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COMPARING ORAL SQUAMOUS CELL CARCINOMA IN YOUNG VS OLD PATIENTS: CLINICAL FEATURES, TREATMENT AND PROGNOSIS: A Systematic Review

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ABBREVIATIONS

OSCC: Oral Squamous Cell Carcinoma

COCE: Carcinoma Oral de Células Escamosas

1. ABSTRACT

Introduction: The prognosis of oral squamous cell carcinoma (OSCC) is influenced by various factors including tumor location, tumor stage, differentiation, treatment approach. These factors may differ according to the age of the patient where younger patients may exhibit different aspects compared to older patients. The aim of this systematic review was to compare oral squamous cell carcinoma in young (<40-45 years) and old patients (≥ 40-45 years) regarding prognosis, clinical manifestation, and treatment methodology.

Materials and methods: An electronic search of Medline-PubMed, Web of Science, Scopus, and Lilacs databases was conducted to find indexed articles regarding the clinical manifestation, treatment, and prognosis of OSCC in young (<40-45 years) and old (≥ 40-45 years) from the last 10 years (2014).

Results: From the 210 potentially eligible articles, 6 met the inclusion criteria. All of which compared the two groups of patients. All 6 articles described the location of the OSCC and degree of tumor differentiation. Only 2 articles described the tumor morphology. The treatment was observed in 4 articles, the recurrence rate in 4 articles and the survival rate in 3 articles. In the group of young patients, the recurrence rate was 19.10%, the regional recurrence rate was 5%, the distal recurrence rate 13%, the local control rate was 65%, and local failure was 45%. As for the survival rate it was 56.4% and the disease specific survival rate was 81.4%. In the group of old patients, the overall recurrence rate was 25.40%, the regional recurrence rate was 11%, the distal recurrence rate 9%, the local control rate was 78%, and local failure was 34%. As for the survival rate it was 53.50% and the disease specific survival rate was 76%.

Conclusion: Older patients exhibited a worse prognosis for OSCC compared to younger patients. Although younger patients revealed a lower local control rate, they had a lower overall recurrence rate and better degree of overall survival rate and disease specific survival rate compared to older patients.

2. RESUMEN

Introducción: Diversos factores influyen en el pronóstico del carcinoma oral de células escamosas (COCE) como son: la localización del tumor, el estadio tumoral, la diferenciación y el enfoque terapéutico. Estos factores pueden diferir según la edad del paciente, donde los pacientes más jóvenes pueden presentar aspectos diferentes en comparación con los pacientes de más edad. El objetivo de esta revisión sistemática fue comparar el carcinoma oral de células escamosas en pacientes jóvenes (<40-45 años) y pacientes mayores (≥ 40-45 años) con respecto al pronóstico, la manifestación clínica y el tratamiento.

Materiales y métodos: Se realizó una búsqueda electrónica en las bases de datos Medline-PubMed, Web of Science, Scopus y Lilacs para encontrar artículos indexados relativos a la manifestación clínica, tratamiento y pronóstico del COCE en jóvenes (<40-45 años) y pacientes mayores (≥ 40-45 años) de los últimos 10 años (2014).

Resultados: De los 210 artículos potencialmente elegibles, 6 cumplieron los criterios de inclusión. Todos ellos comparaban los dos grupos de pacientes. Los 6 artículos describían la localización del COCE y el grado de diferenciación tumoral. Sólo 2 artículos describían la morfología tumoral. Se estudió el tratamiento en 4 artículos, la tasa de recurrencia en 4 artículos y la tasa de supervivencia en 3 artículos. En el grupo de pacientes jóvenes la tasa de recidiva fue del 19,10%, la tasa de recidiva regional del 5%, la tasa de recidiva a distancia del 13%, la tasa de control local del 65% y la de fracaso local del 45%. En cuanto a la tasa de supervivencia, fue del 56,4% y la tasa de supervivencia específica de la enfermedad fue del 81,4%. En el grupo de pacientes de edad avanzada, la tasa de recurrencia global fue del 25,40%, la tasa de recurrencia regional fue del 11%, la tasa de recurrencia distal fue del 9%, la tasa de control local fue del 78% y el fracaso local fue del 34%. En cuanto a la tasa de supervivencia fue del 53,50% y la tasa de supervivencia específica de la enfermedad fue del 76%.

Conclusiones: Los pacientes de mayor edad mostraron un peor pronóstico para el COCE en comparación con los pacientes más jóvenes. Aunque los pacientes más jóvenes revelaron una menor tasa de control local, presentaron una menor tasa de recurrencia global y un mejor grado de tasa de supervivencia global y tasa de supervivencia específica de la enfermedad en comparación con los pacientes de más edad.

KEYWORDS

“Adults”, “Elderly”, “Old patients”, “Oral squamous cell carcinoma”, “Oral cavity squamous cell carcinoma”, “Young patients”, “Young adult”, “Young age”, “Clinical manifestations”, “Clinical characteristics”, “Signs and symptoms”, “Prognosis”, “Treatment”

3. INTRODUCTION

3.1. Epidemiology

Oral cancer accounts for 2%- 4% of all the occurring cancer cases worldwide. During the years of 2004-2009, over 300,000 new cases of oral and oropharyngeal cancer were diagnosed and among these cases, over 7,000 of the affected individuals died of these cancers (1). The most common malignancy of the head and neck worldwide is the oral squamous cell carcinoma, and it has been detected as more than 90% of all oral neoplasms (1–4).

The pathology is predominantly found in low income communities (5). It has been determined to be the third most common malignancy in south-central Asia (4). There tends to be higher prevalence in certain regions such as parts of Northern France and East Europe, particularly Hungary, and parts of South America and South East Asia (5). In the US, 2-4% of the annual diagnosed malignancy is represented by oral squamous cell carcinoma, having it responsible for 8000 deaths yearly (4).

Often, oral squamous cell carcinoma tends to develop in older adults that have been chronically exposed to mucosal carcinogens incorporated in tobacco, alcohol, and betel nut (2). It is more commonly found in men that are above 40 years of age (4). In the USA, the median age of oral squamous cell carcinoma diagnosis is 62 years. The pathology ratio of male to female is 1.5:1 due to the greater likelihood of high-risk habit indulgence in men than women. Older adults are at a higher probability of developing OSCC due their greater period of exposure to risk factors (5). Even if over the years there has been a global decrease in the consumption of these products, there has been an increase in the overall incidence of OSCC in most countries. The range goes from 0.4% in Australia to as high as 3.3% in Denmark per year since the year of 1970 (2). Among the male patients affected by oral squamous cell carcinoma, only around 0.4 % - 3.9% are less than 40 years old (6).

Over time, a remarkable worldwide increase in the incidence of OSCC in the younger population was detected, outpacing older counterparts in some countries (2). Most studies observed a male predominance in the young adult group (7). Numerous studies highlighted the increased occurrence of OSCC in the younger population as being partially related to the growing prevalence of exposure to smokeless tobacco, electronic cigarettes, and water pipe tobacco among young adults (2). Genetics, nutritional alteration, and HPV infection were also considered contributary to OSCC in the young population (7). Some relations may be misleading since the rise of OSCC already began before electronic cigarettes were available and before the popularity of smokeless tobacco (2). Also, the role of the risk factors in young patients suffering of OSCC is still uncertain due to the short carcinogen exposure time (7,8). The conflicting reason to the rise of oral squamous cell carcinoma in young population led many to postulate that the young adults with the pathology represent a distinct biological process (2).

Even if there has been advances in the therapeutic approach of Oral Squamous Cell carcinoma, there has not been an improvement in the morbidity and mortality percentage during the last 30 years. Percentages of morbidity and mortality in males are 6.6/100,000 and 3.1/100,000 respectively, while in females the same percentages are 2.9/100,000 and 1.4/100,000 (9). The percentage of the 5-year survival for patients with OSCC varies 40-50% (1,8). The key factor for improved prognosis and increased patient survival rate is the early detection of the cancer. Although the oral cavity can be examined easily and assessed through visual inspection, most of the cases are not identified early due to the asymptomatic early stages or because of the ignorance of the patient or physician. Therefore, it is important for physicians to be cautious of the clinical presentation of OSCC and for the patient to be aware about the importance of regular dental visits (1,8,10).

Common sites for the development of oral squamous cell carcinoma include the tongue, lips, and floor of the mouth. Some of the OSCC arise from normal

mucosa, however, a lot of times from premalignant lesions (1). The gingivae, palate, retromolar area and the buccal and labial mucosa are oral sites less frequently affected (8,11). Oral cancer most commonly affects the tongue (5,8,12). The lateral tongue is the most frequent area affected (80%), followed by the ventral and dorsum (3). Since the ventral surface of the tongue and the floor of the mouth is lined by non-keratinised epithelium, they are commonly affected since carcinogens can easily penetrate this epithelium (8,13). These carcinogens are particularly alcohol and tobacco products (5,8). The lateral border and ventral surface of the tongue suffer traumatic lesions from sharp cusps or mispositioned teeth or dentures which may chronically rub against the mucosa predisposing to the cancer (3).

When examining the habits linked to OSCC location, it was detected that 85% to 90% of patients with floor of the mouth and oropharyngeal carcinoma were both smokers and drinkers. However, less than 40% of those with gum and tongue carcinoma exhibited both of these habits (13).

3.2. Risk factors

The cell responsible for the origin of OSCC is the oral keratinocyte (5,13,14). The DNA mutation may be spontaneous, however, the exposure to mutagens will increase the mutation rate (5).

Tobacco and alcohol are known to be the greatest risk factor for oral cancer Smoking tobacco caries a six-fold risk for developing oral cancer when comparing to non-smoking (1). People who are smokers of low/medium and high-tar cigarettes are at an 8.5 and 16.4-fold increased risk to develop the disease (15). Alcohol drinkers are also at a 6-time higher risk of developing the disease than non-drinkers. When combining both alcohol and tobacco, the simultaneous use poses a fifteen-fold risk of oral cancer in users compared to non-users (1). Alcohol may enhance the possibility of the penetration of carcinogens into target tissue by

acting as a solvent (9,16). Moreover, an alcohol metabolite is acetaldehyde which is identified as a carcinogen (5,9,15). Although alcohol frequency had a significant impact on developing OSCC, it should be highlighted that its consumption alone, not related to tobacco smoking demonstrates a weak association with OSCC (7).

Other risk factors include betel quid chewing as well as areca nut, narcotics and cannabis (1). The use of betel quid which contains areca nut and tobacco associates to a higher relative risk of oral cancer of 8-15 times compared to that of 1-4 times associated with the use of quid without tobacco Chewing betel quid may induce mutations or make the buccal mucosa susceptible to its toxic components as it produces reactive oxygen species (ROS) (9).

Viral infections such as human papilloma virus is also a risk factor of oral squamous cell carcinoma (1,5,9). Various studies have detected DNA from HPV in OSCC, particularly implicated in oropharyngeal carcinoma (5). HPV-16 was found to be responsible for more than 80% of HPV-positive patients suffering of OSCC (4). Incontrollable cell proliferation and apoptosis disturbance is created through the functional deregulation of oncosuppresive key molecules: viral protein E6 and E7 (1,17). E6 binds to p53 causing its breakdown, and E7 reacts with retinoblastoma protein (pRb), a tumor suppressor protein, inhibiting its function (1). The malignant transformation of oral mucosal cells is only triggered in the presence of other risk factors (1,9).

Various epidemiological studies have indicated the importance of diet and nutrition in oral neoplasia development (5,9). A protective factor against oral neoplasia includes a diet rich in fruits and vegetables, especially those high in vitamins A and C (9). Antioxidants and folate are found to be protective, whereas mild iron deficiency and low glutathione levels lead to oxidative stress increasing the risk of OSCC (5).

Patients play a crucial role in their own oral health and factors such as self-treatment, fear of seeking professional help, and delayed presentation significantly

impacts the timeliness of diagnosis and treatment. It is important for health professionals to encourage patients to seek medical attention upon symptom detection as oral health awareness is a key component in improving early detection and subsequent outcomes in oral cancer cases (18).

3.3. Clinical manifestations

Pain is a common symptom reported by patients suffering from oral cancer, representing 30-40% of the main complaints (11). During early stages, the neoplasm is painless. It is during more advanced stages where the lesion may develop pain or a burning sensation (1,3). The level of pain ranges between mild discomfort to severe pain. When the cancer is located on the tongue or floor of the mouth, the pain may arise earlier while in areas such as the lip and buccal mucosa, intense pain tends to appear in advanced stages. This could be due to movement of the tongue against the teeth which leads to sooner discomfort (3).

Other oral cancer symptoms include ear pain, bleeding, tooth mobility, breathing problems, difficulty in speech, dysphagia, prosthesis problem, trismus, and paresthesia. In terminal stages, patients may develop skin fistulas, bleeding, severe anaemia, and cachexia (11). Furthermore, advanced stages may associate to neck metastasis which is presented as a cervical lymph node enlargement. (11,19). There would exist fixation or lymph node hardness (11).

Most often, oral squamous cell carcinoma is presented as an ulcer with necrotic center and margins that are fissured or raised (1,20). It could also be presented as a lump (1,11). A lump is found in advanced stages where the tumor is exophytic with ill-defined borders, warty surface, and is hard to palpate (11). Oral squamous cell carcinoma could be suspected in its early stages when the oral lesion persists for more than 3 weeks (11).

OSCC may resemble potentially malignant disorders such as leukoplakia, verrucous leukoplakia, an erythroleukoplakia, or an erythroplakia (1,3,8). These disorders may progress into appearing as a necrotic looking ulcer consisting of an irregular, raised indurated borders, or into an exophytic mass with a broad base and a surface which could be verrucous, pebbled or relatively smooth (8). Approximately, 17 to 35 percent of oral squamous cell carcinomas are believed to develop from pre-existing leukoplakic lesions, while the rest develop spontaneously from normal appearing oral epithelium (14).

The color of the lesion may vary between red, white or a mixed red and white lesion (1). Initially, the clinical presentation is usually in the form of an erythroleukoplastic lesion, consisting of a red or a mix of red and white areas with slight roughness and is well demarcated (11). Generally, when tumors are located on dorsum of the tongue, they are associated to lichen planus or leukoplakia lesions (14).

The size of the lesion is variable, starting off as small as a few millimetres and ranges to several centimeters in the more advanced cases (11).
The presence of lymph nodes is found in 90% of the cases when the lesion reaches more than 4cm (14). Cervical lymph node enlargement may be manifested due to neck metastasis (11).

3.4. Treatment

Approximately 60-80% of oral squamous cell carcinoma patients are diagnosed at advanced stage and there is an estimation of 145,328 patient deaths worldwide yearly(21). Majority of these deaths are contributed by locoregional recurrence of the disease (22). Dental and medical practitioners have great impact in primary prevention and early detection of oral cancer. They could intervene in the onset of the disease through health education and opportunistic mucosal screenings in routine check-ups, especially high-risk individuals who tobacco and

alcohol (18). The 5-year survival rate of patients in early stage of oral squamous cell carcinoma is 55-60% while in advanced stage patients it is 30-40% (21).

The oral cavities most important functions are mastication, deglutition, maintenance of oral competency, and articulation of speech (12). Oral squamous cell carcinoma treatments often affect these fundamental activities leading to significant lifestyle changes and poor functional outcome (19). The treatment modality is selected according to factors such as the disease stage, disease site, the patients' needs and overall health status (23). The affectation on the quality of life and the survival rate must be taken into account (12).

The first line of treatment in oral cancer is usually surgery. When the cancer is small, at an early stage, and hasn't spread, it is often the treatment of election. There exists different types of surgeries which may be performed according on the location and stage of the disease (24). Alternative to surgery was radiotherapy to treat oral cancer at its early stage (12,19,23). They are both considered equally effective (19). In terms of local control and survival rate, surgery and radiotherapy yield similar results. Their oncological and functional results were similar as well (25). Previously they were the choice of treatment for patients with advanced stage 3 and 4 but the results were unsuccessful (23). In advanced stages, the oncological and functional results were poor when compared to those obtained through surgery (with complementary radiotherapy), especially when radiotherapy is not accompanied with chemotherapy (25).

Patients in the advanced stage of the cancer require multidisciplinary therapy (23,25). Chemotherapy or a combination of surgery with post-operative chemotherapy was introduced (19). Other therapeutic modalities include surgery with or without radiotherapy, radiotherapy and radiochemotherapy (25). This advanced towards improving the treatment efficacy, increasing local control as well as the survival rate (23). Radiochemotherapy treatment presented a more favorable tumor evolution in patients with HPV (25).

When undergoing surgical resection, the objective is to clear any present tumoral tissue as the inadequate clearance tends to increase the risk of local and regional recurrence and decreases the long term survival rate (12). Another significant problem which impacts patient survival rate is the high incidence rate of second primary tumors (SPT). A reasonably good locoregional control and survival is observed in surgical resection followed by adjuvant radiotherapy (19). Increasing the resection margin increases the esthetic and functional morbidity when treating oral squamous cell carcinoma, being that a 1 cm resection margin is acceptable (12).

Several studies established radiotherapy treatment to be better than surgical treatment due to the aggressive complications linked to surgery (19). The 5-year locoregional control rate established among patients with oral cavity T1-T2 disease treated only with radiotherapy ranged from 69.5% to 81% and that of oral surgery ranged from 46.6% to 81% (22). It is recommended to use iodone solution as an adjunct in primary tumor resection to detect and delineate the dysplastic epithelium within the cancerous lesion (12). Surgical treatment consists of low risk of postoperative mortality, however, there is a risk of long-term use of tracheostomy and feeding tubes (19). Other studies preferred definitive surgical resection when feasible due to the adverse impact of radiotherapy-related complications on the quality of life (22). There exists significant morbidity with radiotherapy and long-term complications like mucositis in most patients in addition to xerostomia, pain, and dysphagia (19). Further complications include hoarseness, radionecrosis, subcutaneous fibrosis, trismus, loss of taste, thyroid dysfunctional, esophageal stenosis, dental decay, and middle/inner ear damage (22).

Free tissue transfer is a popular and reliable reconstructive surgery technique which is often required to restore oral function and cosmetic appearance (12). It is important to highlight the current presence of various approaches to improve the outcome of patients submitted to surgical treatment such as robotic

surgery, transoral laser resection, advancement in free flap reconstruction, oral rehabilitation which improve the functional capacity (19).

When treating tumors located on the tongue, small tumors (of less than 3 cm diameter) can be treated with partial glossectomy while larger tumors may need hemiglossectomy or subtotal/total glossectomy. Defects of hemiglossectomy may undergo reconstruction with a radical forearm free flap with adequate speech and swallowing function. Subtotal/total glossectomy defects may require reconstruction with anterolateral thigh or rectus abdominsi free flap (12).

The patients who are in a locally advanced stage and are treated with surgery sometimes need a functional sequelae such as total laryngectomy which decreases the quality of life (25).

Neck dissection is currently the only accepted standard treatment for cervical node metastasis. The management of clinical N0 neck is controversial as 20-30% have occult node metastasis. Some clinicians follow the “wait and see approach” although a delay generally favors worse prognosis. Other clinicians follow the elective neck dissection approach which is performed for primary tumor resection or reconstruction (12).

There are problems related to non-specific cell death caused by OSCC treatment modalities such as chemotherapy, surgery, photodynamic therapy, EGFR inhibitors and COX-2 inhibitors (23). The application of nanoengineered systems offered solutions to these problems that minimized the complications of non-specific cell death and maximized the efficacy of the cancer therapeutic agents (23,26). Nanoparticles reduced drug agent side effects and facilitated constant and uniform amount of drug at the cancer lesion site which facilitated drug penetration into the tumor (23). Nano-delivered drugs demonstrate superior anti-tumor effectiveness, extended circulation within the bloodstream, and improved solubility of the medication compared to conventional chemotherapy (26).

Biomedical development detected that most tumors are the over-expression of certain molecules such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) and its receptors, mTOR, CDK, PD-1, and more. The development of targeted therapy corresponded to therapeutic drugs aimed at carcinogenic sites with advantage of high selectivity, low toxicity and high therapeutic index (21).

3.5. Prognosis

There exist high mortality rates due to oral squamous cell carcinoma, especially in patients with a late diagnosis (4,7). There seems to be a controversial correlation between age and prognosis as well as sex and prognosis (4,27).There is no established prognostic difference among male and female, however, some authors reported females to have a lower survival rate due to delayed medical care seeking and lower treatment acceptance (7). In the last decade, particularly between 1998-2000 and 2007-2009, the European incidence rate increased by 25% and 28% for men and women (15). Many authors reported oral squamous cell carcinoma to be less aggressive and have better prognosis in young patients and a worse prognosis in older individuals (27). A study observed a higher locoregional recurrence rate in young adults when comparing them with control groups. There was established a statistically significant difference ($p=0.025$). Other authors determined the presence of higher rates of recurrence in older patients. Regarding survival rate of OSCC, a lot of studies did not detect significant differences among different age groups. Others did not detect significant differences among different age groups (7).

Some influencing factors that must be taken into account when determining prognosis include the anatomical location, clinical stage and treatment modality, as well as socioeconomic and cultural differences as it could impact patient and health professional behavior and healthcare service access (7).

The most adverse prognostic factor is the presence of lymph node metastasis (28). The worse outcome is expected in patients with bilateral nodal involvement, followed by contralateral, then ipsilateral (15). Cancer staging based on TNM system is widely believed to have crucial influence in prognosis (4,7). Tumor DOI is established to be a good prognosticator for early-stage OSCC, where there exists a higher probability of presenting lymph node metastasis, recurrence, and lower survival in tumors with high DOI (28). The five-year survival rate fluctuates based on tumor size, typically categorized as "low-risk tumors" (T1/T2) and "high-risk tumors" (T3/T4) (27). It is indicated that tumor thickness is more accurate in predicting survival rate tan factors like clinical/pathological staging (4,15). It is also more consistent in predicting nodal metastasis (15,27). The diameter of the tumor is not as accurate compared to thickness or depth of invasion when related to prognosis (15). Moore et al established that 84% of the patients that had a tumor diameter <2cm experienced a cancer free period of 3 years compared to 52% patients with a tumor >2 cm (27).
Depth of invasion (DOI) is useful guide for elective neck dissection in OSCC as it enhances patient risk discrimination and facilitates more accurate counseling for individuals previously categorized as low risk for disease progression. Approximately, 20% of these patients will harbor hidden neck metastasis. The approach of “watchful waiting” favors regional and distant dissemination of the disease, however, the approach of elective neck dissection despite conferring microscopic assurance regarding the condition of the neck carries significant risk of major morbidity (28). Larger tumors associated to a decrease in clear surgical margins and deeper tumors associated with higher incidence of metastatic neck disease (29). Some authors found that well differentiated tumors have more favorable prognosis (7).

When tumors were located posteriorly, there was a reduction in the five-year survival rate compared to those located anteriorly which could be linked to the

location lymphatic drainage and the ability of locoregional surgical management (15).

Furthermore, the cumulative effect of tobacco, alcohol, and betel quid chewing increased mortality rate (4,15,27). There exists a higher risk for second primary oral cancer development in smokers and alcohol drinkers highlighting the importance for the patients abandonment to those detrimental habits (4). Cancer outcome could be established through prognostic biomarkers, independent of the received treatment. Certain biomarkers that have raised great interest in scientific community include MMP-2, MMP1, cadherin-1, mucin-1, GLUT-1 (SLC2A1), mucin-4, interleukin-8, HPV-16, EGFR, and p53 (30).

Poor prognosis was perceived in immunosuppressed individuals as well as individuals with lower socioeconomic status and education as they tend to possess worse oral health, hygiene, and more difficulty to access medical assistance (4). When associating oral cancer prognosis to treatment methodology, in early-reported cancer patients, the 5-year survival rate for patients submit to surgery is 92%, radiation therapy is 69%, and combination therapy is 71%. For patients reported in an advanced stage, the 5-year cumulative survival rate for those submit to surgery is 74%, for radiation therapy is 37% and for combination therapy is 51% (27).

4. JUSTIFICATION AND HYPOTHESIS

JUSTIFICATION

Oral squamous cell carcinoma (OSCC) accounts for approximately 90% of oral malignancies and develops on the mucosal epithelium of the oral cavity (31). It is more commonly found in men that are above 40 years of age (4). Over time, there has been a significant increase in its incidence within the younger population, outpacing the older counterparts in certain regions (2). There were 377,713 cases reported globally in the year 2020. The Global Cancer Observatory (GCO) estimated that by the year 2040, the incidence of OSCC will rise by approximately 40%, accompanied by a growth in mortality (31). Local and regional recurrences tend to be the main reason for OSCC-related mortality despite the breakthrough in treatment modalities, where there is a drop from 92% to 30% of the 5-year survival rate in patients with recurrence (32). The oral lesions initially are asymptomatic and may display the appearance as erythroplastic or leukoplastic areas and may be exophytic or ulcerated. As the lesions advance, pain, dysarthria, and dysphagia may result (33). The first line of treatment for OSCC remains to be surgery, and may include adjuvant radiotherapy with or without chemotherapy (34). The disease as well as the treatment modality greatly influence the patient quality of life and it is important to attempt finding an efficient treatment with the least complications and least reduction in the patients quality of life (35). It is important that dental professionals take the responsibility to carefully examine the oral cavity and oropharynx during routine care (33). There only exists a few studies assessing the association between age and OSCC prognosis and no literature examined the possible association between age and local recurrence (31).
The present systematic review focuses on comparing oral squamous cell carcinoma between old and young patients regarding the clinical features, treatment, and prognosis. It contributes to achieving the sustainable development goal 3 (Good Health and Well Being). As it is traditionally associated with older individuals, its increased incidence among the younger populations have been

overlooked. Awareness of clinical manifestations in young patients helps its early detection as they might be misattributed to other causes. The choice of treatment and its intensity may also differ according to patient's age. Certain therapeutic approaches may be more aggressive for younger individuals to tolerate or may have adverse impacts on older patients who could have underlying health issues. The understanding of age-related factors helps determining the most favorable treatment plans to optimize efficacy while minimizing potential side effects and complications.

