. Robertson AG, Soutar DS, Paul J, Webster M, Leonard AG, Moore KP, et al. Early closure of a randomized trial: surgery and postoperative radiotherapy versus radiotherapy in the management of intra-oral tumours. Clin Oncol (R Coll Radiol). 1998;10:155-60.
113. Richard JM, Kramar A, Molinari R, Lefebvre JL, Blanchet F, Jortay A, et al. Randomised EORTC head and neck cooperative group trial of preoperative intra-arterial chemotherapy in oral cavity and oropharynx carcinoma. Eur J Cancer. 1991;27:821-7.
114. Luboinski B. Preliminary results of a randomized study on preoperative intra-arterial chemotherapy combined with surgery and irradiation for carcinomas of the floor of the mouth. Prog Clin Biol Res. 1985;201:199-203.
115. De Stefani A, Forni G, Ragona R, Cavallo G, Bussi M, Usai A, et al. Improved survival with perilymphatic interleukin 2 in patients with resectable squamous cell carcinoma of the oral cavity and oropharynx. Cancer. 2002;95:90-7.
116. Rao RS, Parikh DM, Parikh HK, Bhansali MB, Deshmane VH, Fakih AR. Perioperative chemotherapy in patients with oral cancer. Am J Surg. 1994;168:262-7.
117. Zhong LP, Zhang CP, Ren GX, Guo W, William WN, Jr., Sun J, et al. Randomized phase III trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by surgery versus up-front surgery in locally advanced resectable oral squamous cell carcinoma. J Clin Oncol. 2013;31:744-51.
118. Bossi P, Lo Vullo S, Guzzo M, Mariani L, Granata R, Orlandi E, et al. Preoperative chemotherapy in advanced resectable OCSCC: long-term results of a randomized phase III trial. Ann Oncol. 2014;25:462-6.
119. Licitra L, Grandi C, Guzzo M, Mariani L, Lo Vullo S, Valvo F, et al. Primary chemotherapy in resectable oral cavity squamous cell cancer: a randomized controlled trial. J Clin Oncol. 2003;21:327-33.
120. Molinari R, Jortay A, Sancho-Garnier H, Brugere J, Demard M, Desaulty A, et al. A randomized EORTC trial comparing intra-arterial infusion with methotrexate vs bleomycin as initial therapy in carcinoma of the oral cavity. Eur J Cancer Clin Oncol. 1982;18:807-12.
121. Srivastava S, Mohammad S, Pant AB, Mishra PR, Pandey G, Gupta S, et al. Co-delivery of 5-Fluorouracil and Curcumin Nanohybrid Formulations for Improved Chemotherapy Against Oral Squamous Cell Carcinoma. Journal of maxillofacial and oral surgery. 2018;17:597-610.

122. Noronha V, Joshi A, Patil V, Dhumal S, Agarwal JP, Ghosh-Lashkar S, et al. Cisplatin based adjuvant chemoradiation following neoadjuvant chemotherapy and surgery in advanced oral cavity cancers: A deliverable regimen? Indian journal of cancer. 2016;53:141-2.
123. Chiappelli F. Evidence-Based Dentistry: Two Decades and Beyond. J Evid Based Dent Pract. 2019;19:7-16.
124. France K, Sollecito TP. How Evidence-Based Dentistry Has Shaped the Practice of Oral Medicine. Dental clinics of North America. 2019;63:83-95.
125. Madera M, Franco J, Solà I, Bonfill X, Alonso-Coello P. Screening and diagnosis of oral cancer: a critical quality appraisal of clinical guidelines. Clinical oral investigations. 2019;23:2215-26.
126. BDA. Early detection and prevention of oral cancer: a management strategy for dental practice. The British Dental Association-Occasional paper. 2010:1-37.
127. CDSBC. Guideline for the Early Detection of Oral Cancer in British Columbia 2008. The College of Dental Surgeons of British Columbia. 2008:1-8.
128. RACGP. Early detection of cancers, Guidelines for preventive activities in general practice 8th edition. The Royal Australian College of General Practitioner. 2012:68.
129. AHNCWG. South Australian Head and Neck Cancer Pathway: Optimising outcomes for all South Australians diagnosed with Head and Neck Cancer. Head and Neck Cancer Working Group. 2013: 1-146.
130. Erickson J, Sadeghirad B, Lytvyn L, Slavin J, Johnston BC. The Scientific Basis of Guideline Recommendations on Sugar Intake: A Systematic Review. Annals of internal medicine. 2017;166:257-67.
131. Seiffert A, Zaror C, Atala-Acevedo C, Ormeno A, Martinez-Zapata MJ, Alonso-Coello P. Dental caries prevention in children and adolescents: a systematic quality assessment of clinical practice guidelines. Clinical oral investigations. 2018.
132. Jiang Y, Zhu XD, Qu S, Li L, Zhou Z. Guidelines for squamous cell carcinoma of the head and neck: A systematic assessment of quality. Ear Nose Throat J. 2015;94:E14-24.
133. Shen WQ, Yao L, Wang XQ, Hu Y, Bian ZX. Quality assessment of cancer cachexia clinical practice guidelines. Cancer treatment reviews. 2018;70:9-15.
134. Acuna-Izcaray A, Sanchez-Angarita E, Plaza V, Rodrigo G, de Oca MM, Gich I, et al. Quality assessment of asthma clinical practice guidelines: a systematic appraisal. Chest. 2013;144:390-7.
135. Alonso-Coello P, Irfan A, Sola I, Gich I, Delgado-Noguera M, Rigau D, et al. The quality of clinical practice guidelines over the last two decades: a systematic review of guideline appraisal studies. Qual Saf Health Care. 2010;19:e58.
136. Andrade R, Pereira R, van Cingel R, Staal JB, Espregueira-Mendes J. How should clinicians rehabilitate patients after ACL reconstruction? A systematic review of clinical practice guidelines (CPGs) with a focus on quality appraisal (AGREE II). British journal of sports medicine. 2020;54:512-9.
137. Green T, Willson G, Martin D, Fallon K. What is the quality of clinical practice guidelines for the treatment of acute lateral ankle ligament sprains in adults? A systematic review. BMC musculoskeletal disorders. 2019;20:394.
138. Wang Y, Ye ZK, Li JF, Cui XL, Liu LH. Heparin-induced thrombocytopenia: A critical appraisal of clinical practice guidelines with the AGREE II instrument. Thrombosis research. 2018;166:10-8.
139. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-6.

140. Alonso-Coello P, Schunemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ. 2016;353:i2016.
141. Madera M, Franco JVA, Solà I, Bonfill X, Arévalo-Rodriguez I. [Diagnostic accuracy of salivary biomarkers for oral cancer and potentially malignant disorders: A systematic review protocol]. Medwave. 2020;20:e7938.
142. Madera M, Tirado L, Franco J, Solà I, Bonfill X, Arévalo-Rodriguez I. Diagnostic accuracy of salivary biomarkers for oral cancer and potentially malignant disorders: A systematic review. X. 2020;X:X.
143. Tamayo-Cabeza G, Madera-Anaya M, González-Martinez F. El cáncer bucal y su relación con la proteína translocadora mitocondrial de 18kda %J CES Odontología. 2017;30:17-29.
144. Ballesteros M, Montero N, López-Pousa A, Urrútia G, Solà I, Rada G, et al. Evidence mapping based on systematic reviews of therapeutic interventions for soft tissue sarcomas. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2019;21:1398-412.
145. Posso M, Puig T, Carles M, Rué M, Canelo-Aybar C, Bonfill X. Effectiveness and cost-effectiveness of double reading in digital mammography screening: A systematic review and meta-analysis. European journal of radiology. 2017;96:40-9.
146. Delgado-Noguera M, Tort S, Bonfill X, Gich I, Alonso-Coello P. Quality assessment of clinical practice guidelines for the prevention and treatment of childhood overweight and obesity. European journal of pediatrics. 2009;168:789-99.
147. Seron P, Lanas F, Pardo Hernandez H, Bonfill Cosp X. Exercise for people with high cardiovascular risk. The Cochrane database of systematic reviews. 2014;2014:Cd009387.
148. Serón P, Lanas F, Ríos E, Bonfill X, Alonso-Coello P. Evaluation of the quality of clinical guidelines for cardiac rehabilitation: a critical review. Journal of cardiopulmonary rehabilitation and prevention. 2015;35:1-12.
149. Alarcon JD, Rubiano AM, Chirinos MS, Valderrama A, Gich I, Bonfill X, et al. Clinical practice guidelines for the care of patients with severe traumatic brain injury: a systematic evaluation of their quality. The journal of trauma and acute care surgery. 2013;75:311-9.
150. Alarcon JD, Rubiano AM, Okonkwo DO, Alarcón J, Martinez-Zapata MJ, Urrútia G, et al. Elevation of the head during intensive care management in people with severe traumatic brain injury. The Cochrane database of systematic reviews. 2017;12:Cd009986.
151. Simancas-Racines D, Montero-Oleas N, Vernooij RWM, Arevalo-Rodriguez I, Fuentes P, Gich I, et al. Quality of clinical practice guidelines about red blood cell transfusion. Journal of evidence-based medicine. 2019;12:113-24.
152. Sox HC. Assessing the trustworthiness of the guideline for management of high blood pressure in adults. Jama. 2014;311:472-4.



