SYSTEMATIC REVIEW

Is there a difference between disease-free survival of oral squamous cell carcinoma referred by dentists versus other physicians? A systematic review

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Abstract

Objective: To compare disease-free survival rates in oral squamous cell carcinoma patients initially attended and referred by dentists versus other physicians.

Methods: The systematic review was conducted after registration with the International prospective register of systematic reviews at the University of York, the United Kingdom, and comprised search on Medline, PubMed, Cochrane and CINAHAL Plus databases for studies published up to December 2021. The Population-Intervention-Comparison-Outcomes-Study criteria was used to search for studies involving patients diagnosed with oral squamous cell carcinoma receiving referrals by dentist or by other healthcare providers. Disease-free survival of patients was taken as the main outcome. Customized data collection proforma was used to record data in line with the Preferred Reporting Items in Systematic Reviews and Meta-Analysis guidelines. Data was subjected to systematic, qualitative review.

Results: Of the 344 studies found, 8(2.3%) were analysed in detail. Patients referred by dentists ranged from 22.6% to 54%. Males comprised 53% to 70.3% of the sample. The highest number of referrals was made by primary physicians, ranging from 27.4% to 71.6%. Upto 67.6% cases were diagnosed with stage 1 and 2 oral cancer. The highest 5-year survival rate was 75% in a study where 59% patients were diagnosed at an early stage of disease.

Conclusion: The relative scarcity of studies makes it impossible to draw an association between oral cancer survival rate and type of referral.

Keywords: Oral squamous cell carcinoma, Cancer-free survival, Early detection, Referrals. (JPMA 73: 2036; 2023)

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Introduction

Globally, despite advances in modern therapeutics, oral cancer has been affiliated with low survival rates and poor prognosis. Almost 90% of oral cancers are oral squamous cell carcinomas (OSCC), and 1% of all types of cancers and 1% of mortalities caused by cancer are due to OSCC.[1] Reducing the delay in diagnosis and early detection is a key element in improving patient survival. This is largely dependent on the referral system, especially access and quality in the healthcare in a particular country.[2] It's alarming to note that almost 40% of OSCCs are diagnosed with regionally metastatic disease and 6% with distant metastasis.

In the diagnosis of OSSC, there are several referral stages involved. Stage 1 begins from the occurrence of the first symptom to the first consult with a physician or dentist; stage 2 begins from the first consult until a referral letter is provided; stage 3 begins from the referral letter to the consultation with a specialist service; stage 4 begins from the specialised consultation till a definitive diagnosis is achieved.[3]

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The National Institute for Health and Care Excellence (NICE) of the United Kingdom has recommended that for any lesion suspicious of OSCC, the general practitioners must refer to the specialists if the patient has an unexplained persistent mouth ulcer for 3 weeks, or an unexplained neck lump is present. It also recommends a within two weeks appointment if the presentation is with erythroplakia or erythroleukoplakia. A lump found in the lip or in the oral cavity or a red or white lesion should get an immediate referral.[4]

A marked correlation has been observed between delay in patient presentation and diagnosis of tumour stage. Some studies have elaborated on the interrelationship between patients suffering from advanced stage of the disease during diagnosis and patient delay.[5,6] Recent evidence indicates that early diagnosis can greatly reduce the morbidity and may enhance long-term survival among patients.[7] Greater delays have been known to make survival worse.[1,2]

There are several factors that contribute to the delay in diagnosis. The most significant one is the delay in the presentation of the patients to the clinicians. Usually, primary clinicians can detect lesions suspicious of oral cancers and make an early referral, but not all clinicians have similar competency in that domain, and a subset still

ends up in misdiagnosis and mistreatment of patients. Tobacco users and alcoholics should be frequently screened and referral made when a suspicion arises. This is the responsibility of medical or dental practitioner they visit. Indirect referrals may lead to diagnostic delay which can be avoided if during referrals the practitioner makes it clear as to who would be treating the condition. It should be considered normal for practitioners to contact the specialists without any hesitance, and to discuss referrals and cases that are suspicious of malignancy.[8]

Despite the therapeutic advances, there have been no significant improvements in the mortality and morbidity of OSCC in the last three decades. The 5-year survival rate of OSCC still ranges 40-50%. Despite the quick and convenient access to the oral cavity, OSCC is usually diagnosed in late stages. Incorrect initial diagnosis by the physicians and ignorance from the patient side are amongst the most relevant reasons for the delay in management.[9]