Understanding age-specific patterns of oral squamous cell carcinoma aids in the development of targeted public health strategies. This includes educational campaigns, screening programs, and awareness initiatives tailored to the demographics most at risk.

Younger patients may display different disease behavior and outcomes compared to older patients making age a potential prognostic factor in oral squamous cell carcinoma. The prognostic assessment based on age sets realistic expectations for the patient as well as for healthcare individuals.

Tailoring support services to address the unique psychosocial challenges related to lifestyle, relationships, and career, depending on age, is crucial for comprehensive care in individuals affected by oral cancer.

HYPOTHESIS

Null Hypothesis:

The prognosis of oral squamous cell carcinoma is worst in younger patients than in older patients.

The alternative hypothesis:

The prognosis of oral squamous cell carcinoma is better in younger patients than in older patients.

5. OBJECTIVES

Principle Objective

1. Evaluate the comparison of prognosis in younger and older patients with oral squamous cell carcinoma.

Secondary Objectives

2. Compare the clinical features in younger and older patients with oral squamous cell carcinoma.

3. Evaluate the treatment of oral squamous cell carcinoma in younger and older patients.

6. MATERIALS AND METHODS

This systematic review complies with the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (36).

6.1. Focus question

The focus question was established according to the PICO structured question:
P (population): Older patients (≥ 40-45 years).
I (intervention): Oral squamous cell Carcinoma.
C (comparison): Younger patients (<40-45 years).
O (outcomes): Clinical manifestations, treatment, and prognosis.

- O1: Compare the prognosis in younger and older patients
- O2: Compare the clinical features in younger and older patients
- O3: Compare the treatment in younger and older patients

6.2. Eligibility criteria

The inclusion criteria consists of:

- **Study design:** Clinical trials and randomized controlled trials, prospective and retrospective cohort studies, case series; publication in English, from the last 10 years (2014-2024).
- **Patient:** Young patients (<40-45 years) and old patients (≥ 40-45 years).
- **Intervention:** Oral squamous cell carcinoma.
- **Outcomes:** Studies that include data related to the prognosis of oral squamous cell carcinoma in older and younger patients. As secondary variables, studies that include data related to the clinical manifestations and treatment of oral squamous cell carcinoma in older and younger patients.

The exclusion criteria consists of: Systemic reviews, meta-analysis, letters or comments to the editor, expert reports, in vitro and animal experimental studies.

Moreover, the studies published in languages other than English, the studies published earlier than year 2014, the studies that did not distinguish between our two age ranges (<40-45 and (≥ 40-45), as well as studies that did not evaluate the clinical characteristics, treatment, or prognosis of oral squamous cell carcinoma in young or old population.

6.3. Information sources and data search:

An automatized electronic and manual literature searches were conducted in four major electronic databases (PubMed, Scopus, Web of Science, and Lilacs) with the following keywords: “adults”, “elderly“, "old patients", "oral squamous cell carcinoma", "oral squamous cell carcinomas“, "oral cavity squamous cell carcinoma", "young patients“, “young adult”, "young age", "clinical manifestations", "clinical characteristics", “signs and symptoms”, “prognosis“, “treatment“. Keywords were combined with a combination of the controlled terms (MeSH for Pubmed) to obtain the best search results.

The following search strategy in Pubmed was carried out: (("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields] OR "adult s"[All Fields] OR ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR "elderlys"[All Fields]) OR "old patients"[All Fields]) AND (("clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND "english"[Language]) AND (("oral squamous cell carcinoma"[All Fields] OR "oral squamous cell carcinomas"[All Fields] OR "oral cavity squamous cell carcinoma"[All Fields]) AND (("clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND "english"[Language])) AND (("young patients"[All Fields] OR "young adult"[All Fields] OR "young age"[All Fields]) AND (("clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND "english"[Language])) AND (("clinical manifestations"[All Fields] OR "clinical characteristics"[All Fields] OR "signs and symptoms"[All Fields] OR ("prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields]) OR ("therapeutics"[MeSH Terms] OR

"therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatments"[All Fields])) AND (("clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type]) AND "english"[Language]))) AND ((y_10[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]) AND (english[Filter]))

The following search strategy in Scopus was carried out: ((adults) OR (elderly) OR ("old patients")) AND (("oral squamous cell carcinoma") OR ("oral squamous cell carcinomas") OR ("oral cavity squamous cell carcinoma")) AND (("young patients") OR ("young adult") OR ("young age")) AND (("clinical manifestations") OR ("clinical characteristics") OR ("signs and symptoms") OR (prognosis) OR (treatment)) AND PUBYEAR > 2013 AND PUBYEAR < 2025 AND (LIMIT-TO (SUBJAREA , "DENT")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (OA , "all"))

The following search strategy in Web of Science was carried out: (((ALL=((adults) OR (elderly) OR ("old patients"))) AND ALL=(("oral squamous cell carcinoma") OR ("oral squamous cell carcinomas") OR ("oral cavity squamous cell carcinoma"))) AND ALL=(("young patients") OR (“young adult”) OR ("young age"))) AND ALL=(("clinical manifestations") OR ("clinical characteristics") OR (“signs and symptoms”) OR (prognosis) OR (treatment))

The following search strategy in Lilacs was carried out: ((adults) OR (elderly) OR ("old patients")) AND (("oral squamous cell carcinoma") OR ("oral squamous cell carcinomas") OR ("oral cavity squamous cell carcinoma")) AND (("young patients") OR (“young adult”) OR ("young age")) AND (("clinical manifestations") OR ("clinical characteristics") OR (“signs and symptoms”) OR (prognosis) OR (treatment))

6.4. Process of study selection:

Three stages were carried out during the selection process. The study selection was carried out by two reviewers (CJ, ARA). The first stage of the screening eliminated irrelevant publications according to the titles. In the second stage, abstracts were screened according to the type of study, the patient age range, the type of intervention, and the outcome variables. When the abstract of a study provided insufficient information or more information than just the variables evaluated, or was unstructured to determine its exclusion, it was assigned for full text evaluation. The third stage consisted of complete reading of each text using a predetermined data extraction form in order to confirm the eligibility of the study according to the predetermined inclusion and exclusion criteria. Disagreements or doubts between reviewers, at each of the phases, were resolved by discussion. The degree of agreement regarding the inclusion of potential studies was calculated by k-statistics (Cohen kappa test) for the second and third stage of selection.

6.5. Data extraction

The following information was extracted from the studies and arranged in tables according to the type of procedure (comparing oral squamous cell carcinoma regarding clinical features, treatment, and prognosis, in old patients and young patients), authors with the year of publication, type of study (randomized controlled, clinical trials, prospective, retrospective, case series), number of patients, age of the patients (in years), sex (male or female), clinical features (location, degree of differentiation, tumor morphology), TNM stage, treatment (according to the age of the patient), and prognosis (recurrence rate and survival rate).

Principle Variable

- **Prognosis:** The prognosis of oral squamous cell carcinoma in old patients (≥ 40-45 years) compared to that of young patients (<40-45 years). It is measured through recurrence rate and survival rate in percentage.

Secondary Variables

- **Clinical features:** The clinical features of oral squamous cell carcinoma in old patients (≥ 40-45 years) compared to that of young patients (<40-45 years). It is measured through tumor location (oral cavity), degree of differentiation, and tumor morphology.
- **Treatment:** The treatment of oral squamous cell carcinoma in old patients (≥ 40-45 years) compared to that of young patients (<40-45 years). It is determined mainly according to age, as well as the TNM stage and tumor location.

The way these endpoints (clinical features, treatment, and prognosis) were measured for each of the studies is described in Table 2.

6.6. Quality and risk of bias assessment:

Two reviewers (CJ, ARA) independently evaluated the methodological quality of the included studies.

Cochrane 5.1.0 (http://handbook.cochrane.org) guidelines were used to evaluate the quality of randomized controlled clinical trials; publications were considered "low risk of bias" when they met all criteria, "high risk of bias" when one or more criteria were not met and therefore the study is considered to present a possible bias that weakens the reliability of the results and "uncertain bias" (due to lack of information).

The Newcastle-Ottawa scale (37) was used to measure the quality of non-randomized observational studies; it was considered "low risk of bias" in the case of a star score > 6 and "high risk of bias" for a score ≤ 6.

6.7. Data assessment

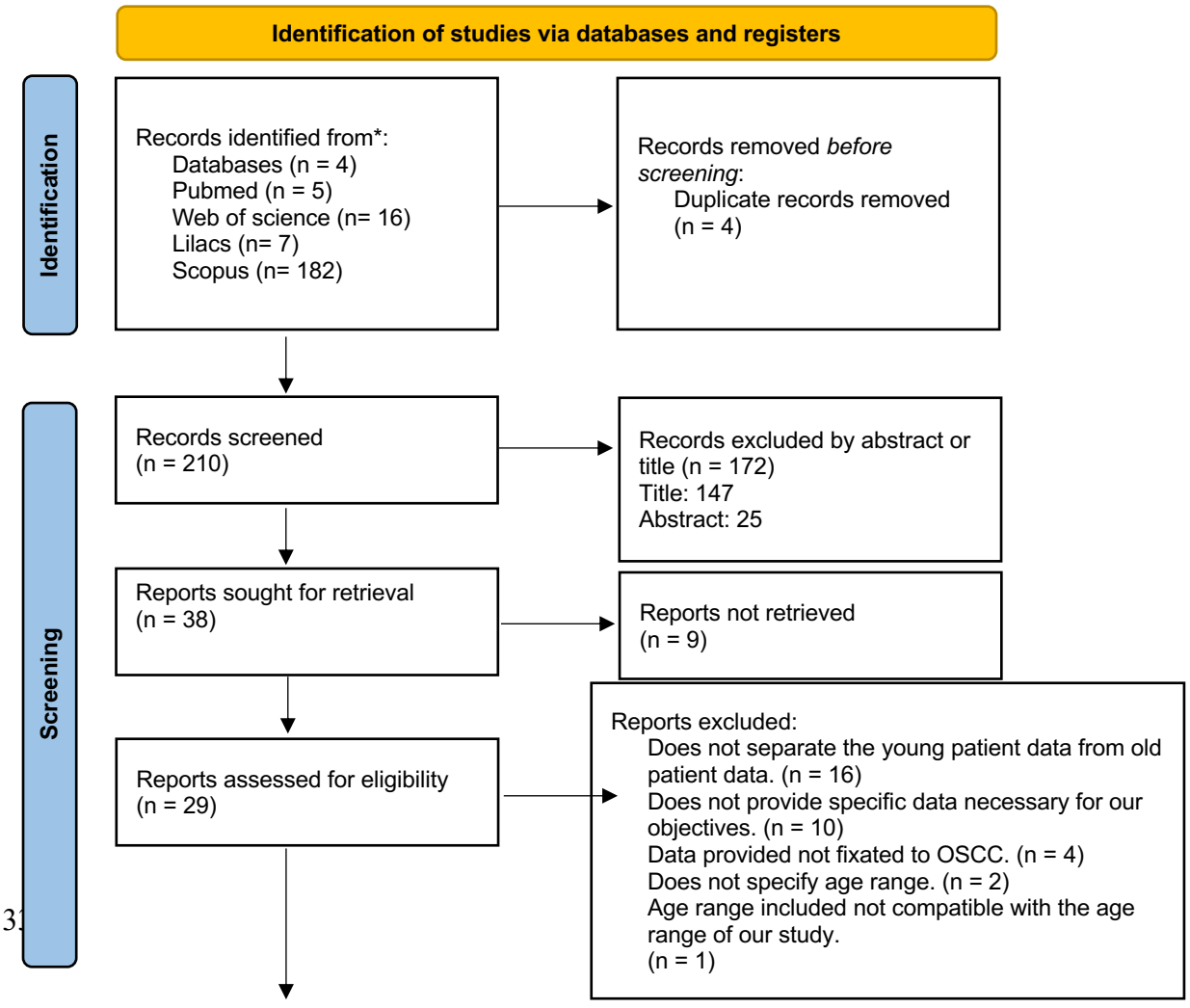
With the aim of summarizing and comparing studies, average data on main variables were grouped for each study group. As the average data found in the analyzed studies came from different samples, weighted arithmetic mean was calculated to obtain feasible outcomes. A meta-analysis was not able to be performed due to the lack of randomized studies comparing both procedures.

7. RESULTS

7.1. Study Selection

A total of 210 articles were obtained from the initial search process: Medline-PubMed (n=5), SCOPUS (n=182) and the Web of Science (n=16), Lilacs (n=7). Of these publications, 37 were identified as potentially eligible articles through screening by titles and abstracts. The full-text articles were subsequently obtained and thoroughly evaluated. As a result, 6 articles met the inclusion criteria and were finally included in this systematic review (Fig. 1). The information related to the articles excluded as well as the reason for their exclusion is presented in Table 2. The k value for inter-reviewer agreement for study inclusion was 0.87 (titles and abstracts) and 1.0 (full texts) indicating ‘‘good’’ and ‘‘full’’ agreement, respectively, according to the Landis and Koch criteria (38).

7.2. Analysis of the Characteristics of the Studies Reviewed



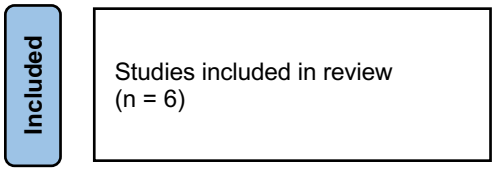


Fig. 1. Diagram of the search flow and title selection process during the systematic review.

Table 1: Articles excluded (and their reason for exclusion) from this systematic review

Author	Publication	Motive of exclusion
Oliveira mlc *et al.* 2015 (39)	Brazil oral res	Does not separate the young patient data from old patient data.
Eder-Czembirek C *et al.* 2018 (40)	Clinics	Compares two methods of intra-arterial chemotherapy as treatment for OSCC without any relation to age.
Leite AA *et al.* 2018 (41)	São Paulo med j	Does not provide specific data necessary for our objectives. Does not separate the young patient data from old patient data.
Csurgay K, Zalatnai A *et al.* 2021 (42)	Pathology & oncology research	Data focused more on HPV and immunoexpression.
Gong Y, Ju HY *et al.* 2019 (43)	Journal of cancer	Does not provide specific data necessary for our objectives.

Yoshioka Y, Sakaue T *et al.* 2021 (44)	Oral science international	Data related to oral cancer in general and not specific to oral squamous cell carcinoma.
Zhang BX *et al.* 2019 (45)	Cancer management and research.	Does not provide specific data necessary for our objectives.
Hasegawa Y *et al.* 2021 (44)	Journal of Clinical Oncology.	Data related to oral cancer in general and not specific to oral squamous cell carcinoma. Does not provide specific data necessary for our objectives. Does not separate the young patient data from old patient data.
Monteiro LS *et al.* 2014 (46)	Medicina Oral, Patologia Oral y Cirugia Bucal.	Does not separate the young patient data from old patient data.
Yu YH, Morales J, Feng L *et al.* 2015 (47)	Oral Pathology and Oral Radiology	Does not separate the young patient data from old patient data. Data provided not specific to our objectives.
Santos HBP et *al.* 2016 (48)	Medicina Oral Patologia Oral y Cirugia Bucal	Only includes patients younger than 45 years and data more related to risk factors
Elzahaby IA *et al.* 2015 (49)	BMC Oral Health	Does not separate the young patient data from

		old patient data. Only includes 3 patients who have developed local recurrence.
Magalhaes MAO *et al.* 2016 (50)	Oral Medicine, Oral Pathology and Oral Radiology.	Data provided is insufficient to answer objectives
Park JW *et al.* 2017 (51)	Journal of the Korean Association of Oral and Maxillofacial Surgeons.	Does not separate the young patient data from old patient data.
Flores-Ruiz R *et al.* 2018 (52)	Medicina Oral Patologia Oral y Cirugia Bucal.	Data provided not specific to oral squamous cell carcinoma.
Aittiwarapoj A *et al.* 2019 (53)	European Journal of Dentistry.	Data mainly discusses the differential diagnosis between OSCC and OPMDS.
Gu X *et al.* 2019 (2)	Journal of Oral Pathology and Medicine.	Data provided only discusses prognostic marker for young patients with tongue OSCC
Nóbrega TD *et al.* 2018 (54)	Medicina Oral Patologia Oral y Cirugia Bucal.	Does not separate the young patient data from old patient data.
Zhu Z *et al.* 2019 (26)	Journal of Oral Pathology and Medicine.	Does not separate the young patient data from old patient data.
Rodrigues RM *et al*. 2020 (55)	Journal of Applied Oral Science	Does not separate the young patient data from old patient data.

Chang WC *et al.* 2019 (56)	Oral Oncology	Does not separate the young patient data from old patient data.
De Barros-Silva PG *et al.* 2020 (57)	Medicina Oral Patologia Oral y Cirugia Bucal.	Age range included (<65 and ≥ 65) was not compatible with the age range of our study.
Van Lanschot CGF *et al.* 2020 (58)	Oral Oncology.	Does not specify age range.
Ajalyakeen H *et al.* 2020 (59)	Dental and Medical Problems	Does not specify age range.
Valero C *et al.* 2022 (60)	Oral Oncology.	Does not provide specific data necessary for our objectives.
Wang Y *et al.* 2022 (61)	Head and Face Medicine	Does not provide specific data necessary for our objectives.
Kim MG *et al.* 2022 (62)	Journal of the Korean Association of Oral and Maxillofacial Surgeons.	Does not provide specific data necessary for our objectives.
Liang L *et al.* 2023 (63)	International Journal of Oral Science.	Data provided related to mutation associated transcripts of oral tongue SCC.
Rogers SN *et al.* (2020, washington) (64)	Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology.	Does not separate the young patient data from old patient data.
Ferreira AKA *et al.* (2021, Brazil) (65)	Medicina Oral Patologia Oral y Cirugia Bucal.	Does not separate the young patient data from old patient data.

Yong-Seok Choi *et al.* (2022, Korea) (66)	Journal of the Korean Association of Oral and Maxillofacial Surgeons.	Does not separate the young patient data from old patient data.
Sean R. Quinlan-Davidson *et al.* (2017, Texas) (67)	Oral Oncology.	Does not separate the young patient data from old patient data.

Table 2: Characteristics, Treatment, and Prognosis of the studies reviewed

Authors (year and country)	Type of Study	N. patients	Sex	Age (years)	Location of carcinoma (%)	Degree of differentiation (%)	Tumor morphology/manifestation
Ledesma-Montes C, *et al.* (2018, Brazil)	Cohort Retrospective Review	60	M: 32 F: 28	≥ 45	BT: 23 MT: 37	**BT** WD: 6 (10%) MD: 34 (56.7%) PD:14 (23.3%) CIS: 6 (10%) **MT** WD: 3 (8.1%) MD: 22 (59.4%) PD: 8 (21.6%) CIS: 4 (10.8%)	-
Subramaniam N *et al.* (2020, India)	Cohort Prospective Review	425	M: 88 (77%) F: 26 (23%) M: 217 (70%) F: 94(30%)	<45 ≥ 45	T: Unspecified	MD/PD: 62 (53%) MD/PD: 135 (43%)	-
Cariati P *et al. (*2017, Spain)	Cohort Retrospective Review	133	M: 18 F: 15	<45	T: 35 FOM: 20 RR: 14 BM: 9 O: 8 Mx: 7	WD: 13 MD: 17 PD: 3	-

			M: 67 F: 33	≥ 45	P: 5 G:2 T: 18 (54.5%) FOM: 5 (15.1%) AR: 1 (3.03%) BM: 4 (12.1%) O: 3 (9.09%) Mx: 1 (3.03%) G:1 (3.03%)	WD: 8 MD: 66 PD: 26	
Xu QS *et al.* (2019, China)	Cohort Review	2,782					
	Retrospective Part	2,443	M: 94 (65.7%) F: 49 (34.3%)	≤40	T: 102 (71.3%) LG: 12 (8.4%) BM: 6 (4.2%) FOM: 13 (9.1%) UG: 8 (5.6%) HP: 2 (1.4%)	WD: 54 (40%) MD: 71 (52.6%) PD: 10 (7.4%)	E: 29 (23.0%) U: 52 (41.3%) I: 45 (35.7%) VEP: 2 (3.6%) VEA: 53 (96.4%)
			M: 1169 (55.6%) F: 933 (44.4%)	41–75	T: 850 (40.4%) LG: 383 (18.2%) BM: 365 (17.4%) FOM: 235 (11.2%) UG: 203 (9.7%) HP: 66 (3.1%)	WD: 976 (47.7%) MD: 966 (47.2%) PD: 105 (5.1%)	E: 748 (37.8%) U: 704 (35.6%) I: 525 (26.6%) VEP: 29 (4.4%) VEA: 634 (95.6%)
			M: 115 (58.1%) F: 83 (41.9%)	>75	T: 70 (35.4%) LG: 45 (22.7%) BM: 4 (22.2%) FOM:3 (1.5%) UG:33 (16.7%) HP: 3 (1.5%)	WD: 86 (45.3%) MD: 91 (47.9%) PD: 13 (6.8%)	E: 97 (52.2%) U: 60 (32.2%) I: 29 (15.6%) VEP: 3 (4.6%) VEA: 62 (95.4%)
	Prospective Part	339	M: 187 (55.2%) F: 152 (44.8%)	≤40	T: 18 (58.1%) LG: 2 (6.5%) BM: 4 (12.9%) FOM: 1 (3.2%) UG: 3 (9.7%) HP: 3 (9.7%)	WD: 6 (24.0%) MD: 17 (68.0%) PD: 2 (8.0%)	E: 8 (25.8%) U: 9 (29.0%) I: 14 (45.2%)
				41–75	T: 111 (40.2%) LG: 54 (19.6%) BM: 60 (21.7%) FOM: 27 (9.8%) UG: 14 (5.1%) HP: 10 (3.6%)	WD: 59 (26.1%) MD: 163 (72.1%) PD: 4 (1.8%)	E: 70 (25.4%) U: 97 (35.3%) I: 108 (39.3%)
				>75	T: 8 (25.8%) LG: 8 (25.8%) BM: 10 (32.3%)	WD: 5 (18.5%) MD: 20 (74.1%) PD: 2 (7.4%)	E: 7 (23.3%) U: 15 (50.0%) I: 8 (26.7%)

					UG: 5 (16.1%)		
Komolmalai N *et al.* (2015, Thaliand)	Cohort Retrospecti ve study	874	M: 23 (63.9%) F: 13 (36.1%)	<40	L: 1 (2.8%) T: 27 (75.0%) FOM: 2 (5.6%) P: 2 (5.6%): BM: 2 (5.6%) RR:1 (2.8%) Mouth, NOS: 1 (2.8%)	WD: 18 (50%) MD: 11 (30.6%) PD: 5 (13.9%) UD: 0 (0%) UK: 2 (5.6%)	-
			M: 494 (58.9%) F: 344 (41.1%)	≥ 40	L: 63 (7.5%) T: 309 (36.9%) G: 156 (18.6%) FOM: 69 (8.2%) P: 91 (10.9%) BM: 119 (14.2%) RR:12 (1.4%) Mouth, NOS: 16 (1.9%) Multiple sites: 3 (0.4%)	WD: 487 (58.1%) MD 235 (28.9%) PD: 62 (7.4%) UD: 3 (0.4%) UK: 51 (6.1%)	
Devadass CW *et al.* (2020, India)	Cohort Prospective Review	187	M: 20 (57.1%) F: 15 (42.9%)	≤40	BM:19 (54.3%) LAR: 6 (17.1%) RR: 3 (8.6%) T: 7 (20%)	WD: 10 (28.6%) MD 22 (62.9%) PD: 1 (2.9%) VC: 2 (5.7%)	E: 21 (60%) En: 14 (40%)
			M: 100 (65.8%) F: 52 (34.2%)	>40	L: 2 (1.3%) BM: 79 (52%) LAR: 26 (17.1%) UAR: 3 (2%) RR: 15 (9.9%) FOM: 2 (1.3%) HP: 4 (2.6%) T: 21 (13.8%)	WD: 41 (27%) MD 101 (66.4%) PD: 7 (4.6%) VC: 3 (2%)	E: 92 (60.5%) En: 60 (39.5%)

M: Male; F: Female; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; CIS: Carcinoma in situ; UD: Undifferentiated; UK: Unknown; VC: Verrucous Carcinoma; BT: Base of the tongue; MT: Mobile tongue; T: Tongue; FOM: Floor Of Mouth; RR: Retromolar Region; BM: Buccal Mucosa; O: Oropharynx; Mx: Maxilla; G: Gingiva; P: Palate; AR: Alveolar Ridge; UAR: Upper Alveolar Ridge; LAR: Lower Alveolar Ridge; LG: Lower Gingiva; UG: Upper Gingiva; HP: Hard Palate; NOS: Not Otherwise Specified; L: Lip; E: Exophytic; En: Endophytic; U: Ulcerative; I: Infiltrative; VEP: Vascular Emboli Present; VEA: Vascular Emboli Absent