APPENDICES

APPENDICES

***Appendix 1**. The Appraisal of Guidelines for Research and Evaluation (AGREE II) Instrument. Item, by Domain*

Scope and purpose

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Stakeholder involvement

4. The guideline development group includes individuals from all the relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.

Rigor of development

7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.

Clarity of presentation

15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.

Applicability

18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/ or auditing criteria.

Editorial independence

22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

Overall guideline assessment

1. Rate the overall quality of this guideline.
2. I would recommend this guideline for use.

Appendix 2. *Other publications related to this doctoral thesis topic*

Publication 1. Madera M, Franco JVA, Solà I, Bonfill X, Arévalo-Rodriguez I. [Diagnostic accuracy of salivary biomarkers for oral cancer and potentially malignant disorders: A systematic review protocol]. Medwave 2020;20(5):e7938.

Publication 2. Tamayo-Cabeza G, Madera M, González-Martinez F. [Oral cancer and its relation with the 18kda mitochondrial translocator protein]**.** Rev. CES Odont 2017; 30(1):17-29.

Precisión diagnóstica de biomarcadores salivales para cáncer oral y desórdenes potencialmente malignos: protocolo de revisión sistemática

Diagnostic accuracy of salivary biomarkers for oral cancer and potentially malignant disorders: A systematic review protocol

Meisser Madera[a,b,*], Juan Víctor Ariel Franco[c], Ivan Solà[b,d], Xavier Bonfill[b,d], Ingrid Arévalo-Rodriguez[e]

[a] Departamento de Investigaciones, Facultad de Odontología, Universidad de Cartagena, Cartagena, Colombia
[b] Centro Cochrane Iberoamericano, Instituto de Investigación Biomédica Sant Pau, Barcelona, España
[c] Cochrane Argentina, Instituto Universitario Hospital Italiano, Buenos Aires, Argentina
[d] Servicio de Salud Pública y Epidemiología Clínica, Hospital Sant Pau, Barcelona, España
[e] Unidad de Bioestadística Clínica, Hospital Universitario Ramón y Cajal, Madrid, España

*Autor de correspondencia
mmaderaa@unicartagena.edu.co

Citación Meisser Madera, Juan Víctor Ariel Franco, Ivan Solà, Xavier Bonfill, Ingrid Arévalo-Rodriguez. Diagnostic accuracy of salivary biomarkers for oral cancer and potentially malignant disorders: A systematic review protocol. *Medwave* 2020;20(5):e7938

Doi 10.5867/medwave.2020.05.7938

Fecha de envío 18/02/2020
Fecha de aceptación 01/6/2020
Fecha de publicación 24/06/2020

Origen No solicitado

Tipo de revisión Con revisión por pares externa, por tres árbitros a doble ciego

Palabras clave mouth neoplasms, biomarkers, saliva, diagnosis, sensitivity, specificity

Resumen

Introducción

El cáncer oral tiene una tasa de supervivencia a los cinco años de 50%, debido a que frecuentemente su diagnóstico es realizado en estadios avanzados. Por lo tanto, son necesarias nuevas ayudas diagnósticas. Actualmente, existe un número significativo de publicaciones científicas sugiriendo el uso de biomarcadores salivales para el diagnóstico de cáncer oral. Sin embargo, son desconocidas las propiedades diagnósticas de estos biomarcadores. El objetivo de esta revisión sistemática es evaluar la evidencia sobre la precisión diagnóstica de biomarcadores salivales usados en la identificación de cáncer oral y desórdenes potencialmente malignos.

Métodos

Este protocolo es reportado en concordancia con el Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P). Se incluirán estudios evaluando la precisión diagnóstica de biomarcadores salivales para cáncer oral y desórdenes potencialmente malignos. Estos deberán reportar sensibilidad y especificidad, y utilizar como estándar de referencia un diagnóstico histopatológico. Se realizará una búsqueda en MEDLINE, EMBASE, Cochrane Library y literatura gris. Dos autores independientemente seleccionarán los estudios y extraerán los datos. La calidad metodológica de los estudios será determinada usando The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2).

Resultados esperados y conclusión

Los hallazgos de esta revisión sistemática proporcionarán información acerca de la precisión diagnóstica de los biomarcadores salivales para diagnóstico de cáncer oral y desórdenes potencialmente malignos.

Abstract

Introduction

Oral cancer has a 5-year survival rate of 50% because diagnosis is commonly performed at an advanced stage of the disease, so new diagnostic tools are needed. Nowadays, there is a vast number of publications suggesting the use of salivary biomarkers for oral cancer and potentially malignant disorders diagnosis, but their diagnostic accuracy is unclear. Thus, the goal of this systematic review is to evaluate the diagnostic accuracy of salivary biomarkers for oral cancer and potentially malignant disorders.

Methods

This protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P). We will include primary studies assessing the diagnostic accuracy of salivary biomarkers for oral cancer and potentially malignant disorders. Studies must report data about sensitivity and specificity; gold standard must be the histopathology diagnosis. We will search MEDLINE, EMBASE, the Cochrane Library, and gray literature. Two authors will independently select the studies and extract the data. The methodology quality of studies will be determined using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2).

Expected results and conclusion

Our findings will provide information about the diagnostic accuracy of salivary biomarkers for oral cancer and potentially malignant disorders.

Ideas clave

- El cáncer oral tiene una baja tasa de supervivencia a los 5 años, debido a diagnósticos tardíos.
- El uso de biomarcadores salivales podría ser una alternativa para lograr un diagnóstico oportuno.
- Este protocolo anticipa los métodos para la revisión sistemática sobre la precisión diagnóstica de biomarcadores salivales de cáncer oral y desórdenes potencialmente malignos.

Introducción

Los tumores de la cavidad oral son considerados el sexto cáncer más frecuente en todo el mundo. Su incidencia ha aumentado en las últimas décadas, registrándose aproximadamente 350 000 nuevos casos anualmente en países como Estados Unidos[1]. El cáncer se desarrolla por múltiples factores: genéticos, ambientales, inmunológicos y estilos de vida. En la células se origina como consecuencia de trastornos genómicos, derivados de aberraciones cromosómicas, activación de oncogenes e inactivación de genes supresores tumorales[2]. El cáncer oral más común es el carcinoma de células escamosas, representando cerca del 95% de todos los casos que afectan el sistema estomatognático[3,4].

Existe evidencia que el uso de tabaco y consumo de alcohol son los principales factores de riesgos involucrados en la etiología del cáncer oral[4,5]. Asimismo, un nivel socioeconómico bajo está asociado con alta incidencia y poca supervivencia. Del mismo modo, la mayoría de los casos ocurren en hombres mayores de 50 años[6,7]. Entre las principales opciones terapéuticas para el cáncer oral se encuentra la cirugía sola o en combinación con radioterapia o quimioterapia, dependiendo de la extensión del tumor[8].

Se ha establecido que la vida media de supervivencia de individuos con cáncer oral es de cinco años, luego del diagnóstico generalmente realizado en lesiones de fase avanzada[4,6,9]. Por lo tanto, es necesario contar con pruebas diagnósticas que establezcan de manera precoz el riesgo de padecer esta enfermedad, a través de la identificación de las lesiones potencialmente malignas. El diagnóstico de estas lesiones inicia con el examen clínico visual y es confirmado con el estudio histopatológico[4]. Sin embargo, en este último solo se observa la presencia y grado de la displasia, lo cual no permite determinar el grado de invasión y el potencial metastásico[2]. Por esta razón, se deben emplear de forma selectiva otros exámenes más específicos que permitan valorar las alteraciones celulares y establecer un diagnóstico precoz de cáncer oral.

En los últimos años se ha evidenciado un creciente esfuerzo en la investigación del cáncer oral, centrándose en la identificación de biomarcadores salivales para el diagnóstico y determinación del pronóstico[10-13]. La utilización de la saliva se considera una alternativa no invasiva con relación a las muestras de plasma[14]. Además, se ha sugerido que en la saliva se podrían encontrar biomarcadores celulares y tisulares que desde una perspectiva molecular, proporcionan información adicional a la obtenida en el estudio histopatológico[2]. En este sentido, un biomarcador ha sido definido como un indicador objetivamente medible, que puede estar asociado a procesos biológicos o patológicos[2].

De acuerdo al proceso tumoral, los biomarcadores pueden ser clasificados en las siguientes categorías:

i) Crecimiento tumoral.
ii) Supresión tumoral.

iii) Angiogénesis.
iv) Invasión tumoral.
v) Celulares de superficie.
vi) Intracelulares.
vii) Enzimáticos y derivados del ácido araquidónico[2].

Para el diagnóstico de cáncer oral se han propuesto un número considerable de biomarcadores con funciones diversas tales como interleuquinas, metaloproteinasas de matriz, proteína p53, telomerasa, carbonilos, endotelinas, fosfato sérico, lactato deshidrogenasa y transferrinas[15-18]. Sin embargo, la precisión diagnóstica de estos biomarcadores no es completamente clara. Por lo tanto, se requiere una evaluación de la evidencia sobre las propiedades diagnósticas de los biomarcadores salivales para el diagnóstico de cáncer oral.

Objetivo

Evaluar la evidencia sobre la precisión diagnóstica de biomarcadores salivales usados en la identificación de cáncer oral y desórdenes potencialmente malignos.

Objetivos secundarios

Describir las características de los estudios incluidos.

Identificar los biomarcadores salivales más frecuentes evaluados en el diagnóstico de cáncer oral y desórdenes potencialmente malignos.

Comparar la precisión diagnóstica de los diferentes biomarcadores salivales identificados.

