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A Rare Synchronous Existence of Warthin's Tumour and Oral Cancer

A systematic review

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Abstract

Oral squamous cell carcinoma (OSCC) is one of the most common malignancies worldwide while Warthin's tumor (WT) is a common type of benign salivary gland neoplasm mostly seen in the parotid gland but rarely involves extra parotid tissues. Extra parotid WT is itself a rare entity and its synchronous occurrence with OSCC is an unusual phenomenon. It is vital to accurately identify the pathology as confusion may arise due to its rare occurrence and an intriguing presentation of resembling metastasis in lymph nodes. In the present review, a systematic literature search was performed and case reports and series in which synchronous existence of WT and OSCC were included. Total 13 papers have been included with 17 cases of synchronous WT and OSCC. Quality assessment for cases was done based on the CARE guidelines. The given results describe the histological features and site of WT in individuals who also had OSCC. Most of the studies described the histological findings of WT, which were seen involving the lymph nodes. More than 50% of the included cases had a history of tobacco chewing or smoking. The cases that have reported for follow up showed no evidence of any recurrence. WT with OSCC synchronous occurrence at a different site from the primary tumor can mimic a metastatic

lesion from a primary lesion. It is a diagnostic challenge and could alter the management of these patients if not identified accurately. Awareness about this synchronous occurrence can avoid the overtreatment in such cases. Majority of the WTs described were seen in cervical lymph nodes.

***Keywords*:** Oral cancer; Warthin tumor; Benign Neoplasm; Mixed salivary gland tumor; Synchronous neoplasm; metastasis; Second malignancy; Prognosis.

Introduction:

Oral cancer stands as a substantial contributor to worldwide mortality, emerging as one of the prevalent malignancies that significantly impacts the global population.[1] The diagnosis and management of this condition is sometimes complicated by coexistence of second primary lesions. Patients with head and neck squamous cell carcinoma (HNSCC) show a higher incidence rate of second primary lesions by over 2-3% annually. It means they may occur with other benign or malignant neoplasms.[2] These second primary tumors (SPTs) can either be synchronous or metachronous. The cases in which the SPT is detected within 26 weeks of the primary tumor signifies synchronous tumor while the cases in which the SPT is diagnosed more than 26 weeks after the diagnosis of the first primary tumor represents metachronous tumor.[3] Metachronous SPTs (20% to 30%) are more commonly identified than the synchronous ones (1% to 6%) in HNSCC cases. The most frequently involved sites are head and neck, pulmonary, and esophageal mucosal regions. These are the sites that are exposed to carcinogens like tobacco or alcohol and are thus suspected to display the phenomenon of field cancerization.[3-10]

The occurrence of the contemporaneous parotid or any major salivary gland neoplasms is an extremely rare event. The risk factors for OSCC comprise deleterious habits such as tobacco chewing and smoking, alcohol consumption, use of betel nut and betel quid along with direct or indirect association with various oncoviruses like human papilloma virus and Epstein Barr virus (EBV). Warthin's tumour (WT) also known as papillary cystadenoma lymphomatosum is a benign tumour of the salivary glands, mainly affecting the parotid gland. It is among the most common benign parotid neoplasms and the most common bilaterally occurring neoplasm in the parotid.[11] The main predisposing factors for WT are tobacco smoking, exposure to various radiations and infections caused by viruses like EBV. The cases in which there is synchronous association of WT and OSCC are rarely seen and documented in the literature.

Thus, there is an infrequent incidence of association of WT at a different site from the primary OSCC, which may imitate as a metastatic lesion of the primary OSCC making it necessary to diagnose the coexisting neoplasms for accurate management of the patients. Thus, the current paper presents a systematic analysis of all the cases representing synchronous existence of OSCC and WT in the available medical literature focusing on the clinical and histopathological features. It also elaborates the rare possibility of the occurrence of WT in extra-parotid sites, usually cervical lymph nodes.

Methods

Focused Question

Participants, Intervention, Control and Outcomes (PICO) protocol advocated in the Preferred Reporting Items in Systematic Reviews and Meta-Analysis (PRISMA)].[12] has been followed to frame a focused question: What are the complications, rate of recurrence, prognosis post-intervention in the patients with synchronous occurrence of OSCC and WT? The systematic review is registered with PROSPERO (registration number 425093).