Table 3: Stage, Treatment, recurrence rate, and survival rate of the studies reviewed

Authors (year and country)	Type of Study	N. patients	Sex	Age (years)	Stage (TNM/ AJCC 7th Cancer Staging Manual)	Treatment	Recurrence (%)	Rate of survival
Ledesma-Montes C, *et al.* (2018, Brazil)	Cohort Retrospective Review	60	M: 32 F: 28	≥ 45	**TNM** T2N0M0: 47 T3N0M0: 2 T3N2bM0: 1 T4aN0M0:3 T4dN2bM0: 7 AJCC: II: 48 III: 3 Iva: 9	**MD-OSCC** Wide excision or hemiglosectomy **PD-OSCC** Wide local excision or hemiglosectomy **WD-OSCC** Wide excision or hemiglosectomy **CIS** Wide local excision or hemiglosectomy, possibly with neck dissection	OR: 9 (15%) **MD-OSCC** 11.8%: further excision or neck dissection **PD-OSCC** 21.4%: further excision or neck dissection **WD-OSCC** 1 case: further excision **CIS** 1 case: further excision	-

Subramaniam N *et al.* (2020, India)	Cohort Prospective Review	425	M: 88 (77% F: 26 (23%) M: 217 (70%) F: 94 (30%)	<45 ≥ 45	LI: 38 (33%) PI: 47 (41%) DF: 60 (53%) CM: 4 (4%) EE: 43 (38%) LI: 66 (21%) PI: 87 (28%) DF: 146 (47%) CM: 8 (3%) EE: 72 (23%)	S: 51 (45%) S + R: 11 (10%) S + CCRT: 52 (45%) S: 161 (52%) S + R: 41 (13%) S + CCRT: 109 (35%)	LCR: 65% RRR: 5% DRR: 13% LCR: 78% RRR: 11% DRR: 9%	OS: 65% DSS: 67% OS: 71% DSS: 74% P value: OS: (p = 0.481) P value DSS: (p = 0.156).
Cariati P *et al.* (2017, Spain)	Cohort Retrospective Review	133	M: 18 F: 15 M: 67 F: 33	<45 ≥ 45	T1: 57,5%, (n=19) T2: 27,2%, (n=9) T3: 3,03% (n=2) T4: 3,03% (n=3) NI: 48,4% (n=16) T1: 27% (n=27) T2: 37% (n=37) T3: 29% (n=29) T4: 7% (n=7) NI: 33% (n=33)	-	LF: 45.4% (n=15) LF: 34% (n=34)	5y-OS: 48.4% (n=16) 5y-OS: : 62% (n=62) P value: OS: (p=0.17)
Xu QS *et al.* (2019, China)	Cohort Review	2,782						
	Retrospective Part		M: 94 (65.7%) F: 49 (34.3%)	≤40	**cT stage** T1: 33 (23.1%) T2: 58 (40.5%) T3: 19	S: 55 (47.8%)	OR: 38.2%	DSS: 77.2%

					(13.3%) T4 33 (23.1%) **<u>pN stage</u>** N0: 72 (55.8%) N1: 25 (19.4%) N2: 30 (23.3%) N3: 2 (1.5%) PI: 17 (28.8%) No PI: 42 (71.2%) DI: 18 (32.7%) No DI: 37 (67.3%)	S+R: 47 (40.9%) S+CCRT: 13 (11.3%)		
			M: 1169 (55.6%) F: 933 (44.4%)	41–75	**<u>cT stage</u>** T1:487 (23.2%) T2: 817 (38.9%) T3: 209 (9.9%) T4: 589 (28%) **<u>pN stage</u>** N0: 1053 (59.1%) N1: 301 (16.9%) N2: 424 (23.8%) N3: 4 (0.2%) PI: 155 (21.7%) No PI: 559 (78.3%) DIP: 244 (36.6%) No DI: 422	S: 908 (60.4%) S+R: 466 (31.0%) S+CCRT: 130 (8.6%)	OR: 46.7%	DSS: 69.7%
			M: 115 (58.1%)					

			F: 83 (41.9%)	>75	(63.4%) **<u>cT stage</u>** T1: 58 (29.3%) T2: 84 (42.4%) T3: 19 (9.6%) T4: 37 (18.7%) **<u>pN stage</u>** N0: 81 (62.8%) N1: 15 (11.6%) N2: 33 (25.6%) N3: 0 (0%) PI: 10 (14.7%) No PI: 58 (85.3%) DI: 40 (61.5%) No DI: 25 (38.5%)	S 113 (76.4%) S+R: 29 (19.6%) S+CCRT: 6 (4.0%)	OR: 52.0% Total recurrence:1, 006/2443 patients (46.6%)	DSS: 55.4% Total DSS: 1487/2157 patients (68.9%)
	Prospective Part		M: 15 (48.4%) F: 16 (51.6%)	≤40	**<u>cT stage</u>** T1: 7 (22.6%) T2: 14 (45.2%) T3: 5 (16.1%) T4: 5 (16.1%) **<u>pN stage</u>** N0: 25 (80.6%) N1: 4 (12.9%) N2: 2 (6.5%) N3: 0 (0.0%)	S: 19 (61.3%) S+R: 12 (38.7%) S+CCRT: 0 (0%)	OR: 0.0%	DSS 100.0%

			M: 161 (58.1%) F: 116 (41.9%) M: 11 (35.5%) F: 20 (64.5%)	41–75 >75	**<u>cT stage</u>** T1: 70 (25.3%) T2: 81 (29.2%) T3: 30 (10.8%) T4: 96 (34.7%) **<u>pN stage</u>** N0: 197 (71.1%) N1: 29 (10.4%) N2: 50 (18.1%) N3: 1 (0.4%) **<u>cT stage</u>** T1: 8 (25.8%) T2: 10 (32.3%) T3: 1 (3.2%) T4: 12 (38.7%) **<u>pN stage</u>** N0: 24 (77.4%) N1: 2 (6.5%) N2: 5 (16.1%) N3: 0 (0.0%)	S: 194 (70.1%) S+R: 76 (27.4%) S+CCRT: 7 (2.5%) S: 30 (96.8%) S+R: 1 (3.2%) S+CCRT: 0 (0.0%)	OR: 15.7% OR: 30.0% Total recurrence: 326/339 patients	DSS: 94.8% DSS: 80.0%
Komolmalai N *et al.* (2015, Thaliand)	Cohort Retrospecti ve Review	419	M: 23 (63.9%) F: 13 (36.1%)	<40	**<u>Clinical stage</u>** I: 3 (8.3%) II: 11 (30.6%) III: 1 (2.8%) IVA: 12 (33.3%) IVB: 0 (0.0%) IVC: 1 (2.8%) UK: 8 (22.2%)	S: 1 (2.8%) R: 9 (25%) C:1 (2.8%) S+R: 12 (33.3%) S+R+C: 2 (5.6%) S+C: 0 (0.0%) R+C: 6 (16.7%)	-	5-y OS: 56.2%

			M: 494 (58.9%) F: 344 (41.1%)	≥ 40	**Clinical stage** I: 83 (9.9%) II: 169 (20.2) III: 105 (12.5%) IVA: 275 (32.8%) IVB: 17 (2.0%) IVC: 14 (1.7%) UK: 175 (20.9%)	P: 2 (5.6%) UK:3 (8.3%) S: 119 (14.2%) R:242 (28.9%) C: 26 (3.1%) S+R: 156 (18.6%) S+R+C: 26 (3.1%) S+C: 7 (0.8%) R+C: 58 (6.9%) P: 108 (12.9%) UK: 96 (11.5%)		5-y OS: 27.4% **5-y survival rate:** F: 33.7% M: 25.3% Stage I: 54.6% Stage II: 18%
Devadass CW *et al.* (2020, India)	Cohort Prospective Review	187	M: 20 (57.1%) F: 15 (42.9%)	≤40	PI: 3 (8.6%) EE: 5 (14.2%) LI: 14 (40%) **cT stage** T1:5 (14.3%) T2: 10 (28.6%) T3: 13 (37.1%) T4: 7 (20%) **pN stage** N0: 21 (60%) N1: 7 (20%) N2: 5 (14.3%) N3: 2 (5.7%) **TNM stage** I: 1 (2.9%) II:7 (20%) III: 15 (42.9%)	-	-	-

			M: 100 (65.8%) F: 52 (34.2%)	>40	IV: 12 (34.3%) PI: 14 (9.2%) EE:14 (9.2%) LI:42 (27.6%) **cT stage** T stage: T1: 16 (10.5%) T2: 65 (42.8%) T3: 45 (29.6%) T4: 26 (17.1%) **pN stage** N0: 113 (74.3) N1: 16 (10.5) N2: 18 (11.8) N3: 5 (3.3) **TNM stage** I: 9 (5.9) II: 39 (25.7) III: 56 (36.8) IV: 48 (31.6)			

M: Male; F: Female; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; CIS: Carcinoma in situ; UD: Undifferentiated; UK: Unknown; VC: Verrucous Carcinoma; BT: Base of the tongue; MT: Mobile tongue. S: Surgery; R: Radiotherapy; C: Chemotherapy; CCRT: Concurrent Chemoradiotherapy; P: Palliative; LI: Lymphovascular Invasion; PI: Perineural invasion; DF: Discohesive Front; CM: Close Margin (< 5 mm); EE: Extranodal Extension; OR: Overall Recurrence; OS: Overall Survival; DSS: Disease Specific Survival; LCR: Local Control Rate; RRR: Regional Recurrence Rate; DRR: Distal Recurrence Rate; NI: Node Involvement; LF: Locoregional Failure; DI: Diffuse Infiltration

The descriptive results of the characteristics and variables of each of the 6 studies included in the present systematic review are presented in Table 2 and Table 3. The studies of the included articles were conducted in the following countries: Brazil (1) , India (68,69), China (70), Spain (71), and Thailand (72).

In terms of the type of study, of the 6 articles included in this review, 3 were retrospective cohort studies (71–73), 2 were prospective cohort studies (68,69), and 1 included a retrospective section and prospective section of the study (70).

All of the 6 articles included described the carcinoma location and the degree of differentiation (68–73). Among them, only 2 expressed the tumor morphology (69,70). Within the studies reviewed, the location of the oral squamous cell carcinoma was found in the tongue, floor of the mouth, retromolar region, buccal mucosa, oropharynx, palate, gingiva, lips, and the alveolar ridge. Furthermore, some cases lacked specific details regarding the exact location of the carcinoma. Conversely, other cases provided more precise localization, specifying areas such as the upper or lower gingiva, upper or lower alveolar ridge, and the hard palate.

The degree of tumor differentiation was categorized as well-differentiated, moderately differentiated, poorly differentiated, or moderate to poorly differentiated, and some cases being undifferentiated. Additionally, certain studies mentioned carcinoma *in situ* (73) or verrucous carcinoma (69), while others had cases with an unknown degree of differentiation (72).

Tumor morphology was characterized as exophytic, endophytic, ulcerative, or infiltrative. Among the three reviews detailing tumor morphology, one also assessed the presence or absence of vascular emboli (70).

The staging of the oral cancer was described in all 6 of the articles included in this review (68–73). The studies included in this review utilized the TNM (Tumor, Node, Metastasis) and AJCC (American Joint Committee on Cancer) staging systems for the cancer staging. The authors compared the staging system according to the age groups of the patients. The perineural invasion and lymphovascular invasion were evaluated in 2 articles (69,72).

Regarding the treatment methodology, 4 studies introduced the treatment techniques implemented, comparing them according to the age group (1–4). Treatment for oral squamous cell carcinoma (OSCC) varied depending on the characteristics and severity of the cancer. Some cases could be managed with a

single modality such as surgery, radiotherapy, or chemotherapy, while others required combination therapies like surgery with radiotherapy or chemotherapy, or concurrent chemoradiotherapy. Additionally, radiotherapy combined with chemotherapy was another treatment option. Surgical approaches ranged from wide excision or wide local excision to procedures like hemi-glossectomy or neck dissection, depending on the extent of the tumor. More extensive surgeries sometimes involved free flap reconstruction or radical neck dissection, which could be modified, selective, elective, or extensive. Palliative treatments were also administered to some patients as part of their care. Moreover, the treatment approach for certain cases remained unknown.

The recurrence rate of the cancer was mentioned in four of the studies included in this review (68,70,71,73). Two of these studies mentioned the overall recurrence rate (70,73), where one of them also mentioned the recurrence according to the tumor differentiation aggressivity (73), and the other mentioned the recurrence according to age (70). In the study discussing recurrence rates based on tumor differentiation, it was indicated that further excision or neck dissection was performed for moderately and poorly differentiated oral squamous cell carcinoma. Conversely, for well-differentiated oral squamous cell carcinomas and carcinoma *in situ*, further excision was performed (73). One study evaluated the locoregional failure (71) and another study evaluated the local control rate, regional recurrence rate, and the distal recurrence rate (68).

Out of the 6 articles included in this review, 4 indicated the survival rate of the diagnosed patients (68,70–72). The overall survival was described in three studies (68,71,72) in which they were described according to the defined age groups. The disease specific survival was described in two studies according to the defined age group (68,70).

The 6 studies included in the final analysis had heterogeneous populations in terms of sample size, age range, tumor manifestations, carcinoma stage,

treatment modalities, and recurrence and survival rates. In total, 4,461 patients were diagnosed and studied regarding oral squamous cell carcinoma clinical manifestations, prognosis, and/or treatment. Of the 4,006 patients, 2,624 (65.5%) were male and 1,837 (45.9%) were female.

Regarding the age of the patients treated, there was heterogeneity according to the type of study. Two studies considered the age range of less than 45 years and more than or equal to 45 years (72,73). One study only investigated patients more than or equal to 45 years (73). Two studies investigated patients less than or equal to 40 years or more than 40 years (69,70). One investigated patients less than 40 years and more than or equal to 40 years (69).

7.3. Evaluation of methodological quality and bias risk

The Newcastle-Ottawa scale was used to measure the quality of non-randomized observational studies (37); "low risk of bias" was supposed in the case of a star score ≥6 and "high risk of bias" was supposed in the case of a star score <6. Of the 6 studies included in this review, 2 of them were considered to be at low risk of bias and the remaining 4 were considered at high risk of bias (Table 4). “Comparison of Clinicopathological Profile of Oral Squamous Cell Carcinoma between Younger and Older Indian Adults” was the item with the highest risk of bias (Table 4).

7.3.1 Representation of the bias risk

Table 4: Measurement of the risk of bias of non-randomized observational studies with the Newcastle-Ottawa scale - observational cohort studies without a control group.

	Definition of the cases	Representation of the cohort	Selection of the controls	Definition of the controls	Comparability (factor most important)	Comparability (Other factors)	Measure of results	Sufficient Follow-up	Attrition rate	Total
Ledesma-Montes C, *et*	★	-	-	-	★	★	★	★	★	6

al. (2018, Brazil)										
Subramaniam N et al. (2020, India)	★	-	★	★	-	-	★	-	★	5
Cariati P et al. (2017, Spain)	★	-	★	★	★	-	★	-	-	5
Xu QS et al. (2019, China)	★	-	-	-	★	★	★	★	-	5
Komolmalai N (2015, Thaliand)	★	★	-	★	-	★	★	-	★	6
Devadass CW et al. (2020, India)	★	★	-	-	★	-	★	-	-	4

8.4 Synthesis of results

Table 5: Oral squamous cell carcinoma clinical manifestations in patients aged less than 40-45 years

ARTICLE		LOCATION															DEGREE OF DIFFERENTIATION								TUMOR MORPHOLOGY					
	Tongue	Floor of the Mouth	Retromolar Region	Buccal Mucosa	Oropharynx	Maxilla	Palate	Gingiva	Lower Gingiva	Upper Gingiva	Hard Palate	Lip	Mouth -unspecified	Alveolar Region	Lower Alveolar	Upper Alveolar	Well Differentiation	Moderate	Poor Differentiated	Moderately-Poorly	Carcinoma *In situ*	Verrucous carcinoma	Undifferentiated	Unknown	Exophytic	Endophytic	Ulcerative	Infiltrative	Vascular Emboli	Vascular Emboli
Subramaniam N *et al*. (2020, India)	Not Specified																			62										
Cariati P et al. (2017, Spain)+A4: AD4	35	20	14	9	8	7	5	2									13	17	3											
Xu Qs et al. (2019, China) (retrospective part)	102	13		6					12	8	2						54	71	10						29		52	45	2	53
Xu QS et al. (2019, China) (prospective part)	18	1		4					2	3	3		1				6	17	2						8		9	14		
Komolmalai N et al. (2015, Thaliand)	27	2	1	2			2					1	1				18	11	5				0	2						

Devadass CW et al. (2020, India)	7		3	19											6		10	22	1			2			21	14				
Total Mean	37.8	9	6	8	8	7	3.5	2	7	5.5	2.5	1	1	0	6	0	20.2	27.6	4.2	62	0	2	0	2	19.33	14	30.5	29.5	2	53

<u>Table 6</u>: Oral squamous cell carcinoma clinical manifestations in patients aged more than or equal to 40-45 years

ARTICLE	**LOCATION**																**DEGREE OF DIFFERENTIATION**								**TUMOR MORPHOLOGY**					
	Tongue	Floor of the Mouth	Retromolar Region	Buccal Mucosa	Oropharynx	Maxilla	Palate	Gingiva	Lower Gingiva	Upper Gingiva	Hard Palate	Lip	Mouth -unspecified	Alveolar Region	Lower Alveolar	Upper Alveolar	Well Differentiation	Moderate	Poor Differentiated	Moderately-Poorly	Carcinoma *In situ*	Verrucous carcinoma	Undifferentiated	Unknown	Exophytic	Endophytic	Ulcerative	Infiltrative	Vascular Emboli	Vascular Emboli
Ledesma-Montes C, *et al*. (2018, Brazil)	60								-								9	56	22		10						-			
Subramaniam N et al. (2020, India)	Not								-											135							-			
Cariati P et al. (2017, Spain)+A4:AD4	18	5		4	3	1			1					1			8	66	26								-			

Xu Qs et al. (2019, China) (retrospective part)	920	238		369					428	236	69						1062	1057	118						845		764	554	32	696
Xu Qs et al. (2019, China) (prospective part)	119	27		70					62	19	10						64	183	6						77		112	116		
Komolmalai N (2015, Thaliand)	309	69	12	119			91	156				63	16				487	235	62				3	51						
Devadass CW et al. (2020, India)	21	2	15	79							4	2			26	3	41	101	7			3			92	60				
Total Mean	241.16	68.2	13.5	128.2	3	1	91	156	163.66	127.5	27.666	32.5	16	1	26	3	278.5	283	40.166	135	10	3	3	51	338	60	438	335	32	696

A total of 345 (6.3%) cancer localizations were identified in patients aged below 40-45 years, while 3453 (63.2%) cancer localizations were observed in patients aged 40-45 years and older. As for the remaining 1668 (30.5%) patients, it is unknown to which age range they are categorized in (68–73).

In relation to the localization of the oral squamous cell carcinoma, several studies were assessed to determine the prevalence in patients younger than 40-45 years. Subramaniam N *et al.* (68) only studied the squamous cell carcinoma located on the tongue. Cariati P *et al.* (71) observed 35 tumors on the tongue, 20 on the floor of the mouth, 14 on the retromolar region, 9 on the buccal mucosa, 8 on the oropharynx, 7 in the maxilla, 5 on the palate, and 2 on the gingiva. Xu Qs *et al.* (70) observed 102 tumors on the tongue, 13 on the floor of the mouth, 6 on the buccal mucosa, 12 on the lower gingiva, 8 on the upper gingiva, and 2 on the hard palate in the retrospective part of the study. In the prospective part of the study, Xu Qs *et al.* (70) observed 18 tumors on the tongue, 1 on the floor of the mouth, 4 on the buccal mucosa, 2 on the lower gingiva, 3 on the upper gingiva, and 3 on the hard palate. Komolmalai N *et al.* (72) identified 27 tumors on the tongue, 2 on the floor of the mouth, 1 on the retromolar region, 2 on the buccal mucosa, 2 on the palate, 1 on the lip, and 1 in an unspecified location on the mouth. Devadass CW *et al.* (69) observed 7 OSCC tumors on the tongue, 3 on the retromolar region, 19 on the buccal mucosa, and 6 in the alveolar region.

There was determined a total mean of 189 found on the tongue, 36 on the floor of the mouth, 18 in the retromolar region, 40 on the buccal mucosa, 8 in the oropharynx, 7 in the palate, 2.5 particularly on the hard palate, 2 on the gingiva, 7 particularly on the lower gingiva, 5.5 particularly on the upper gingiva, 1 on the lip, 6 on the lower alveolar region,7 on the maxilla, and 1 in an unspecified location in the mouth.

The localization of the oral squamous cell carcinoma for patients aged 40-45 years or older was analyzed in various studies included in this review (68–73). Ledesma-Montes C, *et al.* (73) exclusively examined OSCC occurrences on the

tongue, identifying 60 tumors. Similarly, Subramaniam N *et al.* (68) focused solely on tongue OSCC, but did not specify the number of tumors observed.
Cariati P *et al.* (71) reported OSCC distribution across multiple oral sites, including 18 tumors on the tongue, 5 on the floor of the mouth, 4 on the buccal mucosa, 3 in the oropharynx, 1 in the maxilla, 1 on the lower gingiva, and 1 in the alveolar region. Xu Qs *et al.* (70) conducted a retrospective study identifying 920 tongue tumors, 238 floor of mouth tumors, 369 buccal mucosa tumors, 428 lower gingiva tumors, 236 upper gingiva tumors, and 69 hard palate tumors. In the prospective part of their study, Xu Qs *et al.* (70) observed 119 tongue tumors, 27 floor of mouth tumors, 70 buccal mucosa tumors, 62 lower gingiva tumors, 19 upper gingiva tumors, and 10 hard palate tumors.

Komolmalai N *et al.* (72) identified OSCC occurrences in various oral regions, with 309 tumors on the tongue, 69 on the floor of the mouth, 12 in the retromolar region, 119 on the buccal mucosa, 91 on the palate, 156 on the gingiva, 63 on the lip, and 16 in unspecified oral locations. Additionally, Devadass CW *et al.* (69) reported OSCC occurrences, including 21 on the tongue, 2 on the floor of the mouth, 15 in the retromolar region, 79 on the buccal mucosa, 4 on the hard palate, 2 on the lip, 26 on the lower alveolar region, and 3 on the upper alveolar region. The distribution of the total mean for OSCC across various oral sites was as follows: 241.16 on the tongue, 68.2 on the floor of the mouth, 13.5 in the retromolar region, 128.2 on the buccal mucosa, 3 in the oropharynx, 81 on the palate, and 27.7 specifically on the hard palate. Additionally, there was a total mean of 1 on the alveolar ridge, 26 specifically on the lower alveolar ridge, and 3 on the upper alveolar ridge. The observed total mean in the gingiva was determined as 156, with 163.7 on the lower gingiva and 127.5 on the upper gingiva. Moreover, there was a total mean of 32.5 on the lip, 1 in the maxilla region without specific localization, and 16 mentioned to be located in the oral cavity without further specification.

In terms of the degree of tumor differentiation, among the evaluated cases, 6.7% corresponded to patients younger than 40-45 years, 78.9% corresponded to

patients aged 40-45 years or older, and 14.3% corresponded to patients whose age range was not specifically categorized.

Several studies investigated the differentiation status of oral squamous cell carcinoma (OSCC) tumors in patients younger than 40-45 years (68–73). Subramaniam N *et al.* (69) classified 62 tumors as moderately-poorly differentiated. Cariati P *et al.* (72) observed 13 well differentiated, 17 moderately differentiated, and 3 poor differentiated oral squamous cell carcinoma tumors. In the retrospective part of the study by Xu Qs *et al.* (71) there were 54 well differentiated, 71 moderate differentiated, and 10 poorly differentiated oral squamous cell carcinoma tumors identified. In the prospective part of the study by Xu Qs *et al.* (71) there was 6 well differentiated, 17 moderately differentiated and 2 poorly differentiated oral squamous cell carcinoma tumors. Komolmalai N *et al.* (73) identified 18 well differentiated, 11 moderate differentiated, and 5 poor differentiated oral squamous cell carcinoma while Devadass CW *et al.* (70) reported 10 well-differentiated, 22 moderately differentiated, and 1 poorly differentiated OSCC tumors.

The overall data included a total mean of 20.2 well-differentiated oral squamous cell carcinoma (OSCC) cases, 27.6 moderately differentiated OSCC cases, and 4.2 poorly differentiated OSCC cases. Additionally, there was a total mean of 62 cases classified as moderately to poorly differentiated OSCC. Moreover, there was a total mean of 2 for the cases diagnosed as verrucous carcinoma and a total mean of 2 had an unknown differentiation status.