Métodos

El presente protocolo describe detalladamente los objetivos y métodos que se utilizarán para la realización de una revisión sistemática. La anticipación de los métodos proporciona transparencia y restringe la probabilidad de interpretación sesgada de revisores.

Protocolo y registro

Este protocolo ha sido registrado en PROSPERO (CRD42018104558) y está estructurado según las recomendaciones establecidas por el Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [19].

Criterios para considerar estudios a incluir en la revisión sistemática

Tipo de estudios. Se incluirán estudios que evalúen la precisión diagnóstica de biomarcadores salivales para cáncer oral. Se tendrán en cuenta estudios de pruebas diagnósticas, ensayos clínicos aleatorizados y no aleatorizados, estudios de cohorte, y casos y controles.

Tipo de población. Se incluirán estudios conducidos en adultos bajo sospecha de cáncer oral primario. Es decir, individuos con signos clínicos o síntomas relacionados con lesiones malignas o aquellos con un reciente diagnóstico de esta enfermedad. Se tendrá en cuenta la definición de cáncer oral sugerida por la International Classification of Diseases for Oncology (ICD-O) con códigos C01-C06[20]. Del mismo modo, los desórdenes potencialmente malignos, se refieren a lesiones orales incluyendo leucoplasia, eritroplasia, liquen plano, lupus eritematoso, fibrosis submucosa y queratosis actínica. Serán excluidos estudios que incluyan participantes con enfermedades sistémicas o que hayan recibido cualquier tipo tratamiento para cáncer oral.

Tipo de intervención/exposición. Se incluirán estudios reportando el valor diagnóstico de biomarcadores salivales, incluyendo proteínas, ácidos ribonucleicos (ARN), ácidos desoxirribonucleicos (ADN) y cualquier tipo de metabolito. Todos los umbrales de estos biomarcadores serán aceptados y analizados. Del mismo modo, los biomarcadores salivales pueden ser usados solos o en combinación.

Tipo de comparador. Los estudios tendrán que haber usado con estándar de referencia un reporte histopatológico para el diagnóstico de cáncer oral y desórdenes potencialmente malignos.

Tipo de desenlaces. Se incluirán estudios que reporten sensibilidad y especificidad de los biomarcadores salivales.

Método de búsqueda para identificar estudios

Búsquedas electrónicas. La identificación de estudios primarios se realizará en las bases de datos MEDLINE (vía PubMed), EMBASE (vía Ovid) y registro de Cochrane (vía The Cochrane Library). Con el fin de hacer una búsqueda exhaustiva, no se realizará ningún tipo de restricción de acuerdo con el idioma, año y tipo de publicación. Este procedimiento se realizará por un especialista en la búsqueda de bases de datos (IS). En el Anexo 1 se encuentran detalladas las estrategias de búsqueda.

Otras fuentes. Adicional a las búsquedas electrónicas, se realizará una búsqueda de literatura gris, incluyendo la revisión de la bibliografía de estudios seleccionados. El objetivo de este proceso es identificar potenciales estudios que cumplan con los criterios de inclusión. Además, en caso de ser necesario, se contactarán a expertos en el área para evaluar la posibilidad de incluir estudios que no hayan sido publicados.

Selección de estudios

Los resultados de la búsqueda de la literatura serán manejados a través del software EndNote® (Version X9, Thomson Reuters). Después de remover los duplicados, dos autores (MM, JVAF) revisarán independientemente los títulos y resúmenes con la finalidad de excluir documentos irrelevantes para la revisión sistemática, este procedimiento será realizado a través de la plataforma Rayyan[21]. Inmediatamente, los textos completos serán obtenidos y revisados para una decisión final. Los desacuerdos serán resueltos por consenso, y cuando sea necesario un tercer autor participará hasta conseguir un acuerdo. Además, las razones de exclusión de cualquier documento considerado relevante serán registradas. El proceso detallado de selección de estudios será presentado a través de un diagrama de flujo PRISMA-P.

Extracción y manejo de datos

Utilizando formatos previamente estandarizados, dos revisores (MM, JVAF) independientemente extraerán los datos de los estudios incluidos, tales como característica del estudio (autor, año de publicación, tipo de estudio y país), característica de los participantes (edad, sexo, estrato socioeconómico, factores de riesgo , número de participantes con lesiones, sitio de la lesión y clasificación TNM, del inglés Tumor, Node, Metastases), característica del biomarcador (nombre, tipo, técnica usada para la recolección de saliva, nivel de expresión y metodología para su análisis), información sobre la precisión (estándar de referencia, definición de casos, entrenamiento y calibración del personal) y resultados del estudio (sensibilidad, espe-

cificidad, verdaderos positivos, verdaderos negativos, falsos positivos, falsos negativos, cualquier resultado equívoco o retractado). Para asegurar la consistencia en este proceso, se realizarán ejercicios de calibración antes de iniciar la extracción de datos. Asimismo, los desacuerdos se resolverán por consensos y con la participación de un tercer revisor (IAR), en caso de ser necesario.

Evaluación del riesgo de sesgo de los estudios incluidos

Dos revisores (MM, JVAF) independientemente evaluarán el riesgo de sesgo de los estudios incluidos usando The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [22]. Este instrumento incluye 14 ítems evaluando el riesgo de sesgo y la fuente de variación. Además, tiene cuatro dominios:

i. Muestreo de participantes.
ii. Prueba diagnóstica.
iii. Estándar de referencia.
iv. Flujo y tiempo.

Cada dominio consiste en dos a cuatro preguntas que deben ser contestadas con "sí", "no" o "no claro". Los desacuerdos serán resueltos por consenso y con la participación de un tercer autor, en caso de ser necesario. Se graficarán los riesgos de sesgo de cada dimensión en cada estudio utilizando el software RevMan 5.1.

Análisis de datos

Con fines descriptivos, todos los valores de las propiedades diagnósticas para cada biomarcador o combinación serán incorporados dentro del software Review Manager. Para cada biomarcador, las estimaciones de precisión diagnóstica serán expresadas usando los valores de sensibilidad y especificidad, con sus respectivos intervalos de confianza al 95%. Esta información se presentará usando gráficos de forest plots y trazando curvas ROC (del inglés Receiver Operating Characteristic).

Manejo de datos faltantes

Siempre que sea posible, se intentará contactar a los autores del estudio para obtener los datos faltantes. Si no pudiéramos obtener dichos datos, el estudio podría ser incluido en la revisión, pero no en la síntesis cuantitativa.

Evaluación de la heterogeneidad

Se evaluará cualitativamente el grado de heterogeneidad entre los estudios incluidos, considerando las características de los participantes, propiedades del biomarcador y los resultados. Cuando sea relevante, se analizará estadísticamente la heterogeneidad utilizando el estadístico I2, y se utilizará con guía para interpretación lo establecido en el manual de Cochrane. Además, se evaluarán las posibles fuentes de heterogeneidad mediante análisis de subgrupos, en caso de contar con un número suficiente de estudios.

Síntesis de los datos

Solo se realizarán metanálisis, si existen estudios lo suficientemente homogéneos para cada biomarcador salival, considerando las características de los participantes, técnicas para analizar el biomarcador y desenlaces reportados. Para esto se utilizará un adecuado abordaje que permita estimar un resumen de sensibilidad y especificidad. Los análisis se efectuarán utilizando los softwares STATA 16 y SAS 9.4

En caso de que no sea posible realizar el metanálisis, se presentará una síntesis estructurada de los resultados.

Análisis de subgrupos e investigación de la heterogeneidad

Se utilizarán análisis de meta-regresión para explorar las posibles fuentes de heterogeneidad. Las covariables en estos análisis serán: características de la muestra de estudio tales como clasificación TNM, sexo, edad y factores de riesgos reportados.

Análisis de sensibilidad

Utilizaremos análisis de sensibilidad para evaluar el impacto de la inclusión de estudios con alto riesgo de sesgo.

Presentación de los resultados

Los resultados serán presentados utilizando tablas descriptivas, donde se informe sobre las características de los estudios incluidos. Además, se utilizarán tablas para presentar la evidencia sobre la precisión diagnóstica de biomarcadores salivales. Por cada biomarcador o conjunto de ellos, se informará sobre las técnicas utilizadas para su identificación, propiedades de precisión diagnóstica y el riesgo de sesgo según QUADAS-2.

Notas

Roles de autoría

MM, IAR y JVAF iniciaron y diseñaron el protocolo. Todos los autores contribuyeron significativamente con la conceptualización, metodología, investigación, escritura y revisión de este artículo, aprobando la versión final.

Financiamiento

Los autores declaran que no hubo fuentes de financiación externas para la realización de este artículo. MM recibió soporte financiero del programa de becas Bolívar Gana con Ciencia, Colombia.

Conflictos de intereses

Los autores han completado el formulario de declaración de conflictos de intereses del ICMJE, y declaran no haber recibido financiamiento para la realización del reporte; no tener relaciones financieras con organizaciones que podrían tener intereses en el artículo publicado, en los últimos tres años; y no tener otras relaciones o actividades que podrían influir sobre el artículo publicado. Los formularios pueden ser solicitados contactando al autor responsable o a la dirección editorial de la Revista.

Nota del autor

MM es candidato a Doctor del programa de Metodología de Investigación Biomédica y Salud Pública, Universidad Autónoma de Barcelona, España.