Clinicians should be acquainted with oral red or white lesion, persistent ulcers, tumours, especially anything lasting more than two weeks, that may be an indication of malignancy. A biopsy from these lesions is needed to eliminate the suspicion. The latest advancement in technology is focussing on early diagnosis of OSCC using cytological smears on salivary samples and molecular analysis.[10] In advanced stages, the 5-year survival rate is reported to be around 12%. The life expectancy of such patients is not >30 months post-diagnosis.[11]

According to Scully et al.,[12] clinicians, especially the general medical practitioners, were responsible for the delay in making timely referrals for OSCC subjects. Others suggested that inadequacy of awareness regarding the nature of OSCC has led to the fear of cancer, which resulted in significant delays in patients reaching out for the medical treatment.[13] A study documented that 50% of symptomatic patients who were diagnosed with OSCC delayed almost 3 months or even longer before reaching out for professional help.[14]

There is a difference in the competence of clinicians trained in the detailed examination of oral cavity, and, owing to their clinical training, dentists are likely to pick up suspicious oral lesions earlier than the other physicians. Therefore, it can be speculated that there is a difference between the disease-free survival (DFS) of OSCC patients initially attended and referred by dentists versus other healthcare providers. The current systematic review was planned to evaluate DFS rates in OSCC patients initially attended and referred by dentists versus other healthcare providers.

Materials and Methods

The systematic review was conducted after registration with the International prospective register of systematic reviews (PROSPERO; CRD42021231921)[15] at the University of York, UK, and comprised search on Medline, PubMed, Cochrane and CINAHAL Plus databases for studies published up to December 2021. The search strategy used medical subject heading (MESH) terms as well as free-text terms. The endnote list was further studied to filter out studies for potential inclusion in the review.

A strict selection criterion was employed. The list of research articles gathered went through precise scrutiny to achieve the articles that met the inclusion criteria. Patients with suspected OSCC referred by general dentist and general practitioner were included. Patients of all genders falling in the age group of 18-65 years were included.

The Population-Intervention-Comparison-Outcomes-Study (PICOS) criteria[15] was used where, P=patients diagnosed with OSCC receiving referrals by either dentists or by physicians; I=referral of potential OSCC patients by dentists; C = patients referred by physicians (non-dentists); O = DFS of patients; S; clinical trials, quasi-experimental, cross-sectional and longitudinal studies.

Studies dealing with diseases other than OSCC, or where the referring healthcare provider was neither a dentist nor a physician were excluded. In this way, referrals from traditional healers, alternative, herbal or complementary medicine practitioners were excluded. Patients falling out of the age bracket, or studies published in languages other

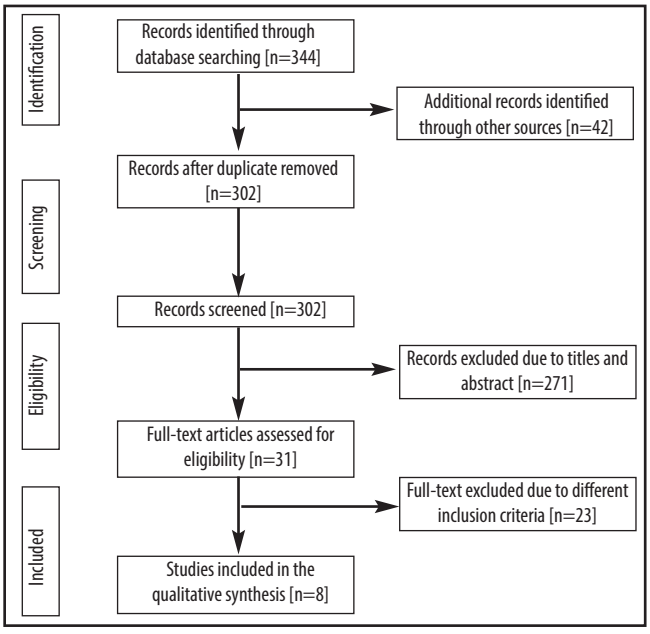

Figure-1:Preferred Reporting Items in Systematic Reviews and Meta-Analysis (PRISMA) flowchart.

than English or studies in which outcome was other than survival were also excluded. Similarly, letters to the editors, case reports, case series, opinion papers, systematic reviews, abstracts and conference proceedings were also excluded.[15]

All the studies initially found were reviewed by two researchers on an end-note document in a non-blinded and independent process. Any paper that met the PICOS and the inclusion criteria proceeded to the next stage, where full-text assessment was done. In this stage, all three researchers reviewed the studies blinded and independently. Any difference in opinions at this stage were resolved by mutual consensus.