When assessing the degree of tumor differentiation in patients aged 40-45 years or older, Ledesma-Montes C, *et al.* (68) identified 9 well differentiated, 56 moderately differentiated, 22 poorly differentiated OSCC tumors, and 10 were diagnosed as carcinoma insitu. Cariati P *et al.* (72) observed 8 well differentiated, 66 moderately differentiated, and 26 poor differentiated oral squamous cell carcinoma tumors. In the retrospective part of the study by Xu Qs *et al.* (71) there were 1062 well differentiated, 1057 moderate differentiated, and 118 poorly differentiated oral squamous cell carcinoma tumors identified. In the prospective

part of the study by Xu Qs *et al.* (71) there was 64 well differentiated, 183 moderately differentiated and 6 poorly differentiated oral squamous cell carcinoma tumors. Komolmalai N *et al.* (73) reported 487 well differentiated, 235 moderate differentiated, and 62 poor differentiated oral squamous cell carcinoma. Devadass CW *et al.* (70) identified 41 well differentiated, 101 moderately differentiated, and 71 poorly differentiated oral squamous cell carcinoma.

The data revealed a total mean of 278.5 well differentiated oral squamous cell carcinoma cases, and a total mean of 283 for the moderately differentiated cases, and 40.1 poorly differentiated, 135 moderately poor differentiated, and 3 undifferentiated. Moreover, a total mean of 10 was observed for the cases diagnosed as carcinoma insitu and 3 for the cases diagnosed as verrucous carcinoma. The cases with an unknown differentiation status had a total mean of 51.

Among the studies included in this review, only two addressed tumor morphology (70,71). Regarding tumor morphology in patients younger than 40-45 years, by Xu Qs *et al.* (71) contributed to identify morphological characteristics in their retrospective and prospective studies. In the retrospective part of the study, they noted 29 exophytic tumors, 52 ulcerative, 45 infiltrative, and 2 with a vascular emboli. In the prospective part they noted 8 exophytic tumors, 9 ulcerative, and 14 infiltrative. Devadass CW *et al.* (70) identified 21 exophytic tumors and 14 endophytic tumors. There was a total mean of 19.3 for the cases with an exophytic appearance, 14 for the cases with an endophytic appearance. Moreover, a total mean of 30.5 presented ulcerative characteristic, 29.5 presented infiltrative appearance. A total mean of 2 was determined for the cases that encompassed a vascular embolus.

Among patients aged 40-45 years or older, the retrospective part of the study by Xu Qs *et al.* (71) identified 845 exophytic tumors, 764 ulcerative, 554 infiltrative, and 32 tumors with a vascular embolus present. Devadass CW *et al.* (70) recognised 92 exophytic tumors and 60 endophytic tumors. The total mean was 383 for the cases with exophytic appearance and 60 for the cases with

endophytic appearance. A total mean of 483 was determined for the cases with ulcerative features and 335 for the cases exhibiting infiltrative characteristics. The total mean for the cases with a vascular embolus was 32.

Table 7: Oral squamous cell carcinoma treatment and prognosis in patients aged less than 40-45 years

ARTICLE	TREATMENT											RECURRENCE RATE					SURVIVAL RATE	
	Surgery	Surgery + Radiotherapy	Concurrent chemoradiotherapy	Surgery + Concurrent Chemoradiotherapy	Radiotherapy	Chemotherapy	Surgery + Radiotherapy + Chemotherapy	Surgery + Chemotherapy	Radiotherapy + Chemotherapy	Palliative	unknown	Overall recurrence	Local Control Rate	Regional Recurrence Rate (%)	Distal Recurrence Rate (%)	Local Failure (%)	Overall Survival Rate (%)	Disease Specific Survival Rate (%)
Subramaniam N et al. (2020, India)	51	11	0	52									65	5	13		65	67
Cariati P et al. (2017, Spain)																45	48	
Xu QS et al. (2019, China) Retrospective part	55	47		13								38.20						77.20
Xu QS et al. (2019, China) Prospective part	19	12		0								0%						100
Komolmalai N et al. (2015, Thailand)	1	12			9	1	2	0	6	2	3						56.20	
Total Mean	31.5	20.5	0	21.67	9	1	2	0	6	2	3	19.10	65	5	13	45	56.40	81.40

Table 8: Oral squamous cell carcinoma treatment and prognosis in patients aged more than or equal to 40-45 years

ARTICLE	TREATMENT											RECURRENCE RATE					SURVIVAL RATE	
	Surgery	Surgery + Radiotherapy	Concurrent chemoradiotherapy	Surgery + Concurrent Chemoradiotherapy	Radiotherapy	Chemotherapy	Surgery + Radiotherapy + Chemotherapy	Surgery + Chemotherapy	Radiotherapy + Chemotherapy	Palliative	unknown	Overall recurrence (%)	5-year recurrence rate	Regional Recurrence Rate (%)	Distal Recurrence Rate	Local Failure (%)	Overall Survival Rate (%)	Disease Specific Survival Rate (%)
Ledesma-Montes C, et al. (2018, Brazil)	Not Specified											15						
Subramaniam N et al. (2020, India)	161	41	109	0									78	11	9		71	74
Cariati P et al. (2017, Spain)																34	62	
Xu QS et al. (2019, China) Retrospective Part	1021	495	136						0			47.20						68.50
Xu QS et al. (2019, China) Prospective Part	224	77	7									14						85.40

Komolmalai N (2015, Thaliand)	119	156		26	242	26	0	7	58	108	96						27.40	
Total Mean	381.25	192.25	84	13	242	26	0	7	58	108	96	25.40	78	11	9	34	53.50	76

The review encompassed various treatment modalities for oral squamous cell carcinoma (OSCC), including surgery, radiotherapy, chemotherapy, palliative care, or a combination thereof. Notably, Cariati P *et al.* (72) did not provide insights into treatment methods.

When examining treatment approaches for patients under 40-45 years, Subramaniam N *et al.* (69) investigated surgical interventions in 51 cases of OSCC, a combination of surgery and radiotherapy in 11 cases, and surgery combined with concurrent chemotherapy in 52 cases. In the retrospective segment of Xu QS e*t al.'s* (71) study, 55 cases underwent surgical treatment, 47 received a combination of surgery and radiotherapy, and 13 received surgery with concurrent chemoradiotherapy. In the prospective segment of the same study, 19 cases underwent surgical procedures, while 12 received surgery combined with radiotherapy.

Komolmalai N *et al.'s* (73) research included various treatment modalities: 1 case underwent surgery, 12 received surgical and radiotherapeutic interventions, 9 underwent radiotherapy alone, 1 received chemotherapy, 2 received a combination of surgery, chemotherapy, and radiotherapy, 6 received radiotherapy and chemotherapy, 2 received palliative care, and 3 cases had unspecified treatments.

For patients under 40-45 years, the total mean number of cases treated surgically was 31.5, 20.5 received a combination of surgery and radiotherapy, 21.7 underwent surgery with concurrent chemoradiotherapy, 9 received radiotherapy alone, 1 underwent chemotherapy, 2 received a combination of surgery, chemotherapy, and radiotherapy, 6 received radiotherapy and chemotherapy, and 2 received palliative care. Additionally, there was a total of 3 cases with unspecified treatments.

When assessing treatment strategies for patients aged 40-45 years or older, Ledesma-Montes C, *et al.* (68) mentioned surgical intervention and a combination of surgery and radiotherapy without specifying the exact numbers. In contrast, Subramaniam N *et al.* (69) investigated surgical treatment in 161 cases of OSCC, a combination of surgery and radiotherapy in 41 cases, and surgery with

concurrent chemotherapy in 109 cases. However, Cariati P *et al.* (72) did not provide information regarding treatment methods.

In the retrospective segment of Xu QS et *al.'s* (71) study, 1021 cases underwent surgical treatment, 495 received a combination of surgery and radiotherapy, and 136 received surgery with concurrent chemoradiotherapy. In the prospective part, 224 cases underwent surgical procedures, 77 received surgery combined with radiotherapy, and 7 received concurrent chemoradiotherapy.

Komolmalai N *et al.*'s (73) study encompassed various treatment modalities, including 119 cases of surgical treatment, 156 cases of surgical and radiotherapeutic interventions, 26 cases of surgery with concurrent chemoradiotherapy, 242 cases of radiotherapy, 26 cases of chemotherapy, 7 cases of surgery combined with chemotherapy, 58 cases of radiotherapy combined with chemotherapy, 108 cases of palliative care, and 96 cases where treatment specifics were unspecified.

For patients aged under 40-45 years, the total mean number of cases undergoing surgical treatment was 119, 156 cases received a combination of surgery and radiotherapy, 84 cases underwent surgery with concurrent chemoradiotherapy, 242 cases received radiotherapy alone, 26 cases received chemotherapy, 7 cases underwent a combination of surgery and chemotherapy, 58 cases received radiotherapy combined with chemotherapy, and 108 cases received palliative care. Additionally, there was a total mean of 96 cases where treatment details were unspecified.

When examining recurrence rates and survival outcomes among patients aged 40-45 years or younger, Subramianiam N *et al.* (69) reported a 65% local control rate, 5% regional recurrence rate, 13% distal recurrence rate, 65% overall survival rate, and 67% disease-specific survival rate. Cariati P *et al.* (72) found a 45% local failure rate and 48% overall survival rate. Xu QS *et al.* (71) documented an overall recurrence rate of 38.2% in the retrospective phase and 0% in the prospective phase of the study. Disease-specific survival rates were 77.2% in the retrospective phase and 100% in the prospective phase. Komolmalai N *et al.* (73)

identified a 56.2% overall survival rate. The data for the total mean is 19.1% overall recurrence, 65% local control rate, 5% regional recurrence rate, 13% distal recurrence rate, 45% local failure, 56.4% overall survival rate, 81.4% disease specific survival rate.

When considering recurrence rates and survival outcomes in patients aged 40-45 years or older, Ledesma-Montes C, *et al.* (68) reported a 15% overall recurrence rate. Subramianiam N *et al.* (69) documented a 78% local control rate, 11% regional recurrence rate, 9% distal recurrence rate, 71% overall survival rate, and 74% disease-specific survival rate. Cariati P *et al.* (72) identified a 34% local failure rate and 62% overall survival rate. Xu QS *et al.* (71) determined an overall recurrence rate of 47.2% in the retrospective phase and 14% in the prospective phase, with disease-specific survival rates of 68.5% and 85.4% respectively. While Komolmalai N *et al.* (73) did not assess the recurrence rate, they reported a 27.4% overall survival rate.

The total mean data indicates an overall recurrence rate of 25.4%, a 78% local control rate, 11% regional recurrence rate, 9% distal recurrence rate, 34% local failure rate, 53.5% overall survival rate, and 76% disease-specific survival rate.

8. DISCUSSION

The present literature review provides evidence-based information on the clinical manifestations, treatment, and prognosis of oral squamous cell carcinoma in old patients in comparison to young patients.

The aim of this review was to evaluate the prognosis by measuring recurrence rate (%) and survival rate (%) for oral squamous cell carcinoma in old patients in comparison with young patients during a follow-up time of 2, 5, or 10 years; and secondarily to study and compare the clinical manifestations and treatment for the disease in older and younger patients (location, degree of differentiation, tumor morphology, tumor stage).

8.1. Clinical Manifestation

8.1.1. Location

The distribution and prevalence of oral squamous cell carcinoma (OSCC) in patients of different age groups reveal notable trends and patterns.

Among patients younger than 40-45 years, the occurrence of OSCC tumors is relatively lower compared to older age groups, as evidenced by the finding that only 6.3% of cancer localizations were identified in this demographic. However, the specific localization of OSCC tumors in this age group varies across studies. While some studies, such as that by Subramaniam N *et al.* (69), focused solely on OSCC tumors located on the tongue without specifying the number, others like Cariati P *et al.* (72) and Xu Qs *et al.* (71) reported OSCC occurrences across multiple oral sites, including the tongue, floor of the mouth, buccal mucosa, and gingiva. The total mean distribution of OSCC tumors in this age group underscores the diversity of its localization, with the tongue being the most prevalent site followed by the buccal mucosa, floor of the mouth, and other regions.

Conversely, in patients aged 40-45 years and older, the prevalence of OSCC tumors is significantly higher, constituting 63.2% of cancer localizations. Studies in this age group primarily focus on OSCC tumors located on the tongue, with Ledesma-Montes C, *et al.* (68) and Subramaniam N *et al.* (69) specifically examining OSCC occurrences in this region. The distribution of OSCC tumors across various oral sites, as reported by studies like Cariati P *et al.* (72) and Xu Qs *et al.* (71), highlights the widespread nature of this malignancy in older patients. The total mean distribution further elucidates the predominance of OSCC tumors in specific oral regions, with the tongue and buccal mucosa being the most prevalent sites.

Overall, the findings underscore the importance of age in understanding the localization and prevalence of OSCC tumors. While younger patients may exhibit a lower overall occurrence of OSCC, the distribution of tumors across various oral sites underscores the need for comprehensive screening and diagnostic protocols.

Conversely, older patients are more likely to present with OSCC tumors, particularly in regions such as the tongue and buccal mucosa, emphasizing the importance of age-specific management strategies and interventions.

In our study, we found that the tongue was the most common site of oral squamous cell carcinoma (OSCC) in both younger and older age groups, which aligns with several other relevant studies.

C.D Llewellyn *et al.* (74) conducted a descriptive analysis consisting of patients younger than 45 years in which a similar trend was observed with majority of the OSCC tumors localized in the tongue, followed by unspecified tongue locations, the oropharynx, and the lip.

Rafael Ferreira e Costa *et al.* (75) who evaluated patients younger than 40 years, Saja Alramadhan *et al.* (76) who evaluated patients younger than 30 years and Lipa Bodner *et al.* (52) who evaluated patients under the age of 20 years, all identified the tongue as the primary site affected by OSCC.

Khadijah Mohideen *et al.* (77) also determined the most predominant location for the oral squamous cell carcinoma to be the tongue having the average percentage of the tongue lesions as 72% in the young group, and 64% in the older group.

Reshma Poothakulath Krishnan *et al.* (78) also determined the tongue as the most common location in both age groups being 27.14% in the old patient group and 33.82% in the young patient group.

As for Samuel E Udeabor *et al.* (79), the floor of the mouth was the commonest site of tumour occurrence both in the general population and in patients less than 40 years of age. This accounted for 42.2% in the general patient population and 39.5% in the group less than 40 years. Only in 1.3% of the overall patient population was the tumour located in the oropharynx and none was found in the oropharynx of the young patient group.

Abdulla R *et al.* (80), found that, tongue (29%) followed by buccal mucosa (27.9%) and alveolus (13.9%) were the common sites in the young in contrast to older patients where buccal mucosa (32.1%) followed by alveolus (16.4%) and tongue (16.1%) were the common sites (80).

Acharya S *et al.* (81) reported buccal mucosa (47%), alveolar process (24%) and tongue and floor of mouth (23%) as the major sites in younger patients and alveolar process (42%), buccal mucosa (37%) and tongue and floor of mouth (14%) as major sites in older patients.

Most of the other studies conducted determined the same results as this study. These comparative insights underscore the importance of considering age-specific variations when assessing OSCC localization patterns. The consistent identification of the tongue as a primary site underscores its importance in OSCC pathology, while variations across other sites highlight the complex nature of this malignancy.

8.1.2. Tumor Differentiation

The degree of tumor differentiation is a critical factor in understanding the aggressiveness and prognosis of oral squamous cell carcinoma (OSCC). Our analysis revealed significant variations in tumor differentiation status across different age groups, shedding light on potential age-related factors influencing OSCC development and progression.

In patients younger than 40-45 years, the proportion of well-differentiated tumors was notably lower compared to older age groups. Studies by Subramaniam N *et al.* (69), Cariati P *et al.* (72), Xu Qs *et al.* (71), Komolmalai N *et al.* (73), and Devadass CW *et al.* (70) highlighted a spectrum of tumor differentiation statuses, ranging from well-differentiated to poorly differentiated OSCC tumors.

The total mean distribution indicated a predominance of moderately differentiated cases, followed by well-differentiated and poorly differentiated cases. Interestingly, cases with an unknown differentiation status were also observed, suggesting potential challenges in accurately characterizing tumor histology in this age group.

In patients aged 40-45 years or older, there was a higher prevalence of moderately and poorly differentiated OSCC tumors. Ledesma-Montes C, *et al.* (68), Cariati P *et al*. (72), Xu Qs *et al.* (71), Komolmalai N *et al.* (73), and Devadass CW

et al. (70) reported varying degrees of tumor differentiation, with the majority of cases classified as moderately differentiated.

The total mean distribution revealed a higher proportion of moderately differentiated cases compared to well-differentiated and poorly differentiated cases. Notably, cases diagnosed as carcinoma in situ and verrucous carcinoma were also identified, albeit in smaller numbers.

Overall, our findings underscore the complex interplay between age and tumor differentiation in OSCC. While younger patients may exhibit a diverse range of tumor differentiation statuses, older patients are more likely to present with moderately and poorly differentiated tumors, reflecting potential age-related factors influencing tumor biology.

In comparison to other relevant studies, *E M O'Regan et al.* (82), *Silvio K Hirota et al.* (83), and *Samuel E Udeabor et al.* (79) observed that well-differentiated tumors were relatively more prevalent in the younger age group. On the contrary, Ferreira e Costa *et al.* (75) observed higher prevalence of moderate-differentiated tumors in the young age group, aligning with our results.

For patients older than 45 years, our results coincide with those from *Ramdass et al.* (84) demonstrating a higher prevalence of moderately differentiated tumors. This differs from the studies by *Hakeem et al.* (85), *M Selvamani et al.* (86), Chuanzheng Sun *et al.* (87), and P Loganathan *et al.* (88) who demonstrate well differentiated tumors as most common, followed by moderately differentiated tumors. Studies by *Mohideen et al.* (77), *Rosenquist* (89), *Shou Yen Kao* (90), and *Soerjomataram et al.* (91) are consistent with our findings, revealing a higher prevalence of moderately differentiated cases in both age groups. Conversely, *Poothakulath Krishnan et al.* (78) observed higher prevalence of well differentiated oral squamous cell carcinoma tumors in both young and old patients.

8.1.3. Tumor Morphology

The assessment of tumor morphology provides crucial insights into the characteristics and behavior of oral squamous cell carcinoma (OSCC). In our review, limited studies specifically addressed tumor morphology, highlighting the

need for further investigation in this area. Notably, Xu Qs *et al.* (71) and Devadass CW *et al.* (70) contributed valuable data regarding tumor morphology in patients across different age groups.

In patients younger than 40-45 years, Xu Qs *et al.* (71) conducted both retrospective and prospective studies to identify morphological characteristics of OSCC tumors. The retrospective analysis revealed a predominance of exophytic and ulcerative tumors, with lesser occurrences of infiltrative morphology. Conversely, the prospective study showed a shift towards a more infiltrative pattern. This observation suggests potential changes in tumor morphology over time or differences in tumor presentation at initial diagnosis versus disease progression. Additionally, Devadass CW *et al.* (71) identified a notable proportion of exophytic tumors in this age group, highlighting the diverse morphological spectrum of OSCC in younger patients.

In contrast, among patients aged 40-45 years or older, Xu Qs *et al.* (71) observed a higher prevalence of exophytic, ulcerative, and infiltrative tumors, consistent with the findings in younger patients. However, the retrospective analysis identified a greater number of exophytic tumors compared to the prospective study, indicating potential variations in tumor morphology over time or differences in study populations. Moreover, Devadass CW *et al.* (70) noted a significant presence of exophytic tumors in older patients, suggesting a persistent pattern across different age groups.

The presence of tumors with a vascular embolus, albeit less frequent, underscores the importance of assessing invasive characteristics that may influence disease progression and treatment outcomes. While the total mean for cases with a vascular embolus was relatively low in both age groups, further investigation into its implications on tumor behavior and patient prognosis is warranted.

Overall, the findings from our review emphasize the heterogeneity of OSCC morphology across different age groups. Understanding these morphological variations is crucial for accurate diagnosis, treatment planning, and prognostic assessment in OSCC patients. The molecular and clinical correlates of tumor

morphology may provide valuable insights into disease pathogenesis and guide personalized therapeutic approaches.

This study detected predominant exophytic morphology in both age groups with is in concordance with the study by Acharya Swetha *et al.* (81). Kuriakose *et al.* (92) observed that lesions in young patients exhibited a predominantly invasive nature compared to the exophytic lesions commonly found in older patients. This implies a potential distinction in the biological behavior of oral squamous cell carcinoma (OSCC) between different age groups. Acharya swetha *et al.* (81) also observed a higher value of endophytic tumors in young patients compared to older patients. This difference might indicate a higher propensity for lymph node metastasis and a less favorable response to treatment in young patients. Generally, the presence of cervical lymph node metastasis in OSCC signifies a poorer prognosis (93).

Poothakulath Krishnan et al. (78) did not note significant difference in the amount of lymphoplamacytic infiltrate between the two age groups contradicting our findings in which older patients contributed higher prevalence of infiltrative features.

8.2. Treatment

In this study, we analyzed various treatment modalities employed for managing oral squamous cell carcinoma (OSCC), encompassing surgery, radiotherapy, chemotherapy, and palliative care, either individually or in combination. Notably, some studies did not provide comprehensive insights into treatment methods.

When exploring treatment approaches for patients under the age of 40-45 years, Subramaniam N *et al.* (69) and Xu QS *et al.* (71) primarily investigated surgical interventions, often combined with radiotherapy or chemotherapy. Komolmalai N *et al.* (73) examined a broader spectrum of treatment modalities, including surgery, radiotherapy, chemotherapy, and palliative care. The distribution of treatment modalities varied among studies, with surgical intervention being a

common approach. However, there were differences in the utilization of adjuvant therapies such as radiotherapy and chemotherapy.

For patients aged 40-45 years or older, similar trends were observed, with surgical intervention being the primary treatment modality. Subramaniam N *et al.* (69) and Xu QS *et al.* (71) also reported a significant utilization of adjuvant therapies in this age group, including radiotherapy and chemotherapy. Komolmalai N *et al.* (73) again provided a comprehensive overview of various treatment modalities, reflecting a diverse approach to managing OSCC in older patients. Overall, the findings suggest that while surgical intervention remains a cornerstone in OSCC treatment across age groups, the utilization of adjuvant therapies may vary, potentially reflecting differences in disease severity, patient preferences, or institutional practices.

Within the studies included in this review, surgical treatments were the most common method used to treat oral squamous cell carcinoma in the younger and older group of patients. Xu Qs *et al.* (71) suggested that a patients poor general condition tends to limit the operation time, the selection of free-flap treatments, postoperative recovery and most importantly the selection of adjuvant therapy. This was observed in the studies done by Linsen *et al.* (46) and Liu *et al.* (21) who reported a significantly lower ratio of elder patients at an advanced age receiving radiotherapy. This may be one of the key reasons to a worse outcome and poor prognosis for elderly patients.

Udeabor *et al.* (79) investigated a cohort of patients aged 40 years and younger, finding surgical treatments to be the preferred approach in 68.4% of cases. Additionally, a combination of surgery with chemotherapy and/or radiotherapy was utilized in 23.7% of patients, while 7.9% received chemotherapy plus radiotherapy alone. Our findings align with this pattern, showing surgery to be the predominant treatment modality in our study as well.

8.3. Prognosis

When comparing the recurrence rates and survival outcomes between the two age groups, several notable differences emerge. Firstly, in patients aged 40-45 years or younger, Subramaniam N *et al.* (69) reported relatively higher local control rates but also exhibited substantial overall recurrence rates. Conversely, in the older age group (40-45 years or older), while Ledesma-Montes C, *et al.* (68) reported a lower overall recurrence rate, the local control rates were slightly lower compared to the younger cohort. This suggests that younger patients may experience more aggressive disease behavior necessitating more intensive local control measures, whereas older patients may have a lower risk of disease recurrence but may still face challenges in achieving optimal local control.

Furthermore, in terms of survival outcomes, younger patients generally demonstrated higher overall and disease-specific survival rates compared to older patients. This is evident from studies such as Subramaniam N *et al.* (69) and Xu QS *et al.* (71) where younger patients exhibited overall survival rates ranging from 56.4% to 65%, whereas older patients showed overall survival rates ranging from 53.5% to 71%. Similarly, disease-specific survival rates were also notably higher in the younger age group, indicating potentially better responses to treatment and a lower risk of disease-related mortality.

These differences in recurrence rates and survival outcomes between age groups underscore the importance of age as a prognostic factor in OSCC. Factors such as tumor biology, treatment response, and overall health status may vary between younger and older patients, influencing disease outcomes and treatment strategies. Therefore, a tailored approach to disease management, taking into account age-related factors, is crucial for optimizing treatment efficacy and improving patient outcomes in OSCC.

Sanabria *et al.* (94) reported that the substandard treatment decreased overall patient survival which is observed in treatment methodology selection in elderly patients. Moreover, Chen *et al.* (95) noted the improved overall survival of elderly patients with aggressive treatments with a curative intent. This is consistent with the study by Xu *et al.* (71) in which it was stated that the outcome of OSCC patients may be impaired according to inadequate treatment selection. Based on

this information, conjunctive and adjuvant therapy should be suggested to patients when appropriate despite the age and the age must not be used to determine the treatment. This was also concluded by Derks *et al.* (96) who discovered that even if younger and older patients had the same co-morbidity score, the patients aged older than 70 years are at a higher probability of receiving substandard treatment which would worsen their prognosis.

Our study detected a better prognosis for younger patients with a greater overall survival rate and disease specific survival rate. This was consistent with the results of other literature including that of Pytynia *et al*. (97), Ho *et al.* (98), and Udeabor *et al.* (79). This finding is also in agreement with those from studies by Warnakulasuriya *et al.* (74), and Fan *et al.* (99) who reported better outcome for younger patients.