Anexo: Estrategias de búsquedas

Referencias

1. Brinkmann O, Wong DT. Salivary transcriptome biomarkers in oral squamous cell cancer detection. Adv Clin Chem. 2011;55:21-34. | CrossRef | PubMed |
2. Madera M. Biomarcadores de cáncer oral en saliva. Av Odontoestomatol 2013;29:293-302. | Link |

3. Chan KK, Glenny AM, Weldon JC, Furness S, Worthington HV, Wakeford H. Interventions for the treatment of oral and oropharyngeal cancers: targeted therapy and immunotherapy. Cochrane Database Syst Rev. 2015 Dec 1;(12):CD010341. | CrossRef | PubMed |
4. Wong T, Wiesenfeld D. Oral Cancer. Aust Dent J. 2018 Mar;63 Suppl 1:S91-S99. | CrossRef | PubMed |
5. Freedman ND, Abnet CC, Leitzmann MF, Hollenbeck AR, Schatzkin A. Prospective investigation of the cigarette smoking-head and neck cancer association by sex.Cancer. 2007 Oct 1;110(7):1593-601. | CrossRef | PubMed |
6. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009 Apr-May;45(4-5):309-16. | CrossRef | PubMed |
7. Conway DI, Petticrew M, Marlborough H, Berthiller J, Hashibe M, Macpherson LM. Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis of case-control studies. Int J Cancer. 2008 Jun 15;122(12):2811-9. | CrossRef | PubMed |
8. Madera Anaya M, Franco JVA, Ballesteros M, Solà I, Urrútia Cuchí G, Bonfill Cosp X. Evidence mapping and quality assessment of systematic reviews on therapeutic interventions for oral cancer. Cancer Manag Res. 2018 Dec 24;11:117-130. | CrossRef | PubMed |
9. Yamada SI, Kurita H, Tomioka T, Ohta R, Yoshimura N, Nishimaki F, et al. Healthy life expectancy of oral squamous cell carcinoma patients aged 75years and older. Oral Oncol. 2017 Jan;64:22-26. | CrossRef | PubMed |
10. Wang X, Kaczor-Urbanowicz KE, Wong DT. Salivary biomarkers in cancer detection. Med Oncol. 2017 Jan;34(1):7. | CrossRef | PubMed |
11. Khurshid Z, Zafar MS, Khan RS, Najeeb S, Slowey PD, Rehman IU. Role of Salivary Biomarkers in Oral Cancer Detection. Adv Clin Chem. 2018;86:23-70. | CrossRef | PubMed |
12. Feng Y, Li Q, Chen J, Yi P, Xu X, Fan Y, et al. Salivary protease spectrum biomarkers of oral cancer. Int J Oral Sci. 2019 Jan 3;11(1):7. | CrossRef | PubMed |
13. Rapado-González Ó, López-López R, López-Cedrún JL, Triana-Martínez G, Muinelo-Romay L, Suárez-Cunqueiro MM. Cell-Free microRNAs as Potential Oral Cancer Biomarkers:From Diagnosis to Therapy. Cells. 2019 Dec 17;8(12):1653. | CrossRef | PubMed |
14. Nagler R, Bahar G, Shpitzer T, Feinmesser R. Concomitant analysis of salivary tumor markers--a new diagnostic tool for oral cancer. Clin Cancer Res. 2006 Jul 1;12(13):3979-84. | CrossRef | PubMed |
15. Kaur J, Jacobs R, Huang Y, Salvo N, Politis C. Salivary biomarkers for oral cancer and pre-cancer screening: a review. Clin Oral Investig. 2018 Mar;22(2):633-640. | CrossRef | PubMed |
16. Hema Shree K, Ramani P, Sherlin H, Sukumaran G, Jeyaraj G, Don KR, et al. Saliva as a Diagnostic Tool in Oral Squamous Cell Carcinoma - a Systematic Review with Meta Analysis. Pathol Oncol Res. 2019 Apr;25(2):447-453. | CrossRef | PubMed |
17. Chattopadhyay I, Panda M. Recent trends of saliva omics biomarkers for the diagnosis and treatment of oral cancer. J Oral Biosci. 2019 Jun;61(2):84-94. | CrossRef | PubMed |
18. Cristaldi M, Mauceri R, Di Fede O, Giuliana G, Campisi G, Panzarella V. Salivary Biomarkers for Oral Squamous Cell Carcinoma Diagnosis and Follow-Up: Current Status and Perspectives. Front Physiol. 2019 Dec 10;10:1476. | CrossRef | PubMed |
19. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;350:g7647. | CrossRef | PubMed |
20. WHO. International Classification of Diseases for Oncology. WHO Library Cataloguing-in Publication Data. 2013. [On line] | Link |
21. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016 Dec 5;5(1):210. | CrossRef | PubMed |
22. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36. | CrossRef | PubMed |

Correspondencia a
Zaragocilla Cra. 50 No. 29-11
Cartagena, Colombia
Código postal: 130014

Artículo de revisión

El cáncer bucal y su relación con la proteína translocadora mitocondrial de 18kda*

Oral cancer and its relation with the 18kda mitochondrial translocator protein

Guillermo Tamayo-Cabeza[1] ✉ CvLAC, Meisser Madera-Anaya[2] ✉ CvLAC, Farith González-Martinez[3] ✉ CvLAC

1. Odontólogo rural de investigación. Departamento de Investigaciones, Facultad de Odontología, Universidad de Cartagena.
2. Magister en Bioquímica, Magister en Epidemiología Clínica. Departamento de Investigaciones, Facultad de Odontología, Universidad de Cartagena.
3. Magíster en Salud Pública. Departamento de Investigación, Facultad de Odontología, Universidad de Cartagena.

* Este artículo pertenece al Grupo de Investigación en Salud Pública GISPOUC. Financiación: trabajo vinculado al proyecto de investigación: "Proteína translocadora mitocondrial 18kDa en saliva como un biomarcador asociado a cáncer bucal", financiado en convocatoria externa concurso IADR proyectos de investigación en Medicina Bucal 01-2013.

Fecha correspondencia:
Recibido: enero de 2016 .
Aceptado: mayo de 2017.

Forma de citar:
Tamayo-Cabeza G, Madera-Anaya M, González-Martinez F. El cáncer bucal y su relación con la proteína translocadora mitocondrial de 18kda. Rev. CES Odont 2017; 30(1): 17-29.

Open access

Ética de publicaciones
Revisión por pares
Gestión por Open Journal System
DOI: http://dx.doi.org/10.21615/cesodon.30.1.2
ISSN 0120-971X
e-ISSN 2215-9185

Resumen

El cáncer bucal posee una alta incidencia y mortalidad a nivel global. A pesar de los avances en el diagnóstico y el pronóstico de esta enfermedad, aún se mantiene una baja tasa de supervivencia de 5 años, lo cual hace necesario el estudio de métodos diagnósticos que sean capaces de detectar la enfermedad en estadios tempranos. Es por esto que avances en proteómica e inmunohistoquímica, han permitido identificar diversos biomarcadores, entre ellos la proteína translocadora (TSPO) mitocondrial de 18kDa, la cual está involucrada en diversos procesos celulares, como el transporte de colesterol, la proliferación celular y la apoptosis. Se ha reportado la presencia de valores alterados de la TSPO en diversos tipos de cáncer, así como la presencia de la TSPO en saliva y tejido de sujetos con cáncer bucal, lo cual representa una oportunidad para entender el proceso de la carcinogénesis bucal e identificar nuevas alternativas para el diagnóstico de esta enfermedad. La presente revisión de tema tiene como objetivo presentar aspectos teóricos en relación con la TSPO como un biomarcador a estudiar en sujetos con cáncer bucal, considerando su implicación en los procesos de apoptosis celular y participación en el estrés oxidativo.

Palabras clave: Cáncer bucal, proteínas salivales, carcinogénesis, estrés oxidativo (DeCs-bvs).

Abstract

Oral cancer has a high incidence and mortality rate globally. Despite the advances in the diagnosis and prognosis of this disease, a 5 years survival rate still remains, which makes it necessary to study diagnostic methods capable to detect the disease in early stages. That is why advances in proteomics and immunohistochemistry had allowed the identification of various biomarkers, including the 18 kDa mitochondrial translocator protein (TSPO), which is involved in some cellular processes, such as cholesterol transport, cellular proliferation and apoptosis. It has been reported the al-

tered TSPO values in various types of cancer, as well as the presence of TSPO in saliva of subjects with oral cancer, which represents an opportunity to understand the oral carcinogenic process and identify new alternatives for the diagnosis of this disease. The objective of this review is to present theoretical aspects related to TSPO as a biomarker to study in subjects with oral cancer, considering its implication in the apoptosis mechanism and participation in oxidative stress.

Keywords: Mouth neoplasms, TSPO Protein, biomarkers, oxidative stress. (MeSH-NCBI).

Resumo

O câncer bucal apresenta alta incidência e mortalidade ao nível mundial. Apesar dos avanços no diagnóstico e prognóstico da doença, uma baixa taxa de sobrevivência de 5 anos ainda é mantida, o que requer o estudo de métodos de diagnóstico capazes de detectar a doença nos estágios iniciais. É por isso que os avanços na proteômica e imuno-histoquímica identificaram diversos biomarcadores, incluindo a proteína translocadora (TSPO) 18 kDa mitocondriais, que está envolvida em diversos processos celulares, tais como o transporte de colesterol, a proliferação celular e a apoptose. Tem sido relatada a presença de valores alterados da TSPO em diferentes tipos de câncer, assim como a presença da TSPO em saliva e tecidos de pacientes com câncer bucal, o que representa uma oportunidade para entender o processo da carcinogênese bucal e identificar novas alternativas para o diagnóstico desta doença. A presente revisão de literatura tem como objetivo apresentar aspectos teóricos em relação ao uso da TSPO como um biomarcador a ser estudado em pacientes com câncer bucal, considerando seu envolvimento nos processos de apoptose celular e participação no estresse oxidativo.