Inclusion and exclusion criteria

Clinical trials (randomized and non-randomized), cross-sectional studies, case reports (CRs), observational studies (retrospective and prospective), case series (CS), grey literature (conference proceedings, non-academic websites etc.); articles in all languages (Google translator to translate studies) are reviewed and only radiologically and histopathologically diagnosed patients coexisting with OSCC and WT have been included in the present review.

Non-human subjects, reviews, commentaries, letters to the editor were excluded. OSCC with other neoplasms, WT with other neoplasms and an inapt study described as a non-CR, such as a review, commentary, or clinical trial were not included from the present review.

Literature search

Two investigators (SM and GS) conducted a thorough search procedure of various databases individually. An electronic search was piloted using the following databases: PubMed, Scopus and Web of Science. Google Scholar was used to explore grey literature aiming on cases with

coexisting WT and OSCC. The medical subject headings (MeSH) were as follows [(Warthin's tumor) OR (papillary cystadenoma lymphomatosum) AND (oral cancer) OR (OSCC) AND (diagnosis) OR (prognosis) OR (recurrence)]. Cross referencing of the included articles was also executed to find any further studies satisfying the inclusion criteria. Disparities were resolved by a dialogue between the investigators for inclusion/exclusion of a paper. Calculation of an inter-examiner reliability score (Kappa score) was done for gauging the agreeability between the examiners.

Data Extraction

The data tabulation was done by two investigators individually based on the criteria: number of participants, number of cases with WT synchronous with OSCC described in each study, chronological age which included the mean or median or the range and gender of the patients, characteristic features like histological, radiographic and clinical features, any WT synchronous with OSCC-related outcome and follow-up. Details of the treatment, rate of the recurrence and details of the complications and prognosis were also recorded.

Quality Assessment

Quality assessment for CR and CS was done based on CARE guidelines.[13] Various characteristics were evaluated such as the title, keywords, quality of the abstract, introduction, reported patient information, clinical findings, timeline, diagnostic evaluation, interventions reported, follow-up and outcome, and quality of the discussion section, standpoint of the patients and inclusion of the informed consent and approval from the scientific and ethics committee stated.

Results

Literature Search

The maiden search of the literature for the topic ensued 3264 papers. Later, 3209 irrelevant papers were excluded. The abstracts and titles of 55 papers were studied for possible annexation, which resulted in exclusion of 42 papers. Thus, 13 articles with full text were logged in for possible inclusion. Thirteen studies (10 CRs [14-24] and 3 [15, 25, 26] CS) were finally included in the present review. There were no further studies uncovered in the reference lists of the

comprised articles. The literature search is represented in the PRISMA flowchart including the exclusion criteria for the selected articles. (Figure 1)

General Characteristics of the Included Studies

WT synchronous with OSCC was found in 17 patients in the included studies.[14-26] In reported 13 studies, a male preponderance was observed with almost twice as many cases (M: 11, F: 6)[14-26] with the age ranging between 42 -86 years, and a mean age of 64 years ± (SD). Majority of cases presented with a habit history of tobacco chewing,[14,16,22] smoking,[14,19,21-24,26] alcohol consumption.[14,22] One case reported of deranged liver function test which can happen in such synchronous pathology patients who have a history of alcohol consumption.[22] In a single case, history of hepatitis C since 11 years was also reported.[16]

The majority of the cases described the primary finding as OSCC with ulcerative lesion [14,21-24,26] and enlarge lymph nodes.[14,15,20,22,23] In one case sensory disturbance of left lower lip is reported. [20] One patient complained burning sensation and limited mouth opening. [22] Site of OSCC was found in tongue, [15,19,21,25,26] buccal mucosa, [14,16,25,26] floor of mouth,[24,25] buccal mucosa and gingiva, [16] lower lip,[17] retromolar triangle,[18] mandible,[20] mandibular gingivobuccal complex, [22] maxillary gingiva,[23] mandibular gingiva.[25] (Table 1 and 2) The size of the lesions mentioned are 10 mm x 5 mm,[16] 5 cm x 4 cm,[14]18 mm x13 mm,[21] 30 mm x15 mm,[24] 4 cm x 4 cm,[26] 2 cm x 2 cm.[26] TNM staging of OSCC is reported as T2N2M0,[19] T4N1M0,[20] T2N0M0,[21] T4aN2bM0,[23] two cases of T3N1M0,[25] two cases of T2N1M0.[25]In some reports the grading of OSCC is noted as well differentiated squamous cell carcinoma, [17,22] moderately differentiated [16,26] and poorly differentiated.[14]