8.4. Limitations

The present review included a limited number of studies meeting the final inclusion studies despite the extensive initial search yielding 210 articles. There were initially 10 included articles within this study in which 4 were further excluded due to the lack of data separation according to age range. This limited pool of studies may not fully represent the breadth of available evidence on the topic. The included search lacked randomized comparative clinical studies and only included cohort studies in which most were of a retrospective nature meaning the absence of pre-study data collection which may affect the result accuracy.

The risk of bias included in the studies was assessed with the Newcastle-Ottawa scale to detect the quality of the non-randomized observational studies where some of these studies deemed to be at high risk of bias which may influence the reliability and validity of the results.

Furthermore, this review may have encompassed language bias as only English reviews were considered. For this reason, certain valuable studies in other languages such as Spanish may have been neglected.

Certain studies lacked essential information such as having an unknown location of the oral squamous cell carcinoma, unknown grade of differentiation or a

unknown treatment which may greatly influence and alter our results and carries a greater risk of imprecision.

Furthermore, the studies included in this systematic review varied greatly in terms of population, characteristics, interventions, and outcomes leading to heterogeneity in the data. This made it challenging to pool results and draw meaningful conclusions for our evaluated objectives.

Although the results heterogenous, they still remain representative, however, they should be interpreted with this factor in mind. The sample size for the group of patients aged 40-45 years or older included in this study surpassed the sample size of patients aged younger than 40-45 years. This may limit the adequate data necessary to achieve solid conclusions. On the whole, this review covered provided reliable and adequate results which have been supported by various literature with the same outcomes.

9. CONCLUSION

Primary Conclusion

1. Older patients exhibited a worse prognosis for oral squamous cell carcinoma compared to younger patients. Younger patients demonstrated better degree of overall survival rate and disease specific survival rate. Although, younger patients did reveal a lower local control rate they had a lower overall recurrence rate compared to older patients.

Secondary Conclusions

2. Older and younger patients exhibited similar clinical manifestations for oral squamous cell carcinoma. The tongue was the most common site of oral squamous cell carcinoma in both younger and older age groups. Moderately differentiated tumors were more prevalent among younger and older patients. The most predominant morphology in both age groups was exophytic tumors.

3. The most common methodology performed to treat oral squamous cell carcinoma for the older and younger age groups was surgical procedures which portrayed better prognostic outcomes.

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ANEX

Prisma 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Home Page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1,3,4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	8-19
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	24
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	26, 27
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	27, 28
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	27, 28
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	29
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	29, 30
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	29, 30
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	30
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	30

Section and Topic	Item #	Checklist item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	26,27
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	26,27
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	29
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	29,30
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	29,30
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	30
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	30
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	30
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	31
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	33,34
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	34-38
Study characteristics	17	Cite each included study and present its characteristics.	38-47
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	50,51
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	52-54, 60-62
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	55-59, 63-65
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	55-59, 63-65
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	47-50

COMPARING ORAL SQUAMOUS CELL CARCINOMA IN YOUNG VS OLD PATIENTS: CLINICAL FEATURES, TREATMENT, AND PROGNOSIS: A Systematic Review

Running Title: Oral Squamous Cell Carcinoma: Prognosis, Treatment, and Clinical Manifestations

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ABSTRACT

Introduction: The prognosis of oral squamous cell carcinoma (OSCC) is influenced by various factors including tumor location, tumor stage, differentiation, treatment approach. These factors may differ according to the age of the patient where younger patients may exhibit different aspects compared to older patients. The aim of this systematic review was to compare oral squamous cell carcinoma in young (<40-45 years) and old patients (≥ 40-45 years) regarding prognosis, clinical manifestation, and treatment methodology.

Materials and methods: An electronic search of Medline-PubMed, Web of Science, Scopus, and Lilacs databases was conducted to find indexed articles regarding the clinical characteristics, treatment methodology, and prognosis of OSCC in young (<40-45 years) and old (≥ 40-45 years) from the last 10 years (2014).

Results: From the 210 potentially eligible articles, 6 met the inclusion criteria. In the group of young patients, the recurrence rate was 19.10%, the regional recurrence rate was 5%, the distal recurrence rate 13%, the local control rate was 65%, and local failure was 45%. As for the survival rate it was 56.4% and the disease specific survival rate was 81.4%. In the group of old patients, the overall recurrence rate was 25.40%, the regional recurrence rate was 11%, the distal recurrence rate 9%, the local control rate was 78%, and local failure was 34%. As for the survival rate it was 53.50% and the disease specific survival rate was 76%.

Conclusion: Older patients exhibited a worse prognosis for OSCC compared to younger patients. Although younger patients revealed a lower local control rate, they had a lower overall recurrence rate and better degree of overall survival rate and disease specific survival rate compared to older patients.

Keywords: “Old patients”, “Oral squamous cell carcinoma”, “Young patients”, “Clinical manifestations”, “Clinical characteristics”, “Prognosis”, “Treatment”, “Treatment methodology”

INTRODUCTION:

Oral squamous cell carcinoma (OSCC) is a prevalent form of oral cancer globally, with tobacco, alcohol, and betel nut use as major risk factors. While historically seen in older adults, there's been a concerning rise in its incidence among young adults (1). Despite therapeutic advancements, morbidity and mortality rates have remained stagnant (2). Early detection is crucial for improving prognosis. OSCC commonly affects the tongue, lips, and floor of the mouth due to their susceptibility to carcinogens (3).

Oral squamous cell carcinoma typically presents as ulcers with necrotic centers or as lumps with ill-defined borders (2), resembling potentially malignant disorders such as leukoplakia or erythroplakia (3). Lesions range from millimeters to several centimeters, with lymph node enlargement indicating advanced disease (4).

The challenges and treatments for oral squamous cell carcinoma (OSCC) are outlined, emphasizing the importance of early detection and prevention (5). Treatment options include surgery, radiotherapy, and chemotherapy, tailored to disease stage and patient needs (6).

High mortality rates in oral squamous cell carcinoma (OSCC) are often due to late diagnosis, with incidence rising in Europe over the past decade (1)Prognosis is influenced by age, sex, tumor characteristics, and treatment modality, with lymph node involvement and tumor thickness playing significant roles. Surgery shows higher survival rates, especially in early-stage cancer (4).

The goal of this review is to compare oral squamous cell carcinoma in young and old patients regarding the clinical manifestations, treatment and prognosis. This supports achieving Sustainable Development Goal 3. Awareness of clinical manifestations in young patients aids early detection, mitigating potential misattributions. Treatment choice and intensity differs according to patient’s age. Certain therapeutic approaches may be difficult for younger individuals to tolerate or may implicate adverse effects on older patients with underlying health issues. Age-related factors must be understood to determine the most favorable treatment plan, optimizing efficacy while minimizing potential side effects and complications. It can also help develop targeted public health strategies: educational campaigns, screening programs, and awareness initiatives tailored to the demographics most at risk.

OBJECTIVES

Principle Objective: Evaluate the comparison of prognosis in younger and older patients with oral squamous cell carcinoma.

Secondary Objectives:

- Compare the clinical features in younger and older patients with oral squamous cell carcinoma.

- Evaluate the treatment of oral squamous cell carcinoma in younger and older patients.

MATERIALS AND METHODS:

This systematic review complies with the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (7).

Focus question:

The focus question was established according to the PICO structured question:

P (population): Older patients (≥ 40-45 years).

I (intervention): Oral squamous cell Carcinoma.

C (comparison): Younger patients (<40-45 years).

O (outcomes): Clinical manifestations, treatment, and prognosis.

- O1: Compare the prognosis in younger and older patients
- O2: Compare the clinical features in younger and older patients
- O3: Compare the treatment in younger and older patients

Eligibility criteria:

The inclusion criteria consists of:

• **Study design:** Clinical trials and randomized controlled trials, prospective and retrospective cohort studies, case series; publication in English, from the last 10 years (2014-2024).

• **Patient:** Young patients (<40-45 years) and old patients (≥ 40-45 years).

• **Intervention:** Oral squamous cell carcinoma.

• **Outcomes:** Studies that include data related to the prognosis of oral squamous cell carcinoma in older and younger patients. As secondary variables, studies that include

data related to the clinical manifestations and treatment of oral squamous cell carcinoma in older and younger patients.

The exclusion criteria consists of: Systemic reviews, meta-analysis, letters or comments to the editor, expert reports, in vitro and animal experimental studies. Moreover, the studies published in languages other than English, the studies published earlier than year 2014, the studies that did not distinguish between our two age ranges (<40-45 and (≥ 40-45), as well as studies that did not evaluate the clinical characteristics, treatment, or prognosis of oral squamous cell carcinoma in young or old population.

Information sources and data search:

An automatized electronic and manual literature searches were conducted in four major electronic databases (PubMed, Scopus, Web of Science, and Lilacs) with the following keywords: “adults”, “elderly“, "old patients", "oral squamous cell carcinoma", "oral squamous cell carcinomas“, "oral cavity squamous cell carcinoma", "young patients“, “young adult”, "young age", "clinical manifestations", "clinical characteristics", “signs and symptoms”, “prognosis“, “treatment“. Keywords were combined with a combination of the controlled terms (MeSH for Pubmed) to obtain the best search results.

Process of study selection:

Three stages were carried out during the selection process by two reviewers (CJ, ARA). The first stage of the screening eliminated irrelevant publications according to the titles. In the second stage, abstracts were screened according to the type of study, the patient age range, the type of intervention, and the outcome variables. In the third stage, a complete reading of each text was performed to confirm the eligibility of the study according to the predetermined inclusion and exclusion criteria.

Data extraction:

The following information was extracted from the studies and arranged in tables regarding the comparison of oral squamous cell carcinoma regarding clinical features, treatment, and prognosis, in old patients and young patients. Authors with the year of

publication, type of study (cohort), number of patients, patient age (years), sex (male or female), clinical features (location, degree of differentiation, tumor morphology), TNM stage, treatment (according to age of the patient), and prognosis (recurrence rate and survival rate). This review compared oral squamous cell carcinoma between old patients (≥ 40-45 years) and young patients (<40-45 years). The principle variable compared the prognosis, measured through recurrence rate and survival rate in percentage. The secondary variables included the comparison of clinical features (tumor location, degree of differentiation, and tumor morphology), and treatment methodology (according to age). (Table 1 and Table 2)

Quality and risk of bias assessment:

Two reviewers (CJ, ARA) independently evaluated the methodological quality of the included studies. The Newcastle-Ottawa scale (8) was used to measure the quality of non-randomized observational studies; it was considered "low risk of bias" in the case of a star score > 6 and "high risk of bias" for a score ≤ 6.

Data assessment:

With the aim of summarizing and comparing studies, average data on main variables were grouped for each study group. As the average data found in the analyzed studies came from different samples, weighted arithmetic mean was calculated to obtain feasible outcomes.

RESULTS

A total of 210 articles were obtained from the initial search process: Medline-PubMed (n=5), SCOPUS (n=182) and the Web of Science (n=16), Lilacs (n=7). Of these publications, 37 were identified as potentially eligible articles through screening by titles and abstracts. The full-text articles were subsequently obtained and thoroughly evaluated. As a result, 6 articles met the inclusion criteria and were finally included in this systematic review (Fig. 1).

The descriptive results of the characteristics and variables of each of the 6 studies included in the present systematic review are presented in Table 2 and Table 3.

The 6 studies included in the final analysis had heterogeneous populations in terms of sample size, age range, tumor manifestations, carcinoma stage, treatment modalities, and recurrence and survival rates. In total, 4,461 patients were diagnosed and studied regarding oral squamous cell carcinoma clinical manifestations, prognosis, and/or treatment. Of the 4,006 patients, 2,624 (65.5%) were male and 1,837 (45.9%) were female. Two studies considered the age range of less than 45 years and more than or equal to 45 years (9,10). One study only investigated patients more than or equal to 45 years (9). Two studies investigated patients less than or equal to 40 years or more than 40 years (11,12). One investigated patients less than 40 years and more than or equal to 40 years (11).

Evaluation of methodological quality and bias risk:

The Newcastle-Ottawa scale was used to measure the quality of non-randomized observational studies (8). Of the 6 studies included in this review, 2 of them were considered to be at low risk of bias and the remaining 4 were considered at high risk of bias. “Comparison of Clinicopathological Profile of Oral Squamous Cell Carcinoma between Younger and Older Indian Adults” was the item with the highest risk of bias.

Synthesis of results

A total of 345 (6.3%) cancer localizations were identified in patients aged below 40-45 years, while 3453 (63.2%) cancer localizations were observed in patients aged 40-45 years and older. As for the remaining 1668 (30.5%) patients, it is unknown to which age range they are categorized in (9–14).

The young patient and old patient groups both established the highest total mean for the location of the oral squamous cell carcinoma on the tongue, being 189 in younger patients and 241.16 in older patients.

In terms of the degree of tumor differentiation, both age groups determined the greatest amount of tumor differentiation being moderately differentiated, having a total mean of 27.6 in the young patients and 135 in old patients.

The most predominant tumor manifestation detected in both age groups was an exophytic morphology with a total mean of 19.3 cases in young patients and 383 cases in old patients.

When examining the OSCC treatment approaches, patients belonging to both age groups mainly received surgical treatments, the total mean being 31.5 for young patients and 119 for old patients.

The prognosis was better in younger patients compared to older patients. In patients aged 40-45 years or younger, the recurrence rate was 19.10%, the regional recurrence rate was 5%, the distal recurrence rate 13%, the local control rate was 65%, and local failure was 45%. As for the survival rate it was 56.4% and the disease specific survival rate was 81.4%. As for older patients, the overall recurrence rate was 25.40%, the regional recurrence rate was 11%, the distal recurrence rate 9%, the local control rate was 78%, and local failure was 34%. As for the survival rate it was 53.50% and the disease specific survival rate was 76%.

DISCUSSION

The present literature review provides evidence-based information on the clinical manifestations, treatment, and prognosis of oral squamous cell carcinoma in old patients in comparison to young patients. The aim of this review was to evaluate the prognosis by measuring recurrence rate (%) and survival rate (%) for oral squamous cell carcinoma in old patients in comparison with young patients during a follow-up time of 2, 5, or 10 years; and secondarily to study and compare the clinical manifestations and treatment for the disease in older and younger patients (location, degree of differentiation, tumor morphology, tumor stage).

Clinical manifestations

Among patients younger than 40-45 years, the occurrence of OSCC tumors is relatively lower compared to older age groups, as evidenced by the finding that only 6.3% of

cancer localizations were identified in this demographic. While some studies, such as that by Subramaniam N et al. (14), focused solely on OSCC tumors located on the tongue, others like Cariati P et al. (13) and Xu Qs et al. (12) reported OSCC occurrences across multiple oral sites. The total mean distribution of OSCC tumors in this age group underscores the diversity of its localization, with the tongue being the most prevalent site followed by the buccal mucosa, floor of the mouth, and other regions.

Conversely, in patients aged 40-45 years and older, the prevalence of OSCC tumors is significantly higher, constituting 63.2% of cancer localizations. They are more likely to present with OSCC tumors, particularly in regions such as the tongue and buccal mucosa. Both younger and older age groups found that the tongue was the most common site of OSCC. Our findings coincide with those by C.D Llewellyn et al. (15) Rafael Ferreira e Costa et al. (16) Khadijah Mohideen et al. (17) Reshma Poothakulath Krishnan (18) having the tongue as the most common localization. However, Samuel E Udeabor et al. (19) determined the floor of the mouth was the commonest site of tumour occurrence both age groups. Acharya S et al. (20) reported the buccal mucosa (47%) as a major site in older patients.

The degree of tumor differentiation is a critical factor in understanding the aggressiveness and prognosis of oral squamous cell carcinoma (OSCC).

In patients younger than 40-45 years, the proportion of well-differentiated tumors was notably lower compared to older age groups. The total mean distribution indicated a predominance of moderately differentiated cases, followed by well-differentiated and poorly differentiated cases. Interestingly, cases with an unknown differentiation status were also observed, suggesting potential challenges in accurately characterizing tumor histology in this age group.

Conversely, in patients aged 40-45 years or older, Ledesma-Montes C, et al. (9), Cariati P et al. (13), Xu Qs et al. (12), Komolmalai N et al. (10), and Devadass CW et al. (11) reported varying degrees of tumor differentiation, with the majority of cases classified as moderately differentiated.

In comparison to other relevant studies, *E M O'Regan et al.* (21) and *Silvio K Hirota et al.* (22), *Samuel E Udeabor et al.* (19) observed that well-differentiated tumors

were relatively more prevalent in the younger age group. On the contrary, Ferreira e Costa et al. (16) observed higher prevalence of moderate-differentiated tumors in the young age group, aligning with our results. *Ramdass et al.* (23) demonstrating a higher prevalence of moderately differentiated tumors in patients older than 45 years, coinciding with our results.This differs from the studies by *Hakeem et al.* (24), *M Selvamani et al.* (25), Chuanzheng Sun et al. (26), P Loganathan et al. (27) which demonstrate well differentiated tumors as most common, followed by moderately differentiated tumors. Studies by *Mohideen et al.* (17), *Rosenquist* (28), *Shou Yen Kao* (29), and *Soerjomataram et al.* (30) are consistent with our findings, revealing a higher prevalence of moderately differentiated cases in both age groups.

In our review, limited studies specifically addressed tumor morphology, highlighting the need for further investigation in this area. Notably, Xu Qs et al. (12) and Devadass CW et al. (11) provided valuable data on tumor morphology in patients across different age groups. In patients younger than 40-45 years, Xu Qs et al. (12) found a predominance of exophytic and ulcerative tumors, with a potential shift towards infiltrative patterns over time. Devadass CW et al. (11) also noted a significant proportion of exophytic tumors in this age group.

Conversely, among patients aged 40-45 years or older, Xu Qs et al. (12) observed a higher prevalence of exophytic, ulcerative, and infiltrative tumors, with variations between retrospective and prospective analyses. Devadass CW et al. (11) similarly identified a significant presence of exophytic tumors in older patients.

This study detected predominant exophytic morphology in both age groups with is inconsistent with the study by Acharya Swetha et al. (20) who observed a higher presence of endophytic tumors in young patients compared to older patients. This difference might indicate a higher propensity for lymph node metastasis and a less favorable response to treatment in young patients. *Poothakulath Krishnan et al.* (18) did not note significant difference in the amount of lymphoplamacytic infiltrate between the two age groups contradicting our findings in which older patients contributed higher prevalence of infiltrative features.

Treatment

In this study, we analyzed various treatment modalities employed for managing oral squamous cell carcinoma (OSCC), encompassing surgery, radiotherapy, chemotherapy, and palliative care, either individually or in combination. Notably, some studies did not provide comprehensive insights into treatment methods.

When exploring treatment approaches for patients under the age of 40-45 years, Subramaniam N et al. (14) and Xu QS et al. (12) primarily investigated surgical interventions, often combined with radiotherapy or chemotherapy. Komolmalai N et al. (10) examined a broader spectrum of treatment modalities, including surgery, radiotherapy, chemotherapy, and palliative care. The distribution of treatment modalities varied among studies, with surgical intervention being a common approach.

For patients aged 40-45 years or older, similar trends were observed, with surgical intervention being the primary treatment modality. Subramaniam N et al. (14) and Xu QS et al. (12) also reported a significant utilization of adjuvant therapies in this age group, including radiotherapy and chemotherapy. Overall, the findings suggest that while surgical intervention remains a cornerstone in OSCC treatment across age groups, the utilization of adjuvant therapies may vary, potentially reflecting differences in disease severity, patient preferences, or institutional practices.

Xu Qs et al. (12) suggested that a patients poor general condition tends to limit the operation time, the selection of free-flap treatments, postoperative recovery and most importantly the selection of adjuvant therapy. This was observed in the studies done by Linsen et al. (31) and Liu et al. (32) who reported a significantly lower ratio of elder patients at an advanced age receiving radiotherapy. This may be one of the key reasons to a worse outcome and poor prognosis for elderly patients.
The study by Udeabor et al. (19) was consistent with our study in which the highest percentage of treatment methodology observed was surgery.

Prognosis

When comparing the recurrence rates and survival outcomes between the two age groups, several notable differences emerge. Firstly, when observing patients aged 40-45 years or younger, Subramaniam N et al. (14) reported relatively higher local control rates but also exhibited substantial overall recurrence rates. Conversely, in the

older age group (40-45 years or older), while Ledesma-Montes C, et al. (9) reported a lower overall recurrence rate, the local control rates were slightly lower compared to the younger cohort. This suggests that younger patients may experience more aggressive disease behavior necessitating more intensive local control measures, whereas older patients may have a lower risk of disease recurrence but may still face challenges in achieving optimal local control.

Furthermore, in terms of survival outcomes, younger patients generally demonstrated higher overall and disease-specific survival rates compared to older patients. This is evident from studies such as Subramaniam N et al. (14) and Xu QS et al. (12) where younger patients exhibited overall survival rates ranging from 56.4% to 65%, whereas older patients showed overall survival rates ranging from 53.5% to 71%.

Similarly, disease-specific survival rates were also notably higher in the younger age group, indicating potentially better responses to treatment and a lower risk of disease-related mortality.

Sanabria et al. (33) reported that the substandard treatment decreased overall patient survival which is observed in treatment methodology selection in elderly patients. Moreover, Chen et al. (34) noted the improved overall survival of elderly patients with aggressive treatments with a curative intent. This is consistent with the study by Xu et al. (12) in which it was stated that the outcome of OSCC patients may be impaired according to inadequate treatment selection. Based on this information, conjunctive and adjuvant therapy should be suggested to patients when appropriate despite the age and the age must not be used to determine the treatment. This was also concluded by Derks et al. (35) who discovered that even if younger and older patients had the same co-morbidity score, the patients aged older than 70 years are at a higher probability of receiving substandard treatment which would worsen their prognosis.

Our study detected a better prognosis for younger patients with a greater overall survival rate and disease specific survival rate. This was consistent with the results of other literature including that of pytynia et al. (36), Ho et al. (37), and Udeabor et al. (19). This finding is also in agreement with those from studies by Warnakulasuriya et al. (15), and Fan et al. (38) who reported better outcome for younger patients.

Limitations

The review encountered limitations despite an extensive initial search, having only 6 studies meet the inclusion criteria out of 210 articles screened. The included studies lacked randomized comparative clinical trials and were primarily retrospective cohort studies, potentially affecting result accuracy. Assessment of bias using the Newcastle-Ottawa scale revealed some studies at high risk, impacting result reliability. Language bias may exist as only English reviews were considered, potentially neglecting valuable studies in other languages. Some studies lacked essential information such as tumor location, grade of differentiation, or treatment, posing a risk of imprecision. Heterogeneity in population, characteristics, interventions, and outcomes among the included studies made it challenging to draw meaningful conclusions. Despite heterogeneous results, they remain representative but should be interpreted with caution.

CONCLUSION

Primary Conclusion

1. Older patients exhibited a worse prognosis for oral squamous cell carcinoma compared to younger patients. Younger patients demonstrated better degree of overall survival rate and disease specific survival rate. Although, younger patients did reveal a lower local control rate they had a lower overall recurrence rate compared to older patients.

Secondary Conclusions

2. Older and younger patients exhibited similar clinical manifestations for oral squamous cell carcinoma. The tongue was the most common site of oral squamous cell carcinoma in both younger and older age groups. Moderately differentiated tumors were more prevalent among younger and older patients. The most predominant morphology in both age groups was exophytic tumors.
3. The most common methodology performed to treat oral squamous cell carcinoma for the older and younger age groups was surgical procedures which portrayed better prognostic outcomes.