Palavras chaves: Neoplasias Bucais, Proteínas Salivares, Carcinogênese, Estresse Oxidativo. (DeCs-bvs).

Introducción

El cáncer bucal es el tipo de cáncer más frecuente en cabeza y cuello, y en su mayoría aparece como el carcinoma oral de células escamosas (1). La célula que da origen a este tipo de carcinoma es el queratinocito de la mucosa bucal. Este es causado, así como muchos cánceres, por la mutación del ácido desoxirribonucleico (ADN), fenómeno que a menudo ocurre de manera espontánea, pero su riesgo aumenta con la exposición de algunos tipos de mutágenos, los cuales pueden ser químicos, físicos o microbiológicos (2). Los diferentes cambios en el ADN pueden favorecer el progreso de un queratinocito normal a uno potencialmente maligno, el cual se caracteriza por su habilidad de proliferación descontrolada (2). En el cáncer, las células se vuelven autónomas y los resultados de éste se caracterizan por la invasión a través de la membrana basal epitelial y finalmente la metástasis hacia los nodos linfáticos, hueso, cerebro, hígado u otros sitios (3).

Este tipo de carcinoma puede aparecer en cualquier lugar de la cavidad bucal, aunque hay algunas áreas en las cuales se puede encontrar con mayor frecuencia (4). La lengua y el piso de la boca, son las áreas más comunes donde se puede localizar y ocurre en un 50 % de los casos (4). Otros lugares de aparición son el área retromolar, encía, paladar blando, y con menos frecuencia, el paladar duro (5).

DOI: http://dx.doi.org/10.21615/cesodon.30.1.2

Este posee cuatro presentaciones clínicas que incluyen una mancha roja, blanca o una lesión endofítica ulcerativa, y menos común, puede aparecer como una masa exofítica con márgenes alterados, ulceración en el centro de la lesión y tejido friable (6).

Teniendo en cuenta la alta incidencia de ésta patología y el impacto que produce su baja tasa de supervivencia a nivel de la salud pública, los esfuerzos en el desarrollo de herramientas diagnósticas eficaces continúan siendo necesarios. El objetivo de esta revisión de tema es presentar aspectos teóricos en relación con la proteína translocadora mitocondrial (TSPO) de 18kDa como un biomarcador asociado al cáncer bucal, considerando su implicación en los procesos de apoptosis celular y participación en el estrés oxidativo.

Epidemiología y etiología del cáncer bucal

A pesar de los avances significativos en términos de prevención y tratamiento de la enfermedad, aún se mantiene una baja tasa de supervivencia de 5 años luego del diagnóstico (7), debido a las lesiones no controladas o recurrentes y a la falta de marcadores adecuados para una detección temprana (8).

El cáncer bucal representa un problema relevante debido a su creciente presencia en muchas partes del mundo. Más de la mitad de los casos a nivel global, y cerca del 66,3 % de las muertes se observa en Asia, seguido de Europa (18,4 %), África (6,1 %), Latinoamérica y el Caribe (5,1%) y Norteamérica (3,1 %)(9). Las tasas más altas se encuentran en regiones del mundo como Melanesia, Maldivas, Sri Lanka, Bangladesh, Francia y Hungría (9).

En la mayoría de los países, el cáncer bucal es más común en hombres que en mujeres (10). Esta diferencia es atribuida a una mayor exposición de factores de riesgo como el alcohol y el tabaco en los hombres y una mayor exposición a la luz solar, relacionada con el tipo de labores que ejercen (11). Además de los factores antes mencionados, el riesgo de desarrollar el cáncer bucal también aumenta con la edad y la mayoría de los casos ocurren en personas mayores de 50 años (12).

Los principales factores de riesgo son fumar y el consumo de alcohol, sin embargo, el desarrollo de la carcinogénesis bucal muestra una etiología multifactorial, donde se involucran factores endógenos (genéticos) y exógenos (ambientales y comportamentales) (13). Entre estos factores se destacan diferentes variables sociodemográficas y económicas, incluyendo a la falta de higiene bucal y la exposición laboral (11). Así mismo existen casos en los que la etiología es desconocida o es causado también por el Virus del Papiloma Humano (14).

Diagnóstico del cáncer bucal

Para la detección temprana del cáncer bucal existen pruebas que evalúan la presencia de la enfermedad en individuos asintomáticos, quienes aparentemente no la padecen; así como pruebas para la detección de casos, en la que se realiza la aplicación de un procedimiento específico en pacientes con una lesión identificada (15). El examen clínico intraoral convencional (examen visual y palpación) es considerada la prueba de referencia para el diagnóstico presuntivo de una lesión potencialmente maligna o cáncer bucal, mientras que el estudio relevante para la detección definitiva de casos es la biopsia y el diagnóstico histopatológico (16).

DOI: http://dx.doi.org/10.21615/cesodon.30.1.2

Asimismo, existen diferentes técnicas complementarias que pueden contribuir al diagnóstico del cáncer bucal como la tinción con azul de toluidina, la citología por cepillado, los sistemas de imágenes ópticas, el uso de la sangre o el análisis de la saliva, entre otros (17).

El análisis de muestras salivales es considerada una alternativa no invasiva comparada con la prueba de suero (18). El uso de la saliva como medio para el diagnóstico se basa en que la saliva lubrica toda la cavidad bucal y por lo tanto, es más probable que represente toda la superficie expuesta y las alteraciones presentes, lo cual no ocurre utilizando el examen por medio de una biopsia invasiva del tejido local, pero ésta a su vez se enfrenta a otras dificultades como la sensibilidad en relación a la contaminación por bacterias y células del sistema inmune (19). La saliva contiene un amplio espectro de péptidos y proteínas, ácidos nucleicos, electrolitos y hormonas que se originan de múltiples fuentes tanto locales como sistémicas; estos podrían considerarse potenciales biomarcadores salivales, los cuales han mostrado correlación con la patogénesis del cáncer bucal (20).

Biomarcadores para el cáncer bucal

Existen más de 100 biomarcadores potenciales para el carcinoma bucal de células escamosas, los cuales han sido reportados en la literatura, basados principalmente en la comparación de los niveles o concentración en sujetos con cáncer bucal y sujetos controles (21), Estos se pueden agrupar en: 1) compuestos no orgánicos, 2) péptidos y proteínas, 3) ADN, ARN mensajero y micro ARN, 4) biomarcadores metabólicos y 5) biomarcadores químicos y de actividad enzimática (20).

Avances en proteómica han permitido la detección de moléculas de poca abundancia en la saliva, como es el caso de algunas proteínas, las cuales son sintetizadas y posteriormente secretadas en la cavidad bucal por las células acinares de las glándulas salivales (22). Estas proteínas al ser producto de las glándulas salivales, pueden estar sujetas a factores internos y externos, pudiendo servir de biomarcadores tanto para patologías locales como sistémicas (21); en la actualidad se han identificado diversas citoquinas, el factor de crecimiento fibroblástico, las metalo-proteinasas de matriz, la glutatión transferasa, la superóxido dismutasa, entre otros (23).

Proteína Translocadora Mitocondrial (TSPO) 18 kDa

Entre los biomarcadores estudiados se encuentra la TSPO, conocida anteriormente como el receptor periférico de benzodiacepinas (PBR) al ser identificada en 1977 como un sitio de unión al diazepam a nivel cerebral (24). Esta se localiza a nivel de las membranas mitocondriales de distintos tipos celulares (25). El nombre de TSPO fue adoptado en el 2006 debido a nuevos hallazgos relacionados con su estructura y función molecular (24). Su secuencia primaria se encuentra altamente conservada (figura 1) y predice una proteína hidrofóbica transmembranal con cinco dominios codificada por ADN nuclear (24) (figura 2), la cual consiste en 169 aminoácidos y es rica en triptófano (26). Los dominios transmembranales en alfa hélices extendidas tienen suficiente longitud para abarcar una bicapa lipídica completamente, esto permite formar complejos que reflejan su función como proteína transportadora de membrana (27). El gen de la TSPO se encuentra localizado en la región q13,3 del brazo largo del cromosoma 22 (26).