Majority of the cases described WT histologically, were seen involving the lymph nodes.[14, 16, 19–24, 26] The site of the WT was noted in cervical lymph nodes,[16, 17 19-22, 25] in submandibular lymph nodes,[18, 23] in periparotid region,[15] tail of parotid,[14, 26] submandibular gland.[24] (Table 1 and 2) The histological findings of cystic space lined by bilayered cuboidal and columnar epithelium is mentioned in most of the cases,[14, 16, 19-24, 26] epithelial arrangement along with lymphoid aggregate is also noted.[14, 16, 20-23, 26] The size of the WT is mentioned as 12mm x 8mm x 6mm,[16]

1.45cm,[20] 5mm x 3mm and 4mm x 3mm [23] and 6mm [24] Ranging from 3mm to 1.45 cm with a mean of 8.3mm.

The investigations done included incisional biopsy,[14] excisional biopsy,[16,21,22,26] excisional biopsy along with CT scan,[16,21] Contrast-enhanced CT showed an enlargement in cervical LN (15mmx11mmx10mm) at contralateral level.[21] Ultrasound showing 12mm x 8mm x 6mm hypo-echoic mass adjoining the sternocleidomastoid muscle border anteriorly and to the external jugular vein posteriorly.[16] PET/CT scan was performed in a few cases,[19,20,23] intense radiotracer uptake i.e., maximum standardized uptake value of 5.2 was observed at the resection site in a case[19] and MRI was performed in one of the studies. FNAC reported RBCs and inflammatory cells in a case.[21] FDG-PET/CT scan was also performed in a few cases,[19,21,23] Intense FDG uptake (SUV max 9.5 and 5.7) in the enlarged LN level II ipsilaterally was observed.[19] SUV max of the primary site and the opposing side cervical LN were 2.2 g/mL and 3.7 g/mL, respectively, [21] with a SUV max of 19.96. SUV max of 6.8, 8.17 and 5.1 was reported in the right submandibular LN [23] and SCC antigen value of 3.3ng/ml was also noted.[23]

Details of various features like clinical, histological, and radiographic characteristics of the WT synchronous with OSCC, are comprehensively described in Table 1.

Management, Recurrence Rate and Post-Op Complications

Four cases described excision of OSCC site and supra-omohyoid neck dissection as a line of treatment.[17,19,20,25] Seven cases underwent excision of OSCC site and modified radicle neck dissection.[14,18,22-26] Three cases reported radiotherapy after excision.[16,24,25] Follow-up was noted in three studies including 6 cases as 6 months, 24 months, 18 months, 35 months, 28 months and 46 months.[17,18,25] No recurrence was found in four patients.[21,23,24,26] Recurrence of OSCC buccal mucosa was noted in one case,[16] which was further treated with radiotherapy. In one case, death due to chemotherapy was reported.[26] One study concluded that OSCC is the key prognostic determinant in such cases and might majorly complicate post-operative management.[18]

Quality Assessment

In six studies (46.15%), the title is stated as type of study,[14,16,18,22,25,26] and in five studies, keywords are used as CR and CS.[16,19,23,24,26] The principal outcomes were reported adequately in the abstract in seven studies.[14,18,21,23-26] Conclusion was included in the abstract in around four studies.[18,24-26] The main findings in the abstract were reported moderately in six studies.[14,18,23-26] A fair introduction was available in five studies.[14,23-26] Patient information with no identification was provided in thirteen studies.[14,15-18,19-26] The main symptoms and finding of the patients were described in ten cases.[14,16,18-24,26] Other findings such as medical and family history along with psychosocial and genetic aspects were not mentioned in any of the included studies but one with partial information.[16] A past interventional history was provided in two cases.[19,20] In four CRs, adequate details about the physical examination of the patients have been provided.[16,22,25,26] The treatment timeline for the included patients has not been included in any of the studies. Diagnostic testing was carried out sufficiently in seven cases.[16,19-23,26] The specialists facing challenges during diagnostic assessment is not reported in any of the cases, but all provided a specific diagnosis of the cases. Adequate information about the prognosis and/or staging was specified in about ten of the cases.[14,16-18,19-26] Surgical intervention or radiotherapy information was provided sufficiently in twelve cases [14,16-18,19-26] but only in one case, no details or level of the surgical intervention was mentioned.[15] Additionally, none of the CRs and CS mentioned about any deviation from the original treatment strategy. Patient or clinician-reported outcomes were mentioned in seven cases.[14,21-26] Adequate information about the follow-up details was available in seven cases.[16,18,21-26] Adherence and tolerability to the follow-up were reported in three cases.[14,16,19] Data regarding post-operative complications were provided in about three cases.[16,20,26] Assessment of discussion sections shows, limitations and weaknesses, were described in about ten studies.[14,15,16,20,21,22-26] The related literature was discussed adequately in twelve studies.[14,15.16,18-25] In around ten CRs, the conclusion was reasonable and justified adequately.[14,16,18,20-26] Recommendations or 'take-away' lessons were given by twelve cases. [14,15,18,19-26] Patient perspectives were not mentioned in any of the studies and information about the patient consent and ethics was mentioned in just two cases.[23,26] A detailed description is provided in Table 3.