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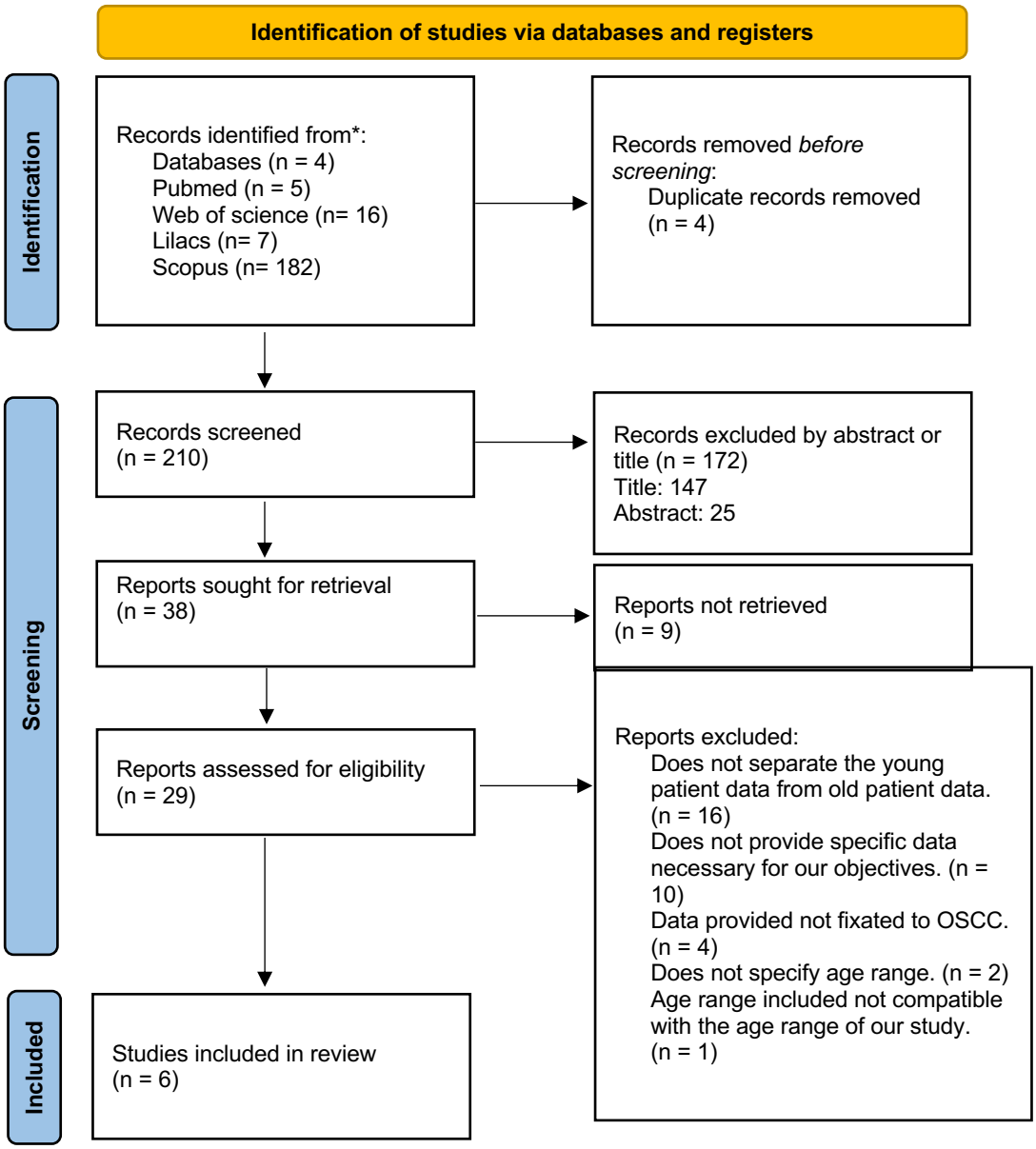

Fig. 1. Diagram of the search flow and title selection process during the systematic review.

Table 1: Characteristics, Treatment, and Prognosis of the studies reviewed

Authores (year and country)	Type of Study	N. patients	Sex	Age (years)	Location of carcinoma (%)	Degree of differentiation (%)	Tumor morphology/manifestation
Ledesma-Montes C, et al. (2018, Brazil)	Cohort Retrospective Review	60	M: 32 F: 28	≥ 45	BT: 23 MT: 37	**BT** WD: 6 (10%) MD: 34 (56.7%) PD:14 (23.3%) CIS: 6 (10%) **MT** WD: 3 (8.1%) MD: 22 (59.4%) PD: 8 (21.6%) CIS: 4 (10.8%)	-
Subramaniam N et al. (2020, India)	Cohort Prospective Review	425	M: 88 (77%) F: 26 (23%) M: 217 (70%) F: 94(30%)	<45 ≥ 45	T: Unspecified	MD/PD: 62 (53%) MD/PD: 135 (43%)	-
Cariati P et al. (2017, Spain)	Cohort Retrospective Review	133	M: 18 F: 15 M: 67 F: 33	<45 ≥ 45	T: 35 FOM: 20 RR: 14 BM: 9 O: 8 Mx: 7 P: 5 G:2 T: 18 (54.5%) FOM: 5 (15.1%) AR: 1 (3.03%) BM: 4 (12.1%) O: 3 (9.09%) Mx: 1 (3.03%) G:1 (3.03%)	WD: 13 MD: 17 PD: 3 WD: 8 MD: 66 PD: 26	-
Xu QS et al. (2019, China)	Cohort Review	2,782					

	Retrospective Part	2,443	M: 94 (65.7%) F: 49 (34.3%)	≤40	T: 102 (71.3%) LG: 12 (8.4%) BM: 6 (4.2%) FOM: 13 (9.1%) UG: 8 (5.6%) HP: 2 (1.4%)	WD: 54 (40%) MD: 71 (52.6%) PD: 10 (7.4%)	E: 29 (23.0%) U: 52 (41.3%) I: 45 (35.7%) VEP: 2 (3.6%) VEA: 53 (96.4%)
			M: 1169 (55.6%) F: 933 (44.4%)	41–75	T: 850 (40.4%) LG: 383 (18.2%) BM: 365 (17.4%) FOM: 235 (11.2%) UG: 203 (9.7%) HP: 66 (3.1%)	WD: 976 (47.7%) MD: 966 (47.2%) PD: 105 (5.1%)	E: 748 (37.8%) U: 704 (35.6%) I: 525 (26.6%) VEP: 29 (4.4%) VEA: 634 (95.6%)
			M: 115 (58.1%) F: 83 (41.9%)	>75	T: 70 (35.4%) LG: 45 (22.7%) BM: 4 (22.2%) FOM:3 (1.5%) UG:33 (16.7%) HP: 3 (1.5%)	WD: 86 (45.3%) MD: 91 (47.9%) PD: 13 (6.8%)	E: 97 (52.2%) U: 60 (32.2%) I: 29 (15.6%) VEP: 3 (4.6%) VEA: 62 (95.4%)
	Prospective Part	339	M: 187 (55.2%) F: 152 (44.8%)	≤40	T: 18 (58.1%) LG: 2 (6.5%) BM: 4 (12.9%) FOM: 1 (3.2%) UG: 3 (9.7%) HP: 3 (9.7%)	WD: 6 (24.0%) MD: 17 (68.0%) PD: 2 (8.0%)	E: 8 (25.8%) U: 9 (29.0%) I: 14 (45.2%)
				41–75	T: 111 (40.2%) LG: 54 (19.6%) BM: 60 (21.7%) FOM: 27 (9.8%) UG: 14 (5.1%) HP: 10 (3.6%)	WD: 59 (26.1%) MD: 163 (72.1%) PD: 4 (1.8%)	E: 70 (25.4%) U: 97 (35.3%) I: 108 (39.3%)
				>75	T: 8 (25.8%) LG: 8 (25.8%) BM: 10 (32.3%) UG: 5 (16.1%)	WD: 5 (18.5%) MD: 20 (74.1%) PD: 2 (7.4%)	E: 7 (23.3%) U: 15 (50.0%) I: 8 (26.7%)
Komolmalai N (2015, Thaliand)	Cohort Retrospective study	874	M: 23 (63.9%) F: 13 (36.1%) M: 494 (58.9%)	<40	L: 1 (2.8%) T: 27 (75.0%) FOM: 2 (5.6%) P: 2 (5.6%): BM: 2 (5.6%) RR:1 (2.8%) Mouth, NOS: 1 (2.8%)	WD: 18 (50%) MD: 11 (30.6%) PD: 5 (13.9%) UD: 0 (0%) UK: 2 (5.6%)	-

			F: 344 (41.1%)	≥ 40	L: 63 (7.5%) T: 309 (36.9%) G: 156 (18.6%) FOM: 69 (8.2%) P: 91 (10.9%) BM: 119 (14.2%) RR:12 (1.4%) Mouth, NOS: 16 (1.9%) Multiple sites: 3 (0.4%)	WD: 487 (58.1%) MD 235 (28.9%) PD: 62 (7.4%) UD: 3 (0.4%) UK: 51 (6.1%)	
Devadass CW et al. (2020, India)	Cohort Prospective Review	187	M: 20 (57.1%) F: 15 (42.9%)	≤40	BM:19 (54.3%) LAR: 6 (17.1%) RR: 3 (8.6%) T: 7 (20%)	WD: 10 (28.6%) MD 22 (62.9%) PD: 1 (2.9%) VC: 2 (5.7%)	E: 21 (60%) En: 14 (40%)
			M: 100 (65.8%) F: 52 (34.2%)	>40	L: 2 (1.3%) BM: 79 (52%) LAR: 26 (17.1%) UAR: 3 (2%) RR: 15 (9.9%) FOM: 2 (1.3%) HP: 4 (2.6%) T: 21 (13.8%)	WD: 41 (27%) MD 101 (66.4%) PD: 7 (4.6%) VC: 3 (2%)	E: 92 (60.5%) En: 60 (39.5%)

M: Male; F: Female; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; CIS: Carcinoma in situ; UD: Undifferentiated; UK: Unknown; VC: Verrucous Carcinoma; BT: Base of the tongue; MT: Mobile tongue; T: Tongue; FOM: Floor Of Mouth; RR: Retromolar Region; BM: Buccal Mucosa; O: Oropharynx; Mx: Maxilla; G: Gingiva; P: Palate; AR: Alveolar Ridge; UAR: Upper Alveolar Ridge; LAR: Lower Alveolar Ridge; LG: Lower Gingiva; UG: Upper Gingiva; HP: Hard Palate; NOS: Not Otherwise Specified; L: Lip; E: Exophytic; En: Endophytic; U: Ulcerative; I: Infiltrative; VEP: Vascular Emboli Present; VEA: Vascular Emboli Absent

Table 2: Stage, Treatment, recurrence rate, and survival rate of the studies reviewed

Authores (year and country)	Type of Study	N. patients	Sex	Age (years)	Stage (TNM/ AJCC 7th Cancer Staging Manual)	Treatment	Recurrence (%)	Rate of survival

Ledesma-Montes C, et al. (2018, Brazil)	Cohort Retrospective Review	60	M: 32 F: 28	≥ 45	**TNM** T2N0M0: 47 T3N0M0: 2 T3N2bM0: 1 T4aN0M0:3 T4dN2bM0: 7 AJCC: II: 48 III: 3 Iva: 9	**MD-OSCC** Wide excision or hemiglosectomy **PD-OSCC** Wide local excision or hemiglosectomy **WD-OSCC** Wide excision or hemiglosectomy **CIS** Wide local excision or hemiglosectomy, possibly with neck dissection	OR: 9 (15%) **MD-OSCC** 11.8%: further excision or neck dissection **PD-OSCC** 21.4%: further excision or neck dissection **WD-OSCC** 1 case: further excision **CIS** 1 case: further excision	-
Subramaniam N et al. (2020, India)	Cohort Prospective Review	425	M: 88 (77% F: 26 (23%) M: 217 (70%) F: 94 (30%)	<45 ≥ 45	LI: 38 (33%) PI: 47 (41%) DF: 60 (53%) CM: 4 (4%) EE: 43 (38%) LI: 66 (21%) PI: 87 (28%) DF: 146 (47%) CM: 8 (3%) EE: 72 (23%)	S: 51 (45%) S + R: 11 (10%) S + CCRT: 52 (45%) S: 161 (52%) S + R: 41 (13%) S + CCRT: 109 (35%)	LCR: 65% RRR: 5% DRR: 13% LCR: 78% RRR: 11% DRR: 9%	OS: 65% DSS: 67% OS: 71% DSS: 74% P value: OS: (p = 0.481)

								P value DSS: (p = 0.156).
Cariati P et al. (2017, Spain)	Cohort Retrospective Review	133	M: 18 F: 15 M: 67 F: 33	<45 ≥ 45	T1: 57,5%, (n=19) T2: 27,2%, (n=9) T3: 3,03% (n=2) T4: 3,03% (n=3) NI: 48,4% (n=16) T1: 27% (n=27) T2: 37% (n=37) T3: 29% (n=29) T4: 7% (n=7) NI: 33% (n=33)	-	LF: 45.4% (n=15) LF: 34% (n=34)	5y-OS: 48.4% (n=16) 5y-OS: : 62% (n=62) P value: OS: (p=0.17)
Xu QS et al. (2019, China)	Cohort Review	2,782						
	Retrospective Part		M: 94 (65.7%) F: 49 (34.3%)	≤40	**<u>cT stage</u>** T1: 33 (23.1%) T2: 58 (40.5%) T3: 19 (13.3%) T4 33 (23.1%) **<u>pN stage</u>** N0: 72 (55.8%) N1: 25 (19.4%) N2: 30 (23.3%) N3: 2 (1.5%) PI: 17 (28.8%)	S: 55 (47.8%) S+R: 47 (40.9%) S+CCRT: 13 (11.3%)	OR: 38.2%	DSS: 77.2%

			M: 1169 (55.6%) F: 933 (44.4%)	41–75	No PI: 42 (71.2%) DI: 18 (32.7%) No DI: 37 (67.3%) **<u>cT stage</u>** T1:487 (23.2%) T2: 817 (38.9%) T3: 209 (9.9%) T4: 589 (28%) **<u>pN stage</u>** N0: 1053 (59.1%) N1: 301 (16.9%) N2: 424 (23.8%) N3: 4 (0.2%) PI: 155 (21.7%) No PI: 559 (78.3%)	S: 908 (60.4%) S+R: 466 (31.0%) S+CCRT: 130 (8.6%)	OR: 46.7%	DSS: 69.7%
			M: 115 (58.1%) F: 83 (41.9%)	>75	DIP: 244 (36.6%) No DI: 422 (63.4%) **<u>cT stage</u>** T1: 58 (29.3%) T2: 84 (42.4%) T3: 19 (9.6%) T4: 37 (18.7%) **<u>pN stage</u>** N0: 81 (62.8%) N1: 15	S 113 (76.4%) S+R: 29 (19.6%) S+CCRT: 6 (4.0%)	OR: 52.0%	DSS: 55.4%

					(11.6%) N2: 33 (25.6%) N3: 0 (0%) PI: 10 (14.7%) No PI: 58 (85.3%) DI: 40 (61.5%) No DI: 25 (38.5%)		Total recurrence:1, 006/2443 patients (46.6%)	Total DSS: 1487/2157 patients (68.9%)
	Prospective Part		M: 15 (48.4%) F: 16 (51.6%) M: 161 (58.1%) F: 116 (41.9%)	≤40 41–75	**cT stage** T1: 7 (22.6%) T2: 14 (45.2%) T3: 5 (16.1%) T4: 5 (16.1%) **pN stage** N0: 25 (80.6%) N1: 4 (12.9%) N2: 2 (6.5%) N3: 0 (0.0%) **cT stage** T1: 70 (25.3%) T2: 81 (29.2%) T3: 30 (10.8%) T4: 96 (34.7%) **pN stage** N0: 197 (71.1%) N1: 29 (10.4%) N2: 50 (18.1%)	S: 19 (61.3%) S+R: 12 (38.7%) S+CCRT: 0 (0%) S: 194 (70.1%) S+R: 76 (27.4%) S+CCRT: 7 (2.5%)	OR: 0.0% OR: 15.7%	DSS 100.0% DSS: 94.8%

			M: 11 (35.5%) F: 20 (64.5%)	>75	N3: 1 (0.4%) **cT stage** T1: 8 (25.8%) T2: 10 (32.3%) T3: 1 (3.2%) T4: 12 (38.7%) **pN stage** N0: 24 (77.4%) N1: 2 (6.5%) N2: 5 (16.1%) N3: 0 (0.0%)	S: 30 (96.8%) S+R: 1 (3.2%) S+CCRT: 0 (0.0%)	OR: 30.0% Total recurrence: 326/339 patients	DSS: 80.0%
Komolmalai N (2015, Thaliand)	Cohort Retrospecti ve Review	419	M: 23 (63.9%) F: 13 (36.1%)	<40	**Clinical stage** I: 3 (8.3%) II: 11 (30.6%) III: 1 (2.8%) IVA: 12 (33.3%) IVB: 0 (0.0%) IVC: 1 (2.8%) UK: 8 (22.2%)	S: 1 (2.8%) R: 9 (25%) C:1 (2.8%) S+R: 12 (33.3%) S+R+C: 2 (5.6%) S+C: 0 (0.0%) R+C: 6 (16.7%) P: 2 (5.6%) UK:3 (8.3%)	-	5-y OS: 56.2%
			M: 494 (58.9%) F: 344 (41.1%)	≥ 40	**Clinical stage** I: 83 (9.9%) II: 169 (20.2) III: 105 (12.5%) IVA: 275 (32.8%) IVB: 17 (2.0%) IVC: 14 (1.7%) UK: 175 (20.9%)	S: 119 (14.2%) R:242 (28.9%) C: 26 (3.1%) S+R: 156 (18.6%) S+R+C: 26 (3.1%) S+C: 7 (0.8%) R+C: 58 (6.9%) P: 108 (12.9%) UK: 96 (11.5%)		5-y OS: 27.4%

								5-y survival rate: F: 33.7% M: 25.3% Stage I: 54.6% Stage II: 18%
Devadass CW et al. (2020, India)	Cohort Prospective Review	187	M: 20 (57.1%) F: 15 (42.9%) M: 100 (65.8%) F: 52 (34.2%)	≤40 >40	PI: 3 (8.6%) EE: 5 (14.2%) LI: 14 (40%) **cT stage** T1:5 (14.3%) T2: 10 (28.6%) T3: 13 (37.1%) T4: 7 (20%) **pN stage** N0: 21 (60%) N1: 7 (20%) N2: 5 (14.3%) N3: 2 (5.7%) **TNM stage** I: 1 (2.9%) II:7 (20%) III: 15 (42.9%) IV: 12 (34.3%) PI: 14 (9.2%) EE:14 (9.2%) LI:42 (27.6%) **cT stage** T stage: T1: 16 (10.5%) T2: 65 (42.8%) T3: 45 (29.6%) T4: 26 (17.1%)	-	-	-

					pN stage N0: 113 (74.3) N1: 16 (10.5) N2: 18 (11.8) N3: 5 (3.3) **TNM stage** I: 9 (5.9) II: 39 (25.7) III: 56 (36.8) IV: 48 (31.6)			

M: Male; F: Female; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; CIS: Carcinoma in situ; UD: Undifferentiated; UK: Unknown; VC: Verrucous Carcinoma; BT: Base of the tongue; MT: Mobile tongue. S: Surgery; R: Radiotherapy; C: Chemotherapy; CCRT: Concurrent Chemoradiotherapy; P: Palliative; LI: Lymphovascular Invasion; PI: Perineural invasion; DF: Discohesive Front; CM: Close Margin (< 5 mm); EE: Extranodal Extension; OR: Overall Recurrence; OS: Overall Survival; DSS: Disease Specific Survival; LCR: Local Control Rate; RRR: Regional Recurrence Rate; DRR: Distal Recurrence Rate; NI: Node Involvement; LF: Locoregional Failure; DI: Diffuse Infiltration;

Table 3: Oral squamous cell carcinoma clinical manifestations

ARTICLE	LOCATION																DEGREE OF DIFFERENTIATION							TUMOR MORPHOLOGY					
	Tongue	Floor of the Mouth	Retromolar Region	Buccal Mucosa	Oropharynx	Maxilla	Palate	Gingigva	Lower Gingiva	Upper Gingiva	Hard Palate	Lip	Mouth -unspecified	Alveolar Region	Lower Alveolar Region	Upper Alveolar Region	Well Differentiation	Moderate	Poor Differentiated	Moderatel-Poorly	Carcinoma Insitu	Veruciys carcinoma	Undifferentiated	Unknown	Exophytic	Endophytic	Ulcerative	Infilterative	Vascular Emboli	Vascular Emboli
< 40-45 years																													
Subramaniam N et al. (2020, India)	Not Specified																			62									
Cariati P et al. (2017, Spain)+ A4:AD4	35	20	14	9	8	7	5	2									13	17	3								-		
Xu Qs et al. (2019, China) (retrospective part)	102	13		6					12	8	2						54	71	10					0	29		52	45	2	53
Xu QS et al. (2019, China) (prospective part)	18	1		4					2	3	3						6	17	2						8		9	14		
Komolmalai N et al. (2015, Thaliand)	27	2	1	2			2					1	1				18	11	5					2						

Devadass CW et al. (2020, India)	7		3	19			3.5									6		10	22	1			2			21	14				
Total Mean	37.8	9	6	8	8	7	3.5	2	7	5.5	2.5	1	1	0	6	0	20.2	27.6	4.2	62	0	2	0	2	19.3333333	14	30.5	29.5	2	53
≥ 40-45 years																														
Ledesma-Montes C, et al. (2018, Brazil)	60	-															9	56	22		10				-					
Subramaniam N et al. (2020, India)	Not Specified	-																		135					-					
Cariati P et al. (2017, Spain)+ A4:AD4	18	5		4	3	1			1				1				8	66	26						-					
Xu Qs et al. (2019, China) (retrospective part)	920	238		369					428	236	69						1062	1057	118						845		764	554	32	696
Xu Qs et al. (2019, China) (prospective part)	119	27		70					62	19	10						64	183	6						77		112	116		
Komolmalai N (2015, Thailand)	309	69	12	119			91	156				63	16				487	235	62				3	51						

Devadass CW et al. (2020, India)	21	2	15	79							4	2			26	3	41	101	7			3			92	60				
Total Mean	241.166667	68.2	13.5	128.2	3	1	91	156	163.666667	127.5	27.666667	32.5	16	1	26	3	278.5	283	40.166667	135	10	3	3	51	338	60	438	335	32	696

Table 4: Oral squamous cell carcinoma treatment and prognosis

ARTICLE	TREATMENT											RECURRENCE RATE							SURVIVAL RATE	
	Surgery	Surgery + Radiotherapy	Concurrent chemoradiotherapy	Surgery + Concurrent Chemoradiotherapy	Radiotherapy	Chemotherapy	Surgery + Radiotherapy + Chemotherapy	Surgery + Chemotherapy	Radiotherapy + Chemotherapy	Palliative	unknown	Overall recurrence	5-year recurrence rate	2-year recurrence rate	Local Control Rate	Regional Recurrence Rate	Distal Recurrence Rate	Local Failure	Overall Survival Rate	Disease Specific Survival Rate
< 40-45 years																				
Subramaniam N et al. (2020, India)	51	11	0	52											65%	5%	13%		65%	67%
Cariati P et al. (2017, Spain)																		45%	48%	
Xu QS et al. (2019, China) Retrospective part	55	47		13								38.20%								77.20%
Xu QS et al. (2019, China) Prospective part	19	12		0								0%								100%

Komolmalai N et al. (2015, Thaliand)	1	12			9	1	2	0	6	2	3								56.20%	
Total Mean	31.5	20.5	0	21.6666667	9	1	2	0	6	2	3	19.10%	0	0	65%	5%	13%	45%	56.40%	81.40%
≥ 40-45 years																				
Ledesma-Montes C, et al. (2018, Brazil)	Not Specified											15%								
Subramaniam N et al. (2020, India)	161	41	109	0											78%	11%	9%		71%	74%
Cariati P et al. (2017, Spain)																		34 (34%)	62%	
Xu QS et al. (2019, China) Retrospective Part	1021	495	136						0			47.20%								68.50%
Xu QS et al. (2019, China) Prospective Part	224	77	7									14%								85.40%
Komolmalai N (2015, Thaliand)	119	156		26	242	26	0	7	58	108	96								27.40%	
Total Mean	381.25	192.25	84	13	242	26	0	7	58	108	96	25.40%	0	0	78%	11%	9%	34%	53.50%	76%

COMPARACIÓN DEL CARCINOMA ORAL DE CÉLULAS ESCAMOSAS EN PACIENTES JÓVENES FRENTE A PACIENTES DE EDAD AVANZADA: CARACTERÍSTICAS CLÍNICAS, TRATAMIENTO Y PRONÓSTICO: Una revisión sistemática

Título: Carcinoma oral de células escamosas: pronóstico, tratamiento y manifestaciones clínicas

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RESUMEN

Introducción: El pronóstico del carcinoma oral de células escamosas (COCE) está influido por diversos factores, como la localización del tumor, el estadio tumoral, la diferenciación y el enfoque terapéutico. Estos factores pueden diferir según la edad del paciente, donde los pacientes más jóvenes pueden presentar aspectos diferentes en comparación con los pacientes de mayor edad. El objetivo de esta revisión sistemática fue comparar el carcinoma oral de células escamosas en pacientes jóvenes (<40-45 años) y pacientes mayores (≥ 40-45 años) con respecto al pronóstico, la manifestación clínica y la metodología de tratamiento.

Materiales y métodos: Se realizó una búsqueda electrónica en las bases de datos Medline-PubMed, Web of Science, Scopus y Lilacs para encontrar artículos indexados relativos a las características clínicas, la metodología de tratamiento y el pronóstico del COCE en jóvenes (<40-45 años) y pacientes mayores (≥ 40-45 años) de los últimos 10 años (2014).

Resultados: De los 210 artículos potencialmente elegibles, 6 cumplieron los criterios de inclusión. En el grupo de pacientes jóvenes, la tasa de recurrencia fue del 19,10%, la tasa de recurrencia regional del 5%, la tasa de recurrencia distal del 13%, la tasa de control local del 65% y la de fracaso local del 45%. En cuanto a la tasa de supervivencia, fue del 56,4% y la tasa de supervivencia específica de la enfermedad, del 81,4%. En el grupo de pacientes de edad avanzada, la tasa de recurrencia global fue del 25,40%, la tasa de recurrencia regional del 11%, la tasa de recurrencia distal del 9%, la tasa de control local del 78% y el fracaso local del 34%. En cuanto a la tasa de supervivencia fue del 53,50% y la tasa de supervivencia específica de la enfermedad fue del 76%.

Conclusiones: Los pacientes de mayor edad mostraron un peor pronóstico del COCE en comparación con los pacientes más jóvenes. Aunque los pacientes más jóvenes revelaron una menor tasa de control local, presentaron una menor tasa de recurrencia global y un mejor grado de tasa de supervivencia global y tasa de supervivencia específica de la enfermedad en comparación con los pacientes de mayor edad.