La TSPO ha sido detectada en varias densidades de diversos tejidos y se ha encontrado altamente expresada a nivel mitocondrial de células inflamatorias fa-

DOI: http://dx.doi.org/10.21615/cesodon.30.1.2

gocitarias (24). También es encontrada en concentraciones pequeñas dentro de compartimentos subcelulares, en la superficie celular como parte de la membrana celular, y en una pequeña cantidad se encuentra en la fracción nuclear de las células (28). Esta se encuentra muy asociada con el poro de transición de permeabilidad mitocondrial (PTPM)(29), el cual está formado por la asociación de la TSPO a un canal aniónico dependiente de voltaje (VDAC abrev. Idioma inglés) de 32kDa, también conocido como porina mitocondrial y se constituye como un complejo junto al translocador de nucleótidos de adenina (ANT abrev. Idioma inglés) de 30kDa, el cual es encontrado frecuentemente en los sitios de contacto de la membrana mitocondrial externa e interna (30) (figura 2). Sin embargo, la existencia de este complejo ha sido controversial en algunos estudios, donde afirman que puede que exista la asociación entre estas moléculas, pero no tomando un papel estructural a nivel de la mitocondria, debido a que análisis genéticos realizados en animales han demostrado que el PTPM se mantiene presente en la mitocondria incluso eliminando cada proteína que lo componen (31).

```
MAPPWVPAMGFTLAPSLGCFVGSRFVHGEGLRWYAGLQKPSWHPPHWVLGPVWGTLYSAM
GYGSYLVWKELGGFTEKAVVPLGLYTGQLALNWAWPPIFFGARQMGWALVDLLLVSGAAA
ATTVAWYQVSPLAARLLYPYLAWLAFTTTLNYCVWRDNHGWRGGRRLPE
```

Figura 1. Secuencia primaria de la TSPO 18kDa de humano

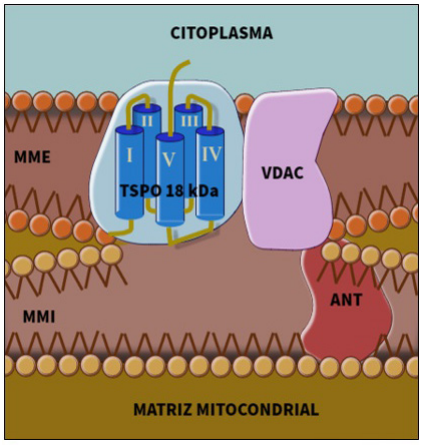


Figura 2. Poro de transición de permeabilidad mitocondrial compuesto por la TSPO 18 kDa (proteína translocadora mitocondrial), VDAC (canal aniónico dependiente de voltaje) y ANT (translocador de nucleótidos de adenina). MME: membrana mitocondrial externa. MMI: membrana mitocondrial interna. **Adaptada de:** Papadopoulos V, Baraldi M, Guilarte TR, Knudsen TB, Lacapère JJ, Lindemann P. Translocator protein (18kDa): new nomenclature for the peripheral-type benzodiazepine receptor based on its structure and molecular function. Trends Pharmacol Sci. 2006;27(8):402-9.

La TSPO fue caracterizada por su habilidad para unir fármacos de pequeñas moléculas, colesterol, y porinas con diversas afinidades (32). En mamíferos, la significancia biológica de la TSPO ha sido estudiada por décadas y ha sido relacionada con múltiples funciones celulares, siendo la regulación del transporte de colesterol a través de las membranas mitocondriales, la función mejor caracterizada (33).

Entre las diferentes funciones de la TSPO se encuentran: la síntesis de hormonas esteroideas, la respiración mitocondrial, la apertura del PTPM, la apoptosis y la pro-

DOI: http://dx.doi.org/10.21615/cesodon.30.1.2

liferación celular (34). Aunque algunas funciones celulares de la TSPO se han conservado, como el transporte de colesterol, su significancia biológica parece estar adaptada para funciones específicas críticas en algunos tejidos (35).

La presencia de la TSPO en el PTPM involucra a la proteína en la regulación de la apoptosis y la muerte celular, con ligandos capaces de abrir el PTPM, resultando en la inducción de la apoptosis (36). Esta hipótesis involucra a la TSPO con procesos de liberación de factores pro-apoptóticos, dónde una vez activada la proteína conduce a una generación de especies reactivas de oxígeno y con esto, produce a su vez un doble efecto con la oxidación de cardiolipinas, la liberación del citocromo C y la activación de los canales aniónicos dependientes de voltaje (36). Esto se debe a que en presencia de agentes inductores de la apoptosis, se produce la apertura del poro de transición de permeabilidad mitocondrial colapsando el potencial de membrana, lo que incrementa la permeabilidad de la membrana mitocondrial externa y favorece la liberación de los factores apoptóticos al citosol (37)(figura 3).

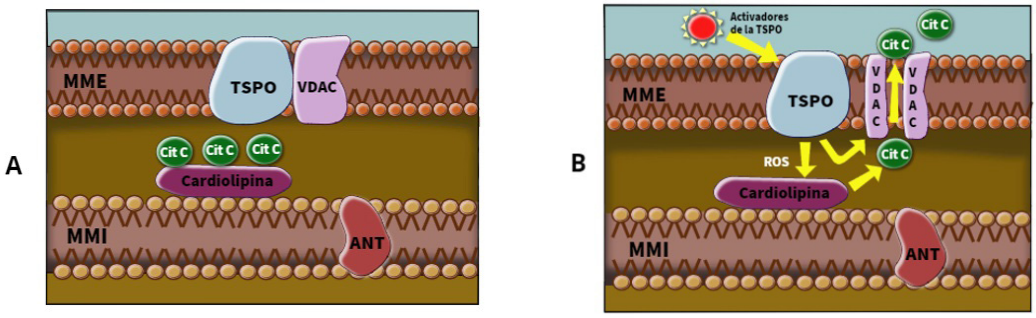


Figura 3. La TSPO y el VDAC conllevan a la iniciación de la vía de la apoptosis. A. Cuando la TSPO y el VDAC no están activados, no se produce la liberación del citocromo C. B. La activación de la TSPO por medio de ligandos, conlleva a la generación de especies reactivas de oxigeno (ROS) resultando en la liberación del citocromo C. por cardiolipinas a nivel de la membrana mitocondrial interna y la formación de un poro a través de VDAC, lo cual permite al citocromo C entrar al citosol. **Adaptada de:** Veenman L, Shandalov Y, Gavish M. VDAC activation by the 18 kDa translocator protein (TSPO), implications for apoptosis. Journal of bioenergetics and biomembranes. 2008 Jun 1;40(3):199-205.

Una vez en el citosol, el citocromo C, el cual es una proteína intermembranal, provoca que los factores inductores de la apoptosis lleguen al núcleo celular, lo cual causa fragmentación del ADN y otros procesos que inducen a la muerte celular programada. El citocromo C y la activación de la cascada de las caspasas, resultan en la destrucción del núcleo celular, el citoesqueleto y la membrana celular (28).

Es por esto que se sugiere una relación de la TSPO y el cáncer, debido a que en combinación con diversos agentes anti-cancerígenos, la TSPO parece mejorar sinérgicamente la muerte de las células cancerosas (37). Varios estudios reportan la correlación de la expresión de la TSPO con el progreso del cáncer y una baja tasa de supervivencia (36).

Los niveles de expresión de la TSPO han sido correlacionados con diferentes estados patológicos (38). Está altamente expresada en células esteroidogénicas como las testiculares, adrenocorticales y células gliales tumorales a nivel cerebral. Así mismo, los niveles de la TSPO están elevados en tejidos cancerosos de mama, ovario, colon y próstata, comparados con tejidos humanos normales (39), sugiriendo un papel importante de la TSPO en la carcinogénesis. Ambas características de localización nuclear

DOI: http://dx.doi.org/10.21615/cesodon.30.1.2

de la TSPO y el transporte de colesterol se han visto aumentadas en la metástasis de cáncer de mama (40) y próstata, indicando un patrón de expresión alterado de la TSPO como resultado de cambios regulatorios con células cancerígenas (41).

La TSPO 18kDa y el estrés oxidativo

El estrés oxidativo se define como un desbalance entre la cantidad de reactivos oxidantes, como las especies reactivas de oxígeno (ERO), y la habilidad de un sistema biológico para la detoxificación de los mismos, o para reparar el daño resultante. Las ERO son moléculas activas que contienen oxígeno, incluyendo los radicales libres (42), los cuales son moléculas o fragmentos moleculares que contienen un electrón desapareado en la capa de valencia y este es capaz de permanecer independiente (43). ERO como los aniones superóxido, radicales hidroxilos, y el peróxido de hidrógeno pueden cambiar el mecanismo de homeostasis oxido-reducción en los tejidos. Estas ERO a menudo inician una disfunción mitocondrial,(39) y juegan un papel tanto en la señalización, el crecimiento y la diferenciación, la regulación de genes, la protección contra patógenos, la regulación de la apoptosis y la supervivencia celular (44).

Diversos estudios han implicado a la TSPO en el papel de las ERO con el cáncer (45). Se han estudiado ligandos específicos como el ErPc3, capaz de producir ERO por ejemplo a través de la oxidación de cardiolipinas (figura 3) (37,46). Esta generación de ERO debido a la TSPO representaría una señal para la inducción de la muerte celular (37). La evidencia ha demostrado que la TSPO está directamente relacionada a los cambios en la generación de ERO: la quinasa sensible a ERO conduce el gen de la TSPO y en tejidos específicos la TSPO tiene un efecto antioxidante (47).

El estrés oxidativo puede estar involucrado en la conversión de tejidos sanos al carcinoma. A su vez, la inflamación crónica presente en las lesiones potencialmente malignas, está asociada con un incremento en la producción de ERO, las cuales causan un daño a nivel de las macromoléculas, incluyendo el ADN. Esta alta tasa de mutaciones localizadas en los tejidos inflamados crónicamente puede aumentar el riesgo de la carcinogénesis (48).