Discussion

In the present systematic review, total 13 papers have been included with 17 cases of synchronous existence of WT and OSCC. The clinical manifestations, TNM staging and grades of OSCC have been reported in these papers. Report of sensory disturbance, burning sensation and limited mouth opening suggests that OSCC can cause various symptoms that may affect the patient's quality of life. Apart from these reports, the results also suggest that WT can occur simultaneously with OSCC. Since tobacco use is a common etiology for both OSCC and WT, the patients with a known history of such habit should be significantly considered for regular oral cancer screenings and lymph node involvement status especially in case of regional metastasis and its diagnosis.

The given results describe the histological features and site of WT in individuals who also had OSCC. Most of the studies described the histological findings of WT, those were seen in involved lymph nodes. Though WT is known to be found exclusively in parotid gland, the site of the WT in the present review was noted in various locations, including cervical lymph nodes, submandibular lymph nodes, periparotid region, tail of parotid, and submandibular gland.[14-26] The histological findings of WT were characterized by a cystic space lined by bilayered cuboidal and columnar epithelium, as well as an epithelial arrangement along with lymphoid aggregate. These features are consistent with the typical histological appearance of WT found in parotid gland.

Warren and Gates have studied multiple primary malignant tumors (MPMTs).[27] They have also proposed detailed criteria to diagnose such type of tumors. According to the given criteria, 1) each tumor must be histologically diagnosed as malignant, 2) each tumor must be separate and distinct geographically, 3) exclusion of the metastasis caused due to prior cancer. There are international guidelines, which have been laid down and have elaborated the criterion. The tumors developing in an organ/ a pair of organs/ a tissue should be contemplated as a single tumor. However, there are 2 variations to this rule: 1) In any individual, systemic cancers involving multiple different organs should be considered only one. 2) Histologically different cancers, even if they are diagnosed at the same site should be considered as multiple tumors.[27]

The reported incidence of MPMTs ranges between 0.52% to 11.7%. Formerly, the pathogenesis for the formation of MPMTs was attributed to field cancerization. It means it was posited that the etiology for multiple oral primary carcinomas developing independently was pervasive exposure of the epithelial cells to the carcinogens. But recent literature supports the common clonal origin, an alternative theory.[28]

To diagnose WT synchronous with OSCC, a similar criterion should be proposed and followed. Both the neoplasms show histologically distinct pictures. Both the neoplasms should be geographically separate and distinct. Because of the proximal association of such salivary gland tumor and regional lymph nodes, and in particular WT, these lesions may clinically show the features of lymph nodes enlargement, leading to a misdiagnosis of metastatic lymph nodes in OSCC patients, which could further obfuscate the treatment plan of these type of patients. Nearly 90% of all oral cancers are OSCCs with 40% of them revealing nodal metastasis.[29] Therefore, associated practitioners (radiologists, head and neck surgeons, and pathologists) should be well aware of the existence of these infrequent findings to prevent overtreatment in these cases. Extra parotid WTs are usually found accidently during neck dissection in approximately 1% of oral cancer patients, and they appear like metastatic lesions, particularly in positron-emission tomography/computed tomography (PET/CT) imaging.[25] This ambiguity can be mitigated by using fine needle aspiration cytology. Considering WT as metastatic lesions can lead to the over diagnosis of the condition leading to an extensive treatment planning. Involvement of the lymph nodes by WT has a better prognosis as compared to the lymph node involvement by OSCC metastasis.[30]