Palabras clave: "Pacientes de edad avanzada", "Carcinoma oral de células escamosas", "Pacientes jóvenes", "Manifestaciones clínicas", "Características clínicas", "Pronóstico", "Tratamiento", "Metodología de tratamiento".

INTRODUCCIÓN

El carcinoma oral de células escamosas (COCE) es una forma prevalente de cáncer oral en todo el mundo, con el tabaco, el alcohol y el consumo de nuez de betel como principales factores de riesgo. Aunque se ha descrito mayor prevalencia en adultos mayores, se ha producido un aumento preocupante de su incidencia entre los adultos jóvenes en los últimos años (1). A pesar de los avances terapéuticos, las tasas de morbilidad y mortalidad han permanecido estancadas (2). La detección precoz es crucial para mejorar el pronóstico. El COCE suele afectar a la lengua, los labios y el suelo de la boca debido a su susceptibilidad a los carcinógenos (3).

El carcinoma oral de células escamosas se presenta típicamente como úlceras con centros necróticos o como tumoraciones con bordes mal definidos (2), se presentan en estadios iniciales como trastornos potencialmente malignos como la leucoplasia o la eritroplasia (3). Las lesiones oscilan entre milímetros y varios centímetros, y la afectación de los ganglios linfáticos indica un estado avanzado de la enfermedad (4).

Se describen los retos y tratamientos del COCE, haciendo hincapié en la importancia de la detección precoz y la prevención (5). Las opciones de tratamiento incluyen cirugía, radioterapia y quimioterapia, adaptadas al estadio de la enfermedad y a las necesidades del paciente (6).

Las elevadas tasas de mortalidad del carcinoma oral de células escamosas se deben a menudo a un diagnóstico tardío, y su incidencia ha aumentado en Europa en la última década (1). El pronóstico depende de la edad, el sexo, las características del tumor y la modalidad de tratamiento, y la afectación de los ganglios linfáticos y el grosor del tumor desempeñan un papel importante. La cirugía presenta tasas de supervivencia más elevadas, especialmente en las fases iniciales del cáncer (4).

El objetivo de esta revisión es comparar el COCE en pacientes jóvenes y de edad avanzada en lo que respecta a las manifestaciones clínicas, el tratamiento y el pronóstico. Esto contribuye a alcanzar el Objetivo de Desarrollo Sostenible 3. El

conocimiento de las manifestaciones clínicas en pacientes jóvenes ayuda a la detección precoz, mitigando posibles atribuciones erróneas. La elección y la intensidad del tratamiento difieren según la edad del paciente. Ciertos enfoques terapéuticos pueden ser difíciles de tolerar para los individuos más jóvenes o pueden implicar efectos adversos en pacientes mayores con problemas de salud subyacentes. Es preciso comprender los factores relacionados con la edad para determinar el plan de tratamiento más favorable, optimizando la eficacia y minimizando al mismo tiempo los posibles efectos secundarios y complicaciones. También puede ayudar a desarrollar estrategias de salud pública específicas: campañas educativas, programas de cribado e iniciativas de concienciación adaptadas a los grupos demográficos de mayor riesgo.

OBJETIVOS

Objetivo principal: Evaluar la comparación del pronóstico en pacientes jóvenes y mayores con carcinoma oral de células escamosas.

Objetivos secundarios:

- Comparar las características clínicas en pacientes jóvenes y mayores con carcinoma oral de células escamosas.
- Evaluar el tratamiento del carcinoma oral de células escamosas en pacientes jóvenes y mayores.

MATERIALES Y MÉTODOS

Esta revisión sistemática cumple la declaración PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (7).

Pregunta de enfoque:

La pregunta central se estableció de acuerdo con la pregunta estructurada PICO:

P (población): Pacientes de edad avanzada (≥ 40-45 años).
I (intervención): Carcinoma oral de células escamosas.
C (comparación): Pacientes más jóvenes (<40-45 años).
O (resultados): Manifestaciones clínicas, tratamiento y pronóstico.
- O1: Comparar el pronóstico en pacientes jóvenes y mayores

- O2: Comparar las características clínicas en pacientes jóvenes y mayores
- O3: Comparar el tratamiento en pacientes jóvenes y mayores

Criterios de elegibilidad:

Los criterios de inclusión consisten en:

• **Diseño del estudio:** Ensayos clínicos y ensayos controlados aleatorizados, estudios de cohortes prospectivos y retrospectivos, series de casos; publicación en inglés, de los últimos 10 años (2014-2024).

• **Paciente:** Pacientes jóvenes (<40-45 años) y pacientes mayores (≥ 40-45 años).

• **Intervención:** Carcinoma oral de células escamosas.

• **Resultados:** Estudios que incluyan datos relacionados con el pronóstico del carcinoma oral de células escamosas en pacientes mayores y jóvenes. Como variables secundarias, estudios que incluyan datos relacionados con las manifestaciones clínicas y el tratamiento del carcinoma oral de células escamosas en pacientes mayores y jóvenes.

Los criterios de exclusión consisten en: Revisiones sistémicas, metaanálisis, cartas o comentarios al editor, informes de expertos, estudios experimentales *in vitro* y en animales. Además, los estudios publicados en idiomas distintos del inglés, los estudios publicados antes del año 2014, los estudios que no distinguían entre nuestros dos rangos de edad (<40-45 y ≥ 40-45), así como los estudios que no evaluaban las características clínicas, el tratamiento o el pronóstico del carcinoma oral de células escamosas en población joven o anciana.

Fuentes de información y búsqueda de datos:

Se realizó una búsqueda bibliográfica automatizada electrónica y manual en cuatro bases de datos electrónicas principales (PubMed, Scopus, Web of Science y Lilacs) con las siguientes palabras clave "adultos", "ancianos", "pacientes ancianos", "carcinoma oral de células escamosas", "carcinomas orales de células escamosas", "carcinoma de células escamosas de la cavidad oral", "pacientes jóvenes", "adulto joven", "edad joven", "manifestaciones clínicas", "características clínicas", "signos y

síntomas", "pronóstico", "tratamiento". Las palabras clave se combinaron con una combinación de los términos controlados (MeSH para Pubmed) para obtener los mejores resultados de búsqueda.

Proceso de selección de estudios:

Dos revisores (CJ, ARA) llevaron a cabo tres etapas durante el proceso de selección. En la primera etapa del cribado se eliminaron las publicaciones irrelevantes según los títulos. En la segunda etapa, se cribaron los resúmenes según el tipo de estudio, el rango de edad de los pacientes, el tipo de intervención y las variables de resultado. En la tercera etapa, se realizó una lectura completa de cada texto para confirmar la elegibilidad del estudio según los criterios de inclusión y exclusión predeterminados.

Extracción de datos:

La siguiente información se extrajo de los estudios y se organizó en tablas relativas a la comparación del carcinoma oral de células escamosas con respecto a las características clínicas, el tratamiento y el pronóstico, en pacientes de edad avanzada y pacientes jóvenes. Autores con el año de publicación, tipo de estudio (cohorte), número de pacientes, edad del paciente (años), sexo (hombre o mujer), características clínicas (localización, grado de diferenciación, morfología del tumor), estadio TNM, tratamiento (según la edad del paciente) y pronóstico (tasa de recurrencia y tasa de supervivencia). Esta revisión comparó el carcinoma oral de células escamosas entre pacientes de edad avanzada (≥ 40-45 años) y pacientes jóvenes (<40-45 años). La variable principal comparó el pronóstico, medido a través de la tasa de recurrencia y la tasa de supervivencia en porcentaje. Las variables secundarias incluyeron la comparación de las características clínicas (localización del tumor, grado de diferenciación y morfología tumoral), y la metodología de tratamiento (según la edad) (Tabla 1 y Tabla 2).

Evaluación de la calidad y del riesgo de sesgo:

Dos revisores (CJ, ARA) evaluaron de forma independiente la calidad metodológica de los estudios incluidos. La escala Newcastle-Ottawa (8) se utilizó para medir la calidad de los estudios observacionales no aleatorizados; se consideró "bajo

riesgo de sesgo" en el caso de una puntuación en estrellas > 6 y "alto riesgo de sesgo" para una puntuación ≤ 6.

Evaluación de los datos:

Con el objetivo de resumir y comparar los estudios, se agruparon los datos medios de las variables principales para cada grupo de estudio. Como los datos medios encontrados en los estudios analizados procedían de muestras diferentes, se calculó la media aritmética ponderada para obtener resultados factibles.

RESULTADOS

Del proceso de búsqueda inicial se obtuvo un total de 210 artículos: Medline-PubMed (n=5), SCOPUS (n=182) y Web of Science (n=16), Lilacs (n=7). De estas publicaciones, 37 se identificaron como artículos potencialmente elegibles mediante el cribado por títulos y resúmenes. Posteriormente se obtuvieron los artículos a texto completo y se evaluaron exhaustivamente. Como resultado, 6 artículos cumplieron los criterios de inclusión y se incluyeron finalmente en esta revisión sistemática (Fig. 1).

Los resultados descriptivos de las características y variables de cada uno de los 6 estudios incluidos en la presente revisión sistemática se presentan en las Tablas 2 y 3.

Los 6 estudios incluidos en el análisis final tenían poblaciones heterogéneas en cuanto al tamaño de la muestra, el rango de edad, las manifestaciones tumorales, el estadio del carcinoma, las modalidades de tratamiento y las tasas de recurrencia y supervivencia. En total, se diagnosticó y estudió a 4.461 pacientes en relación con las manifestaciones clínicas, el pronóstico y/o el tratamiento del carcinoma oral de células escamosas. De los 4.006 pacientes, 2.624 (65,5%) eran varones y 1.837 (45,9%) mujeres. Dos estudios consideraron el rango de edad menor de 45 años y mayor o igual a 45 años (9,10). Un estudio sólo investigó pacientes mayores o iguales a 45 años (9). Dos estudios investigaron pacientes menores o iguales a 40 años o mayores de 40 años (11,12). Se investigó a pacientes menores de 40 años y mayores o iguales de 40 años (11).

Evaluación de la calidad metodológica y del riesgo de sesgo:

La escala Newcastle-Ottawa se utilizó para medir la calidad de los estudios observacionales no aleatorios (8). De los 6 estudios incluidos en esta revisión, 2 de ellos se consideraron de bajo riesgo de sesgo y los 4 restantes de alto riesgo de sesgo. "Comparison of Clinicopathological Profile of Oral Squamous Cell Carcinoma between Younger and Older Indian Adults" fue el artículo con mayor riesgo de sesgo.

Síntesis de los resultados

Un total de 345 (6,3%) localizaciones de cáncer se identificaron en pacientes de edad inferior a 40-45 años, mientras que 3453 (63,2%) localizaciones de cáncer se observaron en pacientes de edad igual o superior a 40-45 años. En cuanto a los 1668 (30,5%) pacientes restantes, se desconoce en qué rango de edad se clasifican (9–14).

Tanto el grupo de pacientes jóvenes como el de pacientes de edad avanzada establecieron la media total más alta para la localización del carcinoma oral de células escamosas en la lengua, siendo de 189 en los pacientes jóvenes y de 241,16 en los pacientes de edad avanzada.

En cuanto al grado de diferenciación tumoral, ambos grupos de edad determinaron la mayor cantidad de diferenciación tumoral siendo moderadamente diferenciada, teniendo una media total de 27,6 en los pacientes jóvenes y 135 en los pacientes ancianos.

La manifestación tumoral más predominante detectada en ambos grupos de edad fue una morfología exofítica con una media total de 19,3 casos en los pacientes jóvenes y 383 casos en los pacientes de edad avanzada.

Al examinar los enfoques de tratamiento del COCE, los pacientes pertenecientes a ambos grupos de edad recibieron principalmente tratamientos quirúrgicos, siendo la media total de 31,5 para los pacientes jóvenes y de 119 para los pacientes de edad avanzada.

El pronóstico era mejor en los pacientes jóvenes que en los de más edad. En los pacientes de 40-45 años o menos, la tasa de recidiva fue del 19,10%, la tasa de recidiva regional del 5%, la tasa de recidiva distal del 13%, la tasa de control local del 65% y la de fracaso local del 45%. En cuanto a la tasa de supervivencia, fue del 56,4% y la tasa de supervivencia específica de la enfermedad fue del 81,4%. En cuanto a los

pacientes de mayor edad, la tasa de recurrencia global fue del 25,40%, la tasa de recurrencia regional del 11%, la tasa de recurrencia distal del 9%, la tasa de control local del 78% y el fracaso local del 34%. En cuanto a la tasa de supervivencia, fue del 53,50% y la tasa de supervivencia específica de la enfermedad, del 76%.

DISCUSIÓN

La presente revisión bibliográfica proporciona información basada en pruebas sobre las manifestaciones clínicas, el tratamiento y el pronóstico del carcinoma oral de células escamosas en pacientes ancianos en comparación con pacientes jóvenes.

El objetivo de esta revisión era evaluar el pronóstico midiendo la tasa de recurrencia (%) y la tasa de supervivencia (%) del carcinoma oral de células escamosas en pacientes ancianos en comparación con pacientes jóvenes durante un tiempo de seguimiento de 2, 5 o 10 años; y en segundo lugar estudiar y comparar las manifestaciones clínicas y el tratamiento de la enfermedad en pacientes ancianos y jóvenes (localización, grado de diferenciación, morfología tumoral, estadio tumoral).

Manifestaciones clínicas

Entre los pacientes menores de 40-45 años, la aparición de tumores de COCE es relativamente menor en comparación con los grupos de mayor edad, como lo demuestra el hallazgo de que sólo el 6,3% de las localizaciones de cáncer se identificaron en este grupo demográfico. Aunque algunos estudios, como el de Subramaniam N *y cols.* (14), se centraron únicamente en los tumores COCE localizados en la lengua, otros como Cariati P *y cols.* (13) y Xu Qs *y cols.* (12) informaron de la aparición de COCE en múltiples localizaciones orales. La distribución media total de los tumores COCE en este grupo de edad subraya la diversidad de su localización, siendo la lengua el lugar más prevalente seguido de la mucosa bucal, el suelo de la boca y otras regiones.

Por el contrario, en los pacientes de 40-45 años o más, la prevalencia de los tumores COCE es significativamente mayor, constituyendo el 63,2% de las localizaciones del cáncer. Es más probable que presenten tumores COCE, sobre todo en regiones como la lengua y la mucosa bucal. Tanto en los grupos de edad más jóvenes como en los de más edad se observó que la lengua era la localización más

frecuente del OSCC. Nuestros hallazgos coinciden con los de C.D Llewellyn *y cols.* (15) Rafael Ferreira e Costa *y cols.* (16) Khadijah Mohideen *y cols.* (17) Reshma Poothakulath Krishnan (18) siendo la lengua la localización más frecuente. Sin embargo, Samuel E Udeabor *y cols.* (19) determinaron que el suelo de la boca era el lugar más frecuente de aparición del tumor en ambos grupos de edad. Acharya S *y cols.* (20) informaron de que la mucosa bucal (47%) era una localización importante en los pacientes de mayor edad.

El grado de diferenciación tumoral es un factor crítico para comprender la agresividad y el pronóstico del carcinoma oral de células escamosas (COCE).
En los pacientes menores de 40-45 años, la proporción de tumores bien diferenciados fue notablemente inferior en comparación con los grupos de mayor edad. La distribución media total indicaba un predominio de casos moderadamente diferenciados, seguidos de casos bien diferenciados y poco diferenciados. Curiosamente, también se observaron casos con un estado de diferenciación desconocido, lo que sugiere posibles retos a la hora de caracterizar con precisión la histología tumoral en este grupo de edad.

Por el contrario, en pacientes de 40-45 años o más, Ledesma-Montes C, *y cols.* (9), Cariati P *y cols.* (13), Xu Qs *y cols.* (12), Komolmalai N *y cols.* (10), and Devadass CW *y cols.* (11) notificaron diversos grados de diferenciación tumoral, clasificándose la mayoría de los casos como moderadamente diferenciados.

En comparación con otros estudios relevantes, *E M* O'Regan *et al.* (21) y Silvio *K* Hirota *y cols.* (22), Samuel E Udeabor *y cols.* (19) observaron que los tumores bien diferenciados eran relativamente más prevalentes en el grupo de edad más joven. Por el contrario, Ferreira e Costa *y cols*. (16) observaron una mayor prevalencia de tumores moderadamente diferenciados en el grupo de edad joven, coincidiendo con nuestros resultados. *Ramdass y cols.* (23) demostrando una mayor prevalencia de tumores moderadamente diferenciados en pacientes mayores de 45 años, coincidiendo con nuestros resultados. Esto difiere de los estudios de Hakeem *y cols.* (24), M Selvamani *y cols.* (25), Chuanzheng Sun *y cols.* (26), P Loganathan *y cols.* (27) que demuestran que los tumores bien diferenciados son los más frecuentes, seguidos de los tumores moderadamente diferenciados. Estudios de *Mohideen y cols.* (17),

Rosenquist (28), Shou Yen Kao (29), and Soerjomataram *y cols.* (30) coinciden con nuestros hallazgos, revelando una mayor prevalencia de casos moderadamente diferenciados en ambos grupos de edad.

En nuestra revisión, pocos estudios abordaron específicamente la morfología tumoral, lo que subraya la necesidad de seguir investigando en este ámbito. En particular, Xu Qs *y cols.* (12) y Devadass CW *y cols.* (11) proporcionó datos valiosos sobre la morfología tumoral en pacientes de distintos grupos de edad. En pacientes menores de 40-45 años, Xu Qs *y cols.* (12) encontraron un predominio de tumores exofíticos y ulcerativos, con un posible cambio hacia patrones infiltrativos con el tiempo. Devadass CW *y cols.* (11) también observaron una proporción significativa de tumores exofíticos en este grupo de edad.

Por el contrario, entre los pacientes de 40-45 años o más, Xu Qs *y cols.* (12) observaron una mayor prevalencia de tumores exofíticos, ulcerativos e infiltrantes, con variaciones entre los análisis retrospectivos y prospectivos. Devadass CW *y cols.* identificaron de forma similar una presencia significativa de tumores exofíticos en pacientes de mayor edad.

Este estudio detectó una morfología exofítica predominante en ambos grupos de edad, lo que no concuerda con el estudio de Acharya Swetha *y cols.* (20) que observaron una mayor presencia de tumores endofíticos en pacientes jóvenes en comparación con pacientes de más edad. Esta diferencia podría indicar una mayor propensión a la metástasis ganglionar y una respuesta menos favorable al tratamiento en los pacientes jóvenes. Poothakulath Krishnan *y cols.* (18) no observaron diferencias significativas en la cantidad de infiltrado linfoplasmocitario entre los dos grupos de edad, lo que contradice nuestros hallazgos en los que los pacientes de mayor edad aportaron una mayor prevalencia de características infiltrativas.

Tratamiento

En este estudio, se analizaron diversas modalidades de tratamiento empleadas para tratar el carcinoma oral de células escamosas (COCE), que abarcan la cirugía, la radioterapia, la quimioterapia y los cuidados paliativos, ya sea individualmente o en combinación. Cabe destacar que algunos estudios no proporcionaron información exhaustiva sobre los métodos de tratamiento.

Al explorar los enfoques de tratamiento para pacientes menores de 40-45 años, Subramaniam N *y cols.* (14) y Xu QS *y cols.* (12) investigaron principalmente intervenciones quirúrgicas, a menudo combinadas con radioterapia o quimioterapia. Komolmalai N *y cols.* (10) examinaron un espectro más amplio de modalidades de tratamiento, incluidas la cirugía, la radioterapia, la quimioterapia y los cuidados paliativos. La distribución de las modalidades de tratamiento varió entre los estudios, siendo la intervención quirúrgica un enfoque común.

En los pacientes de 40-45 años o más, se observaron tendencias similares, siendo la intervención quirúrgica la principal modalidad de tratamiento. Subramaniam N *y cols.* (14) y Xu QS *y cols.* (12) también notificaron una utilización significativa de terapias adyuvantes en este grupo de edad, incluidas la radioterapia y la quimioterapia. En general, los resultados sugieren que, si bien la intervención quirúrgica sigue siendo la piedra angular del tratamiento del COCE en todos los grupos de edad, la utilización de terapias adyuvantes puede variar, lo que podría reflejar diferencias en la gravedad de la enfermedad, las preferencias de los pacientes o las prácticas institucionales.

Xu Qs *y cols.* (12) sugirieron que un mal estado general de los pacientes tiende a limitar el tiempo de la operación, la selección de los tratamientos con colgajo libre, la recuperación postoperatoria y, lo que es más importante, la selección del tratamiento adyuvante. Esto se observó en los estudios realizados por Linsen *y cols.* (31) y Liu *y cols.* (32) que informaron de una proporción significativamente inferior de pacientes de edad avanzada que recibían radioterapia. Esta puede ser una de las razones clave de los peores resultados y el mal pronóstico de los pacientes de edad avanzada. El estudio de Udeabor *y cols.* (19) fue coherente con nuestro estudio, en el que el mayor porcentaje de metodología de tratamiento observada fue la cirugía.

Pronóstico

Al comparar las tasas de recurrencia y los resultados de supervivencia entre los dos grupos de edad, surgen varias diferencias notables. En primer lugar, al observar a los pacientes de 40-45 años o menos, Subramaniam N *y cols.* (14) notificaron tasas de control local relativamente más elevadas, pero también mostraron tasas de recurrencia global considerables. Por el contrario, en el grupo de mayor edad (40-45 años o más), mientras que Ledesma-Montes C, *y cols.* (9) notificaron una tasa de recidiva global más

baja, las tasas de control local fueron ligeramente inferiores en comparación con la cohorte más joven. Esto sugiere que los pacientes más jóvenes pueden experimentar un comportamiento más agresivo de la enfermedad que requiera medidas de control local más intensivas, mientras que los pacientes de más edad pueden tener un menor riesgo de recurrencia de la enfermedad, pero aún así pueden enfrentarse a dificultades para lograr un control local óptimo.

Además, en términos de resultados de supervivencia, los pacientes más jóvenes mostraron en general tasas de supervivencia global y específica de la enfermedad superiores a las de los pacientes de más edad. Así se desprende de estudios como el de Subramaniam N *y cols.* (14) y Xu QS *y cols.* (12), donde los pacientes más jóvenes mostraron tasas de supervivencia global que oscilaban entre el 56,4% y el 65%, mientras que los pacientes de más edad mostraron tasas de supervivencia global que oscilaban entre el 53,5% y el 71%.

Del mismo modo, las tasas de supervivencia específicas de la enfermedad también fueron notablemente superiores en el grupo de edad más joven, lo que indica una posible mejor respuesta al tratamiento y un menor riesgo de mortalidad relacionada con la enfermedad.

Sanabria *y cols.* (33) informó de que el tratamiento deficiente disminuía la supervivencia global de los pacientes, lo que se observa en la selección de la metodología de tratamiento en pacientes ancianos. Además, Chen *y cols.* (34) observaron la mejora de la supervivencia global de los pacientes ancianos con tratamientos agresivos con intención curativa. Esto coincide con el estudio de Xu *y cols.* (12) en el que se afirmaba que el resultado de los pacientes con COCE puede verse perjudicado en función de una selección inadecuada del tratamiento. Basándose en esta información, se debe sugerir a los pacientes una terapia conjuntiva y adyuvante cuando sea apropiada a pesar de la edad y ésta no debe utilizarse para determinar el tratamiento. Esto también fue concluido por Derks *y cols.* (35) que descubrieron que, aunque los pacientes más jóvenes y los de más edad tuvieran la misma puntuación de comorbilidad, los mayores de 70 años tienen más probabilidades de recibir un tratamiento deficiente que empeoraría su pronóstico.

Nuestro estudio detectó un mejor pronóstico para los pacientes más jóvenes, con una mayor tasa de supervivencia global y específica de la enfermedad. Esto concuerda con los resultados de otras publicaciones, como la de pytynia *y cols.* (36), Ho *y cols.* (37), y Udeabor *y cols.* (19). Este resultado también coincide con los de los estudios de Warnakulasuriya *y cols.* (15), y Fan et al. (38) que informaron de mejores resultados en pacientes más jóvenes.

Limitaciones

La revisión encontró limitaciones a pesar de una extensa búsqueda inicial, con sólo 6 estudios que cumplían los criterios de inclusión de los 210 artículos examinados. Los estudios incluidos carecían de ensayos clínicos comparativos aleatorizados y eran principalmente estudios de cohortes retrospectivos, lo que podía afectar a la exactitud de los resultados. La evaluación del sesgo mediante la escala de Newcastle-Ottawa reveló algunos estudios de alto riesgo, lo que afectó a la fiabilidad de los resultados. Puede existir un sesgo lingüístico, ya que sólo se tuvieron en cuenta las revisiones en inglés, lo que podría dejar de lado estudios valiosos en otros idiomas. Algunos estudios carecían de información esencial como la localización del tumor, el grado de diferenciación o el tratamiento, lo que supone un riesgo de imprecisión. La heterogeneidad de la población, las características, las intervenciones y los resultados entre los estudios incluidos dificultó la extracción de conclusiones significativas.

CONCLUSIÓN

Conclusión principal

1. Los pacientes de mayor edad mostraron un peor pronóstico para el carcinoma oral de células escamosas en comparación con los pacientes más jóvenes. Los pacientes más jóvenes mostraron un mejor grado de tasa de supervivencia global y tasa de supervivencia específica de la enfermedad. Aunque los pacientes más jóvenes mostraron una menor tasa de control local, tuvieron una menor tasa de recurrencia global en comparación con los pacientes de más edad.