La TSPO 18kDa y el cáncer bucal

Estudios han analizado la expresión y los niveles de la proteína TSPO en tumores del cáncer bucal (en lengua) utilizando inmunohistoquímica, así mismo se ha examinado la afinidad de la TSPO en células tumorales del cáncer bucal y en la fracción celular de la saliva (49) Los ensayos han mostrado que la expresión de la TSPO podría estar aumentada en los tumores del cáncer bucal, incluso se ha observado en algunos estudios, una relación estadísticamente significativa con la tasa de supervivencia a los 5 años, sobre todo en sujetos con valores negativos de TSPO a nivel tumoral (50). Así mismo, ha sido demostrada una disminución de la TSPO con sitios de unión de alta afinidad, al tener exposición al humo de cigarrillo, lo cual podría ayudar a entender un poco más los mecanismos de la carcinogénesis bucal, en los cuales el humo de cigarrillo ha sido ampliamente reconocido como el principal inductor del cáncer bucal y este representa, como ha sido mencionado anteriormente, un factor de riesgo importante para su aparición(51,52). (Ver tabla 1).

Los mecanismos que involucran a la TSPO en líneas celulares del cáncer, tienen que ver sobre todo con la acción de la TSPO en la activación de la cascada que conduce a la apoptosis y sobre todo está implicada en la iniciación de éste proceso mediante su relación con las especies reactivas de oxígeno (46). Ha sido propuesto que estos mecanismos que relacionan a la TSPO pueden estar defectuosos y previenen que la proteína cumpla su función pro-apoptótica. Siendo así, tomando la hipótesis de

DOI: http://dx.doi.org/10.21615/cesodon.30.1.2

diversos estudios que afirman que los niveles elevados de la TSPO conducen a la muerte celular programada, se podría afirmar que este mecanismo no está completamente en función en los casos de cánceres ya establecidos (30).

Tabla 1. Relación entre el cáncer bucal y la TSPO 18 kDa

Autor y año	Tipo de estudio	Objetivo	Conclusión
Gavish et al. (2017)	Experimental In vitro.	Caracterizar los sitios de unión de la TSPO en células del cáncer bucal y examinar los efectos del humo del cigarrillo.	Existe una disminución de la afinidad de los sitios de unión de la TSPO luego de la exposición al humo del cigarrillo.
Jiang Q. et al. (2014)	Estudio In sílico	Explorar los mecanismos moleculares en el proceso de la carcinogénesis bucal, entre ellos el rol de la TSPO.	La TSPO puede jugar un papel crítico en el desarrollo y progreso del cáncer bucal.
Nagler et al. (2010)	Experimental In vitro.	Estudiar el rol patogénico de la TSPO en el cáncer bucal, en líneas celulares del cáncer y la fracción celular de la saliva.	Los niveles elevados de la TSPO en el cáncer bucal pueden estar relacionados con su mortalidad y pronóstico.
Nagler et al. (2016)	Experimental In vitro.	Investigar el mecanismo de como el humo de cigarrillo induce una reducción en la afinidad de la TSPO en muestras de saliva explorando el posible rol de las ERO.	La reducción de la afinidad de la TSPO generada por el humo de cigarrillo no puede ser revertida por ninguno de los antioxidantes estudiados.

El análisis de la TSPO en los sujetos con cáncer bucal ha demostrado que la alteración de la TSPO puede contribuir a la carcinogénesis bucal, manifestando su relación directa con la mortalidad y el pronóstico de los sujetos que la padecen, pero a su vez se debe reconocer la falta de estudios que establezcan una relación causal entre los factores implicados, identificándose una necesidad potencial para evaluar en estudios experimentales este tipo de biomarcadores que permitan afianzar la evidencia disponible y tener suficiente soporte teórico para su uso en la clínica (53).

Conclusión

La participación de la TSPO de 18kDa en los procesos de muerte celular programada y proliferación celular, hacen que ésta se encuentre posiblemente involucrada en los procesos de la carcinogénesis. Su alteración o cambio en las concentraciones y afinidad en muestras de sujetos con cáncer bucal, demuestran una posible relación, la cual podría representar un importante avance para el desarrollo de un método diagnóstico que utilice esta proteína como un biomarcador para el cáncer bucal.

Conflictos de intereses: ninguno declarado.

Referencias

1. Rettig EM, D'Souza G. Epidemiology of Head and Neck Cancer. Surg Oncol Clin N Am. 2015;24(3):379–396. https://www.ncbi.nlm.nih.gov/pubmed/25979389

2. Del Corso G, Villa A, Tarsitano A, Gohel A. Current trends in oral cancer: A systematic review. Cancer Cell Microenviron. 2016;3:e1332. http://www.smartscitech.com/index.php/CCM/article/view/1332

3. Scully C, Bagan J. Oral squamous cell carcinoma overview. Oral Oncol. 2009;45(4):301-308. https://www.ncbi.nlm.nih.gov/pubmed/19249237

4. Van Zyl AW, Bunn BK. Clinical features of oral cancer: clinical review. S Afr Dent J. 2012;67(10):566-569. https://www.researchgate.net/publication/255984153_Clinical_features_of_oral_cancer

5. Wall I, Bree RD, Brakenhoff R, Coebergh JW. Early diagnosis in primary oral cancer: is it possible?. Med Oral Patol Oral Cir Bucal. 2011;16(3):300-305. https://www.ncbi.nlm.nih.gov/pubmed/21441877

6. Bagan J, Sarrion G, Jimenez Y. Oral cancer: clinical features. Oral Oncol. 2010;46(6):414-417. https://www.ncbi.nlm.nih.gov/pubmed/20400366

7. Fernández A, Córdova P, Badenier O, Esguep A. Epidemiological characterization of oral cancer. Literature review. J Oral Res. 2015;4(2):137-145. http://www.joralres.com/index.php/JOR/article/view/156

8. Taghavi N, Yazdi I. Prognostic factors of survival rate in oral squamous cell carcinoma: clinical, histologic, genetic and molecular concepts. Arch Iran Med. 2015 ;18(5):314-319. https://www.ncbi.nlm.nih.gov/pubmed/25959914

9. Johnson NW, Gupta B, Ariyawardana A, Amarasinghe H. Epidemiology and Site-Specific Risk Factors for Oral Cancer. Contemporary Oral Oncology: Springer; 2017. p. 103-153. https://link.springer.com/chapter/10.1007/978-3-319-14911-0_4

10. Ng JH, Iyer NG, Tan MH, Edgren G. Changing epidemiology of oral squamous cell carcinoma of the tongue: A global study. Head & Neck. 2017;39(2):297-304. https://www.ncbi.nlm.nih.gov/pubmed/27696557

11. Radoi L, Luce D. A review of risk factors for oral cavity cancer: the importance of a standardized case definition. Community Dent Oral Epidemiol. 2013;41(2):97-109. https://www.ncbi.nlm.nih.gov/pubmed/22882534

12. Prince VM, Papagerakis S, Prince ME. Oral Cancer and Cancer Stem Cells: Relevance to Oral Cancer Risk Factors, Premalignant Lesions, and Treatment. Curr Oral Health Rep. 2016;3(2):65-73. https://www.infona.pl/resource/bwmeta1.element.springer-doi-10_1007-S40496-016-0081-3

13. Ernani V, Saba NF. Oral Cavity Cancer: Risk Factors, Pathology, and Management. Oncology. 2015;89(4):187-195. https://www.ncbi.nlm.nih.gov/pubmed/26088938

14. Vargas-Ferreira F, Nedel F, Etges A, Gomes AP, Furuse C, Tarquinio SB. Etiologic factors associated with oral squamous cell carcinoma in non-smokers and non-alcoholic drinkers: a brief approach. Braz Dent J. 2012;23(5):586-590. https://www.ncbi.nlm.nih.gov/pubmed/23306239

15. Ford PJ, Farah CS. Early detection and diagnosis of oral cancer: strategies for improvement. J Cancer Policy. 2013;1(1):e2-7. http://www.sciencedirect.com/science/article/pii/S2213538313000039

DOI: http://dx.doi.org/10.21615/cesodon.30.1.2

16. Iyer S, Thankappan K, Balasubramanian D. Early detection of oral cancers: current status and future prospects. Curr Opin Otolaryngol Head Neck Surg. 2016;24(2):110-114. https://www.ncbi.nlm.nih.gov/pubmed/26963670

17. Güneri P, Epstein JB. Late stage diagnosis of oral cancer: components and possible solutions. Oral Oncol. 2014;50(12):1131–1136. https://www.ncbi.nlm.nih.gov/pubmed/25255960

18. Katakura A, Yamamoto N, Sakuma T, Sugahara K, Onda T, Noguchi S, et al. A screening test for oral cancer using saliva samples: Proteomic analysis of biomarkers in whole saliva. J Oral Maxillofac Surg Med Pathol. 2015;27(1):1-5. http://www.sciencedirect.com/science/article/pii/S2212555813000823

19. Javaid MA, Ahmed AS, Durand R, Tran SD. Saliva as a diagnostic tool for oral and systemic diseases. J Oral Biol Craniofac Res. 2016;6(1):67-76. https://www.ncbi.nlm.nih.gov/pubmed/26937373

20. Cheng YS. Rees T, Wright J. A review of research on salivary biomarkers for oral cancer detection. Clin Transl Med. 2014;3(1):3. https://www.ncbi.nlm.nih.gov/pubmed/24564868

21. Yakob M, Fuentes L, Wang MB, Abemayor E, Wong DT. Salivary biomarkers for detection of oral squamous cell carcinoma - current state and recent advances. Curr Oral Health Rep. 2014;1(2):133-141. https://www.ncbi.nlm.nih.gov/pubmed/24883261