A data-collection proforma was devised using Preferred Reporting Items in Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[16] Only qualitative review was done along with the assessment of the quality of each study reviewed using a customised criterion. Depending upon various parameters of the study, grade 1 meant a poor quality study, grade 2 referred to a study with acceptable quality and grade 3 was assigned to study that satisfied most of the quality criteria.[17]

Results

Of the 344 studies found, 8(2.3%) were analysed in detail (Table 1). Patients referred by the dentists ranged from 22.6%[18] to 54%.[2] The highest number of referrals were made by primary physicians, ranging from 27.4%[19] to 71.6%.[20] Male preponderance was evident, ranging from 53%[21] to 70.3%.[20] The mean age at the time of diagnosis ranged from 57.2 years[21] to 65.8 years.[22] Majority of the cases (up to 67.6%) were diagnosed at stages 1 and 2 of the cancer.[18] The 5-year DFS rate of OSSC was not reported in 5 out of 8 studies. (Table 2)

The highest 5-year DFS rate was reported by Chandu et al. 75%.[2] The patient referral by dentists and physicians in that study was 54% and 46%, respectively.[2] The high survival rate in that study could be attributed to the observation that 59% patients were diagnosed at an early stage of disease.

Table-1: Details of the studies reviewed.

S.No.	Authors	Year	Journal	Study Design	Objectives
1.	Wang et al.[18]	2018	The Permanente Journal	Cohort-Retrospective	To characterize the diagnostic pathway of OCSCC in an integrated health care system
2.	Chandu et al.[2]	2002	Australian Dental Journal	Cohort-Retrospective	To study the referral patterns of patients undergoing surgical management of oral cancer.
3.	Holmes et al.[19]	2003	Journal of Oral Maxillofacial Surgery	Cohort-Retrospective	Is a lower stage of diagnosis related to the diagnosis of OSCC by a healthcare professional?
4.	Hong et al.[20]	2016	British Dental Journal	Cohort-Retrospective	To prospectively explore head and neck patients through the 2- week referral process.
5.	Santos et al.[21]	2010	Brazilian Journal of Otorhinolaryngology	Cross-sectional	To access factors associated with the late diagnosis of oral cancer in the state of Alogoas, Brazil.
6.	Kaing et al.[22]	2016	Australian Dental Journal	Cohort-retrospective	This study identifies changes in referral patterns and delays in diagnosis and treatment of OSCC
7.	Varela et al.[23]	2021	Multidisciplinary Digital Publishing Institute	Cohort-prospective	The impact of presenting symptoms on time intervals, number of visits at the primary care level, and referral pattern of patients with symptomatic oral cancer.
8.	Watson et al.[24]	2009	Community Dentistry & Oral Epidemiology	Cohort-prospective	To examine the characteristics and treatment seeking behaviors of patients diagnosed with oral and pharyngeal cancer.

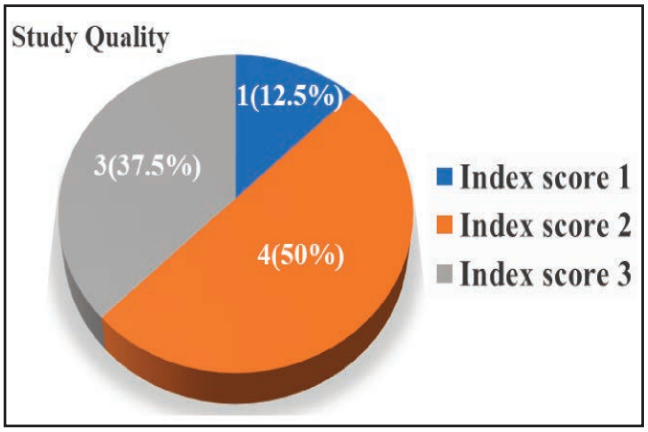

Figure-2: Distribution of the studies according to their quality.

Table-2: Patient characteristics in the studies reviewed.