Conclusiones secundarias

2. Los pacientes de mayor y menor edad presentaron manifestaciones clínicas similares para el carcinoma oral de células escamosas. La lengua fue la localización más frecuente del COCE tanto en los grupos de edad más jóvenes como en los de más edad. Los tumores moderadamente diferenciados fueron más prevalentes en ambos grupos. La morfología más predominante en ambos grupos de edad fueron los tumores exofíticos.
3. La forma de tratamiento más frecuente en los grupos de mayor y menor edad fueron los procedimientos quirúrgicos, ya que presentaban mejores resultados pronósticos.

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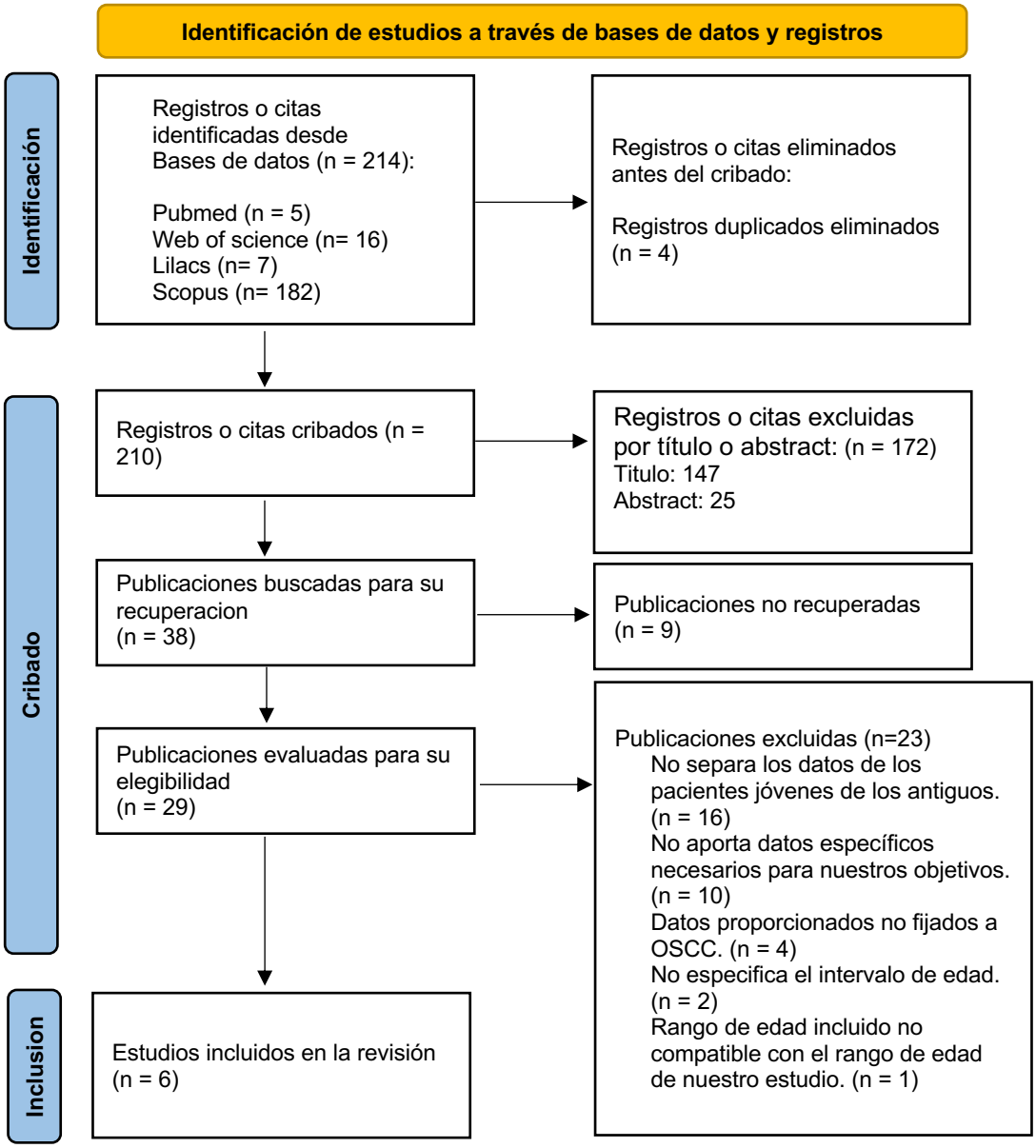

Fig. 1. Diagrama de flujo de búsqueda y proceso de selección de títulos durante la revisión sistemática.

Tabla 1: Características, tratamiento y pronóstico de los estudios revisados

Authores (year and country)	Type of Study	N. patients	Sex	Age (years)	Location of carcinoma (%)	Degree of differentiation (%)	Tumor morphology/manifestation
Ledesma-Montes C, et al. (2018, Brazil)	Cohort Retrospective Review	60	M: 32 F: 28	≥ 45	BT: 23 MT: 37	**BT** WD: 6 (10%) MD: 34 (56.7%) PD:14 (23.3%) CIS: 6 (10%) **MT** WD: 3 (8.1%) MD: 22 (59.4%) PD: 8 (21.6%) CIS: 4 (10.8%)	-
Subramaniam N et al. (2020, India)	Cohort Prospective Review	425	M: 88 (77%) F: 26 (23%) M: 217 (70%) F: 94(30%)	<45 ≥ 45	T: Unspecified	MD/PD: 62 (53%) MD/PD: 135 (43%)	-
Cariati P et al. (2017, Spain)	Cohort Retrospective Review	133	M: 18 F: 15 M: 67 F: 33	<45 ≥ 45	T: 35 FOM: 20 RR: 14 BM: 9 O: 8 Mx: 7 P: 5 G:2 T: 18 (54.5%) FOM: 5 (15.1%) AR: 1 (3.03%) BM: 4 (12.1%) O: 3 (9.09%) Mx: 1 (3.03%) G:1 (3.03%)	WD: 13 MD: 17 PD: 3 WD: 8 MD: 66 PD: 26	-

Xu QS et al. (2019, China)	Cohort Review	2,782					
	Retrospective Part	2,443	M: 94 (65.7%) F: 49 (34.3%)	≤40	T: 102 (71.3%) LG: 12 (8.4%) BM: 6 (4.2%) FOM: 13 (9.1%) UG: 8 (5.6%) HP: 2 (1.4%)	WD: 54 (40%) MD: 71 (52.6%) PD: 10 (7.4%)	E: 29 (23.0%) U: 52 (41.3%) I: 45 (35.7%) VEP: 2 (3.6%) VEA: 53 (96.4%)
			M: 1169 (55.6%) F: 933 (44.4%)	41–75	T: 850 (40.4%) LG: 383 (18.2%) BM: 365 (17.4%) FOM: 235 (11.2%) UG: 203 (9.7%) HP: 66 (3.1%)	WD: 976 (47.7%) MD: 966 (47.2%) PD: 105 (5.1%)	E: 748 (37.8%) U: 704 (35.6%) I: 525 (26.6%) VEP: 29 (4.4%) VEA: 634 (95.6%)
			M: 115 (58.1%) F: 83 (41.9%)	>75	T: 70 (35.4%) LG: 45 (22.7%) BM: 4 (22.2%) FOM:3 (1.5%) UG:33 (16.7%) HP: 3 (1.5%)	WD: 86 (45.3%) MD: 91 (47.9%) PD: 13 (6.8%)	E: 97 (52.2%) U: 60 (32.2%) I: 29 (15.6%) VEP: 3 (4.6%) VEA: 62 (95.4%)
	Prospective Part	339	M: 187 (55.2%) F: 152 (44.8%)	≤40	T: 18 (58.1%) LG: 2 (6.5%) BM: 4 (12.9%) FOM: 1 (3.2%) UG: 3 (9.7%) HP: 3 (9.7%)	WD: 6 (24.0%) MD: 17 (68.0%) PD: 2 (8.0%)	E: 8 (25.8%) U: 9 (29.0%) I: 14 (45.2%)
				41–75	T: 111 (40.2%) LG: 54 (19.6%) BM: 60 (21.7%) FOM: 27 (9.8%) UG: 14 (5.1%) HP: 10 (3.6%)	WD: 59 (26.1%) MD: 163 (72.1%) PD: 4 (1.8%)	E: 70 (25.4%) U: 97 (35.3%) I: 108 (39.3%)
				>75	T: 8 (25.8%) LG: 8 (25.8%) BM: 10 (32.3%) UG: 5 (16.1%)	WD: 5 (18.5%) MD: 20 (74.1%) PD: 2 (7.4%)	E: 7 (23.3%) U: 15 (50.0%) I: 8 (26.7%)
Komolmalai N (2015, Thaliand)	Cohort Retrospective study	874	M: 23 (63.9%) F: 13 (36.1%)	<40	L: 1 (2.8%) T: 27 (75.0%) FOM: 2 (5.6%) P: 2 (5.6%): BM: 2 (5.6%) RR:1 (2.8%) Mouth, NOS: 1	WD: 18 (50%) MD: 11 (30.6%) PD: 5 (13.9%) UD: 0 (0%) UK: 2 (5.6%)	-

					(2.8%)		
			M: 494 (58.9%) F: 344 (41.1%)	≥ 40	L: 63 (7.5%) T: 309 (36.9%) G: 156 (18.6%) FOM: 69 (8.2%) P: 91 (10.9%) BM: 119 (14.2%) RR:12 (1.4%) Mouth, NOS: 16 (1.9%) Multiple sites: 3 (0.4%)	WD: 487 (58.1%) MD 235 (28.9%) PD: 62 (7.4%) UD: 3 (0.4%) UK: 51 (6.1%)	
Devadass CW et al. (2020, India)	Cohort Prospective Review	187	M: 20 (57.1%) F: 15 (42.9%)	≤40	BM:19 (54.3%) LAR: 6 (17.1%) RR: 3 (8.6%) T: 7 (20%)	WD: 10 (28.6%) MD 22 (62.9%) PD: 1 (2.9%) VC: 2 (5.7%)	E: 21 (60%) En: 14 (40%)
			M: 100 (65.8%) F: 52 (34.2%)	>40	L: 2 (1.3%) BM: 79 (52%) LAR: 26 (17.1%) UAR: 3 (2%) RR: 15 (9.9%) FOM: 2 (1.3%) HP: 4 (2.6%) T: 21 (13.8%)	WD: 41 (27%) MD 101 (66.4%) PD: 7 (4.6%) VC: 3 (2%)	E: 92 (60.5%) En: 60 (39.5%)

M: Male; F: Female; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; CIS: Carcinoma in situ; UD: Undifferentiated; UK: Unknown; VC: Verrucous Carcinoma; BT: Base of the tongue; MT: Mobile tongue; T: Tongue; FOM: Floor Of Mouth; RR: Retromolar Region; BM: Buccal Mucosa; O: Oropharynx; Mx: Maxilla; G: Gingiva; P: Palate; AR: Alveolar Ridge; UAR: Upper Alveolar Ridge; LAR: Lower Alveolar Ridge; LG: Lower Gingiva; UG: Upper Gingiva; HP: Hard Palate; NOS: Not Otherwise Specified; L: Lip; E: Exophytic; En: Endophytic; U: Ulcerative; I: Infiltrative; VEP: Vascular Emboli Present; VEA: Vascular Emboli Absent

Tabla 2: Estadio, tratamiento, tasa de recurrencia y tasa de supervivencia de los estudios revisados

Authores (year and country)	Type of Study	N. patients	Sex	Age (years)	Stage (TNM/ AJCC 7th Cancer Staging Manual)	Treatment	Recurrence (%)	Rate of survival

Ledesma-Montes C, et al. (2018, Brazil)	Cohort Retrospective Review	60	M: 32 F: 28	≥ 45	**TNM** T2N0M0: 47 T3N0M0: 2 T3N2bM0: 1 T4aN0M0:3 T4dN2bM0: 7 AJCC: II: 48 III: 3 Iva: 9	**MD-OSCC** Wide excision or hemiglosectomy **PD-OSCC** Wide local excision or hemiglosectomy **WD-OSCC** Wide excision or hemiglosectomy **CIS** Wide local excision or hemiglosectomy, possibly with neck dissection	OR: 9 (15%) **MD-OSCC** 11.8%: further excision or neck dissection **PD-OSCC** 21.4%: further excision or neck dissection **WD-OSCC** 1 case: further excision **CIS** 1 case: further excision	-
Subramaniam N et al. (2020, India)	Cohort Prospective Review	425	M: 88 (77% F: 26 (23%) M: 217 (70%) F: 94 (30%)	<45 ≥ 45	LI: 38 (33%) PI: 47 (41%) DF: 60 (53%) CM: 4 (4%) EE: 43 (38%) LI: 66 (21%) PI: 87 (28%) DF: 146 (47%) CM: 8 (3%) EE: 72 (23%)	S: 51 (45%) S + R: 11 (10%) S + CCRT: 52 (45%) S: 161 (52%) S + R: 41 (13%) S + CCRT: 109 (35%)	LCR: 65% RRR: 5% DRR: 13% LCR: 78% RRR: 11% DRR: 9%	OS: 65% DSS: 67% OS: 71% DSS: 74% P value: OS: (p = 0.481)

								P value DSS: (p = 0.156).
Cariati P et al. (2017, Spain)	Cohort Retrospective Review	133	M: 18 F: 15 M: 67 F: 33	<45 ≥ 45	T1: 57,5%, (n=19) T2: 27,2%, (n=9) T3: 3,03% (n=2) T4: 3,03% (n=3) NI: 48,4% (n=16) T1: 27% (n=27) T2: 37% (n=37) T3: 29% (n=29) T4: 7% (n=7) NI: 33% (n=33)	-	LF: 45.4% (n=15) LF: 34% (n=34)	5y-OS: 48.4% (n=16) 5y-OS: : 62% (n=62) P value: OS: (p=0.17)
Xu QS et al. (2019, China)	Cohort Review	2,782						
	Retrospective Part		M: 94 (65.7%) F: 49 (34.3%)	≤40	**<u>cT stage</u>** T1: 33 (23.1%) T2: 58 (40.5%) T3: 19 (13.3%) T4 33 (23.1%) **<u>pN stage</u>** N0: 72 (55.8%) N1: 25 (19.4%) N2: 30 (23.3%) N3: 2 (1.5%) PI: 17 (28.8%)	S: 55 (47.8%) S+R: 47 (40.9%) S+CCRT: 13 (11.3%)	OR: 38.2%	DSS: 77.2%

			M: 1169 (55.6%) F: 933 (44.4%)	41–75	No PI: 42 (71.2%) DI: 18 (32.7%) No DI: 37 (67.3%) **<u>cT stage</u>** T1:487 (23.2%) T2: 817 (38.9%) T3: 209 (9.9%) T4: 589 (28%) **<u>pN stage</u>** N0: 1053 (59.1%) N1: 301 (16.9%) N2: 424 (23.8%) N3: 4 (0.2%) PI: 155 (21.7%) No PI: 559 (78.3%) DIP: 244 (36.6%) No DI: 422 (63.4%)	S: 908 (60.4%) S+R: 466 (31.0%) S+CCRT: 130 (8.6%)	OR: 46.7%	DSS: 69.7%
			M: 115 (58.1%) F: 83 (41.9%)	>75	**<u>cT stage</u>** T1: 58 (29.3%) T2: 84 (42.4%) T3: 19 (9.6%) T4: 37 (18.7%) **<u>pN stage</u>** N0: 81 (62.8%) N1: 15	S 113 (76.4%) S+R: 29 (19.6%) S+CCRT: 6 (4.0%)	OR: 52.0%	DSS: 55.4%

					(11.6%) N2: 33 (25.6%) N3: 0 (0%) PI: 10 (14.7%) No PI: 58 (85.3%) DI: 40 (61.5%) No DI: 25 (38.5%)		Total recurrence:1, 006/2443 patients (46.6%)	Total DSS: 1487/2157 patients (68.9%)
	Prospective Part		M: 15 (48.4%) F: 16 (51.6%)	≤40	**<u>cT stage</u>** T1: 7 (22.6%) T2: 14 (45.2%) T3: 5 (16.1%) T4: 5 (16.1%) **<u>pN stage</u>** N0: 25 (80.6%) N1: 4 (12.9%) N2: 2 (6.5%) N3: 0 (0.0%)	S: 19 (61.3%) S+R: 12 (38.7%) S+CCRT: 0 (0%)	OR: 0.0%	DSS 100.0%
			M: 161 (58.1%) F: 116 (41.9%)	41–75	**<u>cT stage</u>** T1: 70 (25.3%) T2: 81 (29.2%) T3: 30 (10.8%) T4: 96 (34.7%) **<u>pN stage</u>** N0: 197 (71.1%) N1: 29 (10.4%) N2: 50 (18.1%)	S: 194 (70.1%) S+R: 76 (27.4%) S+CCRT: 7 (2.5%)	OR: 15.7%	DSS: 94.8%

			M: 11 (35.5%) F: 20 (64.5%)	>75	N3: 1 (0.4%) **cT stage** T1: 8 (25.8%) T2: 10 (32.3%) T3: 1 (3.2%) T4: 12 (38.7%) **pN stage** N0: 24 (77.4%) N1: 2 (6.5%) N2: 5 (16.1%) N3: 0 (0.0%)	S: 30 (96.8%) S+R: 1 (3.2%) S+CCRT: 0 (0.0%)	OR: 30.0% Total recurrence: 326/339 patients	DSS: 80.0%
Komolmalai N (2015, Thaliand)	Cohort Retrospecti ve Review	419	M: 23 (63.9%) F: 13 (36.1%)	<40	**Clinical stage** I: 3 (8.3%) II: 11 (30.6%) III: 1 (2.8%) IVA: 12 (33.3%) IVB: 0 (0.0%) IVC: 1 (2.8%) UK: 8 (22.2%)	S: 1 (2.8%) R: 9 (25%) C:1 (2.8%) S+R: 12 (33.3%) S+R+C: 2 (5.6%) S+C: 0 (0.0%) R+C: 6 (16.7%) P: 2 (5.6%) UK:3 (8.3%)	-	5-y OS: 56.2%
			M: 494 (58.9%) F: 344 (41.1%)	≥ 40	**Clinical stage** I: 83 (9.9%) II: 169 (20.2) III: 105 (12.5%) IVA: 275 (32.8%) IVB: 17 (2.0%) IVC: 14 (1.7%) UK: 175 (20.9%)	S: 119 (14.2%) R:242 (28.9%) C: 26 (3.1%) S+R: 156 (18.6%) S+R+C: 26 (3.1%) S+C: 7 (0.8%) R+C: 58 (6.9%) P: 108 (12.9%) UK: 96 (11.5%)		5-y OS: 27.4%

								5-y survival rate: F: 33.7% M: 25.3% Stage I: 54.6% Stage II: 18%
Devadass CW et al. (2020, India)	Cohort Prospective Review	187	M: 20 (57.1%) F: 15 (42.9%) M: 100 (65.8%) F: 52 (34.2%)	≤40 >40	PI: 3 (8.6%) EE: 5 (14.2%) LI: 14 (40%) **cT stage** T1:5 (14.3%) T2: 10 (28.6%) T3: 13 (37.1%) T4: 7 (20%) **pN stage** N0: 21 (60%) N1: 7 (20%) N2: 5 (14.3%) N3: 2 (5.7%) **TNM stage** I: 1 (2.9%) II:7 (20%) III: 15 (42.9%) IV: 12 (34.3%) PI: 14 (9.2%) EE:14 (9.2%) LI:42 (27.6%) **cT stage** T stage: T1: 16 (10.5%) T2: 65 (42.8%) T3: 45 (29.6%) T4: 26 (17.1%)	-	-	-

					pN stage N0: 113 (74.3) N1: 16 (10.5) N2: 18 (11.8) N3: 5 (3.3) **TNM stage** I: 9 (5.9) II: 39 (25.7) III: 56 (36.8) IV: 48 (31.6)			

M: Male; F: Female; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; CIS: Carcinoma in situ; UD: Undifferentiated; UK: Unknown; VC: Verrucous Carcinoma; BT: Base of the tongue; MT: Mobile tongue. S: Surgery; R: Radiotherapy; C: Chemotherapy; CCRT: Concurrent Chemoradiotherapy; P: Palliative; LI: Lymphovascular Invasion; PI: Perineural invasion; DF: Discohesive Front; CM: Close Margin (< 5 mm); EE: Extranodal Extension; OR: Overall Recurrence; OS: Overall Survival; DSS: Disease Specific Survival; LCR: Local Control Rate; RRR: Regional Recurrence Rate; DRR: Distal Recurrence Rate; NI: Node Involvement; LF: Locoregional Failure; DI: Diffuse Infiltration;

Tabla 3: Manifestaciones clínicas del carcinoma oral de células escamosas

ARTICLE	LOCATION																DEGREE OF DIFFERENTIATION							TUMOR MORPHOLOGY					
	Tongue	Floor of the Mouth	Retromolar Region	Buccal Mucosa	Oropharynx	Maxilla	Palate	Gingigva	Lower Gingiva	Upper Gingiva	Hard Palate	Lip	Mouth -unspecified	Alveolar Region	Lower Alveolar Region	Upper Alveolar Region	Well Differentiation	Moderate Differentiated	Poor Differentiated	Moderatel-Poorly Differentiated	Carcinoma Insitu	Veruciys carcinoma	Undifferentiated	Unknown	Exophytic	Endophytic	Ulcerative	Infilterative	Vascular Emboli	Vascular Emboli
< 40-45 years																													
Subramaniam N et al. (2020, India)	Not Specified																			62									
Cariati P et al. (2017, Spain)+ A4:AD4	35	20	14	9	8	7	5	2									13	17	3								-			
Xu Qs et al. (2019, China) (retrospective part)	102	13		6					12	8	2						54	71	10						29		52	45	2	53
Xu QS et al. (2019, China) (prospective part)	18	1		4					2	3	3						6	17	2						8		9	14		
Komolmalai N et al. (2015, Thaliand)	27	2	1	2			2					1	1				18	11	5				0	2						

Devadass CW et al. (2020, India)	7		3	19			3.5	2		7	5.5	2.5	1	1	0	6	0	10	22	1		2	0	0	21	14				
Total Mean	37.8	9	6	8	8	7	3.5	2	7	5.5	2.5	1	1	0	6	0	20.2	27.6	4.2	62	0	2	0	2	19.3333333	14	30.5	29.5	2	53
≥ 40-45 years																														
Ledesma-Montes C, et al. (2018, Brazil)	60	-															9	56	22		10				-					
Subramaniam N et al. (2020, India)	Not Specified	-																		135					-					
Cariati P et al. (2017, Spain)+ A4:AD4	18	5		4	3	1			1				1				8	66	26						-					
Xu Qs et al. (2019, China) (retrospective part)	920	238		369					428	236	69			1062	1057	118								845		764	554	32	696
Xu Qs et al. (2019, China) (prospective part)	119	27		70					62	19	10			64	183	6								77		112	116		
Komolmalai N (2015, Thailand)	309	69	12	119			91	156				63	16				487	235	62				3	51						

Devadass CW et al. (2020, India)	21	2	15	79							4	2			26	3	41	101	7			3			92	60				
Total Mean	241.166667	68.2	13.5	128.2	3	1	91	156	163.666667	127.5	27.66666667	32.5	16	1	26	3	278.5	283	40.16666667	135	10	3	3	51	338	60	438	335	32	696

Tabla 4: Tratamiento y pronóstico del carcinoma oral de células escamosas

ARTICLE	TREATMENT											RECURRENCE RATE							SURVIVAL RATE	
	Surgery	Surgery + Radiotherapy	Concurrent chemoradiotherapy	Surgery + Concurrent Chemoradiotherapy	Radiotherapy	Chemotherapy	Surgery + Radiotherapy + Chemotherapy	Surgery + Chemotherapy	Radiotherapy + Chemotherapy	Palliative	unknown	Overall recurrence	5-year recurrence rate	2-year recurrence rate	Local Control Rate	Regional Recurrence Rate	Distal Recurrence Rate	Local Failure	Overall Survival Rate	Disease Specific Survival Rate
< 40-45 years																				
Subramaniam N et al. (2020, India)	51	11	0	52											65%	5%	13%		65%	67%
Cariati P et al. (2017, Spain)																		45%	48%	
Xu QS et al. (2019, China) Retrospective part	55	47		13								38.20%								77.20%

Xu QS et al. (2019, China) Prospective part	19	12		0								0%								100%
Komolmalai N et al. (2015, Thaliand)	1	12			9	1	2	0	6	2	3								56.20%	
Total Mean	31.5	20.5	0	21.6666667	9	1	2	0	6	2	3	19.10%	0	0	65%	5%	13%	45%	56.40%	81.40%
≥ 40-45 years																				
Ledesma-Montes C, et al. (2018, Brazil)	Not Specified											15%								
Subramaniam N et al. (2020, India)	161	41	109	0											78%	11%	9%		71%	74%
Cariati P et al. (2017, Spain)																		34 (34%)	62%	
Xu QS et al. (2019, China) Retrospective Part	1021	495	136						0			47.20%								68.50%
Xu QS et al. (2019, China) Prospective Part	224	77	7									14%								85.40%
Komolmalai N (2015, Thaliand)	119	156		26	242	26	0	7	58	108	96								27.40%	

Total Mean	381.25	192.25	84	13	242	26	0	7	58	108	96	25.40%	0	0	78%	11%	9%	34%	53.50%	76%