22. Radhika T, Jeddy N, Nithya S, Muthumeenakshi RM. Salivary biomarkers in oral squamous cell carcinoma - An insight. J Oral Biol Craniofac Res. 2016;6(1):S51-S54. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5122805/

23. Panta P, Venna VR. Salivary RNA Signatures in Oral Cancer Detection. Anal Cell Pathol. 2014; 2014. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4333915/

24. Papadopoulos V, Baraldi M, Guilarte TR, Knudsen TB, Lacapere JJ, Lindemann P, et al. Translocator protein (18kDa): new nomenclature for the peripheral-type benzodiazepine receptor based on its structure and molecular function. Trends Pharmacol Sci. 2006;27(8):402-409. https://www.ncbi.nlm.nih.gov/pubmed/16822554

25. Papadopoulos V, Lecanu L. Translocator protein (18 kDa) TSPO: an emerging therapeutic target in neurotrauma. Exp Neurol. 2009;219(1):53-57. https://www.ncbi.nlm.nih.gov/pubmed/19409385

26. Chen MK, Guilarte TR. Translocator protein 18 kDa (TSPO): molecular sensor of brain injury and repair. Pharmacol Ther. 2008;118(1):1-17. https://www.ncbi.nlm.nih.gov/pubmed/18374421

27. Taliani S, Pugliesi I, Da Settimo F. Structural requirements to obtain highly potent and selective 18 kDa Translocator Protein (TSPO) Ligands. Curr Top Med Chem. 2011;11(7):860-886. https://www.ncbi.nlm.nih.gov/pubmed/21291396

DOI: http://dx.doi.org/10.21615/cesodon.30.1.2

28. Scarf AM, Ittner LM, Kassiou M. The translocator protein (18 kDa): central nervous system disease and drug design. J Med Chem. 2009;52(3):581-592. https://www.ncbi.nlm.nih.gov/pubmed/19133775

29. Cosenza-Nashat M, Zhao ML, Suh HS, Morgan J, Natividad R, Morgello S, et al. Expression of the translocator protein of 18 kDa by microglia, macrophages and astrocytes based on immunohistochemical localization in abnormal human brain. Neuropathol Appl Neurobiol. 2009;35(3):306-328. https://www.ncbi.nlm.nih.gov/pubmed/19077109

30. Veenman L, Papadopoulos V, Gavish M. Channel-like functions of the 18-kDa translocator protein (TSPO): regulation of apoptosis and steroidogenesis as part of the host-defense response. Curr Pharm Des. 2007;13(23):2385-2405. https://www.ncbi.nlm.nih.gov/pubmed/17692008

31. Šileikytė J, Blachly-Dyson E, Sewell R, Carpi A, Menabò R, Di Lisa F, et al. Regulation of the mitochondrial permeability transition pore by the outer membrane does not involve the peripheral benzodiazepine receptor (translocator protein of 18 kDa (TSPO)). JBC. 2014;289(20):13769-13781. https://www.ncbi.nlm.nih.gov/pubmed/24692541

32. Scarf A, Auman K, Kassiou M. Is there any correlation between binding and functional effects at the translocator protein (TSPO)(18 kDa)?. Curr Mol Med. 2012;12(4):387-397. https://www.researchgate.net/publication/314745716_Is_there_Any_Correlation_Between_Binding_and_Functional_Effects_at_the_Translocator_Protein_TSPO_18_kDa

33. Fan J, Lindemann P, Feuilloley MG, Papadopoulos V. Structural and functional evolution of the translocator protein (18 kDa). Curr Mol Med. 2012;12(4):369-386. https://www.ncbi.nlm.nih.gov/pubmed/22364126

34. Campanella M, Turkheimer FE. TSPO: functions and applications of a mitochondrial stress response pathway. Biochem Soc Trans. 2015;43(4):593-594. https://www.ncbi.nlm.nih.gov/pubmed/26551698

35. Batoko H, Veljanovski V, Jurkiewicz P. Enigmatic Translocator protein (TSPO) and cellular stress regulation. Trends Biochem Sci. 2015;40(9):497-503. https://www.ncbi.nlm.nih.gov/pubmed/26228316

36. Caballero B, Veenman L, Gavish M. Role of mitochondrial translocator protein (18 kDa) on mitochondrial- related cell death processes. Recent Pat Endocr Metab Immune Drug Discov. 2013;7(2):86-101. https://www.ncbi.nlm.nih.gov/pubmed/23368281

37. Veenman L, Gavish M. The role of 18 kDa mitochondrial translocator protein (TSPO) in programmed cell death, and effects of steroids on TSPO expression. Curr Mol Med. 2012;12(4):398-412. https://www.ncbi.nlm.nih.gov/pubmed/22348610

38. Batarseh A, Papadopoulos V. Regulation of translocator protein 18 kDa (TSPO) expression in health and disease states. Mol Cell Endocrinol. 2010;327(1):1-2. https://www.ncbi.nlm.nih.gov/pubmed/20600583

DOI: http://dx.doi.org/10.21615/cesodon.30.1.2

39. Apel K, Hirt H. Reactive oxygen species: metabolism, oxidative stress, and signal transduction. Annu Rev Plant Biol. 2004;55:373-399. https://www.ncbi.nlm.nih.gov/pubmed/15377225

40. Wu X, Gallo KA. The 18-kDa translocator protein (TSPO) disrupts mammary epithelial morphogenesis and promotes breast cancer cell migration. PLoS One. 2013;8(8):e71258. https://www.ncbi.nlm.nih.gov/pubmed/23967175

41. Austin CJ, Kahlert J, Kassiou M, Rendina LM. The translocator protein (TSPO): a novel target for cancer chemotherapy. Int J Biochem Cell Biol. 2013;45(7):1212-1216. https://www.ncbi.nlm.nih.gov/pubmed/23518318

42. Avezov K, Reznick AZ, Aizenbud D. Oxidative stress in the oral cavity: sources and pathological outcomes. Respir Physiol Neurobiol. 2015;209:91-94. https://www.ncbi.nlm.nih.gov/pubmed/25461624

43. Choudhari SK, Chaudhary M, Gadbail AR, Sharma A, Tekade S. Oxidative and antioxidative mechanisms in oral cancer and precancer: a review. Oral Oncol. 2014;50(1):10-18. https://www.ncbi.nlm.nih.gov/pubmed/24126222

44. Wang J, Schipper HM, Velly AM, Mohit S, Gornitsky M. Salivary biomarkers of oxidative stress: A critical review. Free Radic Biol Med. 2015;85:95-104. https://www.ncbi.nlm.nih.gov/pubmed/25889823

45. Gatliff J, East D, Crosby J, Abeti R, Harvey R, Craigen W, et al. TSPO interacts with VDAC1 and triggers a ROS-mediated inhibition of mitochondrial quality control. Autophagy. 2014;10(12):2279-2296. https://www.ncbi.nlm.nih.gov/pubmed/25470454

46. Veenman L, Shandalov Y, Gavish M. VDAC activation by the 18 kDa translocator protein (TSPO), implications for apoptosis. J Bioenerg Biomembr. 2008 ;40(3):199-205. https://www.ncbi.nlm.nih.gov/pubmed/18670869

47. Gatliff J, Campanella M. The 18 kDa translocator protein (TSPO): a new perspective in mitochondrial biology. Curr Mol Med. 2012;12(4):356-368. https://www.ncbi.nlm.nih.gov/pubmed/22364127

48. Buczko P, Zalewska A, Szarmach I. Saliva and Oxidative Stress In Oral Cavity And In Some Systemic Disorders. J Physiol Pharmacol. 2015;66(1):3-9. https://www.ncbi.nlm.nih.gov/pubmed/25716960

49. Bahar G, Feinmesser R, Shpitzer T, Popovtzer A, Nagler RM. Salivary analysis in oral cancer patients: DNA and protein oxidation, reactive nitrogen species, and antioxidant profile. Cancer. 2007;109(1):54-59. https://www.ncbi.nlm.nih.gov/pubmed/17099862

50. Nagler R, Ben-Izhak O, Savulescu D, Krayzler E, Akrish S, Leschiner S, et al. Oral cancer, cigarette smoke and mitochondrial 18kDa translocator protein (TSPO) - In vitro, in vivo, salivary analysis. Biochim Biophys Acta. 2010;1802(5):454-461. https://www.researchgate.net/publication/41087912_Oral_cancer_cigarette_smoke_and_mitochondrial_18kDa_translocator_protein_TSPO_-_In_vitro_in_vivo_salivary_analysis

DOI: http://dx.doi.org/10.21615/cesodon.30.1.2

51. Gavish A, Krayzler E, Nagler R. Two populations of TSPO binding sites in oral cancer SCC-15 cells. Exp Cell Res. 2017;350(1):279-283. http://europepmc.org/abstract/med/27939322

52. Nagler R, Savulescu D, Gavish M. Cigarette smoke-induced reduction in binding of the salivary translocator protein is not mediated by free radicals. Biochimie. 2016;121:1-4. https://www.ncbi.nlm.nih.gov/pubmb
53. ed/26582415

54. Jiang Q, Yu Y-C, Ding X-J, Luo Y, Ruan H. Bioinformatics Analysis Reveals Significant Genes and Pathways to Targetfor Oral Squamous Cell Carcinoma. Asian Pac J Cancer Prev. 2014;15(5):2273-2278. https://www.ncbi.nlm.nih.gov/pubmed/24716969

DOI: http://dx.doi.org/10.21615/cesodon.30.1.2