Study author	n	Referrals by Dentist n (%)	Referrals by Physician n (%)	Males in the study n (%)	Mean Age at diagnosis (years)	Stage 1 and 2 n (%)	Stage 3 and above n (%)	5-year survival (%)
Wang et al.[18]	247	86 (22.6)	161 (65.2)	NA	64.2±14.2	167 (67.6)	80 (32.3)	NA
Chandu et al.[2]	113	61 (54)	52 (46)	61 (54)	61.7±11.9	44 (59)	56 (37)	75
Holmes et al.[19]	51	19 (37.2)	14 (27.4)	28 (56)	62.2±10.2	32 (63)	19 (37)	50
Hong et al.[20]	220	72 (32.7)	148 (67.2)	116 (53)	59.8±dnr	NA	NA	NA
Santos et al.[21]	74	21 (28.4)	53 (71.6)	52 (70.3)	57.2±14.0	16 (21.6)	58 (78.4)	NA
Kaing et al.[22]	101	42 (43)	52 (53)	63 (62)	63.0±9.3	61 (60)	40 (40)	NA
Varela et al.[23]	181	32 (23)	47 (34.1)	115 (63.9)	65.8±12.7	NA	NA	20-50
Watson et al.[24]	131	NA	NA	90 (69)	60±dnr	63 (48)	55(42)	NA

NA: Not applicable; n: Number of participants; dnr: Did not report.

In terms of the quality of studies, 3 out of 8 studies (37.5%) were of good quality (score 3), 4 out of 8 (50%) studies had acceptable quality and only one study was with poor quality (12.5%). (Figure 2)

Discussion

OSCC is a prevalent cancer among males in South Asian countries. It is a public health problem in societies where use of tobacco, alcohol and areca nut is prevalent. Awareness by educating patients about the significance of oral cancer can be undertaken by healthcare workers. This will encourage them to avoid delays and visit a dentist or a physician to get an early referral. The survival of patients can be improved if early diagnosis and timely referral can be made. Due to expertise in the disease of oral cavity, the patients examined by dentists are likely to have better survival rates compared to medical practitioners.

Santos et al.[20] reported an interesting study where physicians made most referrals (over 71%), sample comprised of relatively young males (mean age 57 years) with majority of cases (78%) presenting with 3rd or 4th stage of cancer. Unfortunately, a lot of participants were lost to follow-up and with lack of data stating their 5-year DFS survival.

Overall, the patients referred by dentist were diagnosed at a considerably earlier stage than those that were referred by a general physician. Patients with the correct diagnosis were likely to have the right treatment initiated at an early stage. This decreases the mortality as the patient has better chances of recovery.[19] The current systematic review has limited data to explain the 5-year survival rate of OSCC patients. The main objective of the review was to estimate 5-year DFS rate, but only 3 out of the 8 studies reported that parameter.

Prospective studies with a larger sample size with special emphasis on the referral patterns and survival outcomes are recommended for better analysis. The 5-year survival ranges from 20% to 75%.[2,22] By virtue of their training and practice, dentists focus mostly on the oral cavity and have a better eye to catch any changes or abnormalities. Being expert in dealing with the anatomy and pathology of the oral cavity, dentists are more likely to pick up signs of oral cancer earlier than any other physician. Hence, getting efficient referrals from the clinicians of oro-facial region can certainly benefit patients by saving time. More studies should be planned with a similar research question and longer follow-ups.

The stage of OSCC at the time of diagnosis is one of the most significant prognostic markers for the survival. However, there has not been a significant change in early-stage diagnosis despite the known fact that early detection can reduce morbidity and improve survival rates in patients. This has in turn resulted in the delays in treatment.[23] The Surveillance, Epidemiology, and End Results (SEER) programme at National Cancer Institute analysed that only 28.7% of oral and pharynx cancers were diagnosed before the metastasis (stage 1), the main causes being delay in diagnosis and failure to catch silent symptoms.[24] It has been known that dental practitioners can provide a greater number of consultations to the same patient, whereas general practitioners use less efficient routes which delays and prolongs the referral process.[2]

Moreover, patients tend to get more anxious and stressed due to long waiting times and the uncertainty in diagnosis that comes with long waiting periods.[24,25] In the UK, a two week-wait (2WW) is practised in the referral of oral, pharyngeal and head-and-neck cancer to fast-track patient care. A rapid treatment than routine referral has not

translated into an improvement in survival rates.[26] However, a significant decrease in oral cancer stage and subsequent morbidity has been observed in prompt referrals, specifically in cases where the patients realised something unusual and consulted the doctor timely.[24,25]

The main limitation of the current systematic review is the exclusion of studies other than those in the English language. Studies where the primary attending Health Care Provider was alternative medicine practitioner or traditional healer were also not included in the review. Lastly, due to lack of quantitative data, meta- analysis could not be performed.

Conclusions

The 5-year survival of OSCC patients referred by dentists ranged from 20% to 75%, which is a wide range that needs validation through studies based on referral patterns. The relative scarcity of studies on the matter makes it impossible to draw a definitive association between survival rate and type of referral. Therefore, more studies with strong evidence and longer follow-ups are needed.

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