Synchronous occurrence of WT with other benign neoplasms like oncocytoma, pleomorphic adenoma, sebaceous lymphadenoma and malignant neoplasms like lymphoma have been reported in the literature.[22] With neoplasms like oncocytoma, the reason for the synchronous occurrence could be that the WT sharing a common etiology, biological and clinical features with oncocytoma.[26] There are 2 different theories for WT development: The first hypothesis is related to heterotopia suggesting that the tumor upshots from proliferating salivary gland ductal cells that were entrapped in lymph nodes of the parotid gland during embryonic life. This hypothesis might rationalize about no occurrence of any WT in the lower neck levels, i.e., levels IV and V. And

the second theory proposes that a WT primarily develops in the lymph nodes of parotid in presence to a stimulus, like smoking tobacco.[31] Thus, this explains the 8 times higher incidence of WTs in cases of smokers than that in non-smokers.[32] Moreover, there is a general observation of association of smoking and tobacco consumption habit with male population which might explain the gender predilection towards males in the present systematic review. The present systematic review describes the synchronous occurrence of WT and OSCC occurring in a total of 17 cases. The cases exhibited male predilection of 64 years of mean age. The deleterious habit of tobacco consumption in the form of chewable or smoking was recorded in the history of almost all the patients.

Smoking has a proved connotation with WT development and is evident from the literature. In a retrospective analysis of 96 patients suffering from WT, about 79% reported a history of cigarette smoking.[33] There is oxidative destruction taking place in the mitochondrial DNA of the cells especially oncocytic ones as a response to smoking habit. This damage initiates the tumorigenesis of WT. It has been stated that smokers are at 8 times higher risk of developing the neoplasm compared to non-smokers.[34] On the other hand, the main etiologic factor for OSCC is also tobacco. The strong common link between WT and OSCC is the habit of smoking tobacco. The carcinogens from the smoke mix with the saliva and flushes into the ducts of salivary gland in a retrograde manner resulting in metaplasia of the salivary ducts.[14] The conclusion that 74.8% of WT patients are smokers supplements this hypothesis.[35] Thus, the carcinogen from the smoke affects the salivary ductal cells as well as oral mucosal cells at the same time which might elucidate the synchronous occurrence of WTs and OSCC.

The genetic analysis of WT is an essential factor for understanding its etiopathogenesis and its connection to OSCC as reported in this systematic review.[36] Recently, t(11;19) translocation and its *CRTC1/MAML2* fusion transcript are reported in a few cases of WT which are common with mucoepidermoid carcinoma (MEC), a salivary gland malignancy proposing a common genetic link between a WT and a carcinoma.[37] On the contrary, Sharma et al.[32] have reported 17p13.1 (*TP53*), 9p21.3 (*CDKN2A*), 9q34.3 (*NOTCH1*), and 3q26.32 (*PIK3CA*) with 24 other altered genetic loci in OSCC patients with deleterious habit of smoking in his study. A few of the genetic aberrations altered by smoking are found to be commonly affected in OSCC and WT.

Therefore, there seem to be a lot of scope to find out more genetic and epigenetic details, which are shared by WT and OSCC in their etiopathogeneses.

There is lot of controversy related to the role of oncoviruses in the pathogenesis of OSCC and WT. WT is known to be associated with EBV.[38] Though, there is no direct correlation between EBV and OSCC, there is an evidence present in the literature about their association.[39] EBV-associated oral cancers are comparatively rare, as oral cavity is known for the presence and transmission of EBV. But oral cavity can serve as a primary location for the virus which can seed malignancy at another extra oral site such as the nasopharyngeal or gastrointestinal regions. Consequently, the role of EBV in its associated cancers is co-factorial, which requires presence of other genetic aberrations and other coexistent infections caused by human papilloma virus. EBV infection is believed to be a critical episode in tumorigenesis and is directly associated with rapid progression of the disease and the metastatic tendency. EBV detection in OSCC is very rare and probably difficult to detect because of its known ‘hit-and-run’ phenomenon. Thus, incomplete viral association is often reported. There is evidence of EBV bystander oncogenic effects on the tumor microenvironment. Loss of EBV during evolution of the neoplasm or progression of the disease has also been suggested. EBV-induced epigenetic reprogramming enables the virus to retain the oncogenic phenotypes despite its total absence or absence of its gene expression. Thus, future analyses will be needed to find out a definitive role of EBV in the pathogenesis of OSCC and provide virus-associated biomarkers for OSCC management.[39] HPV also has been lately suggested to play important part in the pathogenesis of WT.[35] On the contrary, the International Agency of Research of Cancer professed that there is a sufficient substantiation that HPV 16 is associated with OSCC.[40] It has been noted that within 20 years of period, out of total OSCC cases, the percentage of HPV-positive OSCC went from <20% to >70% in the USA and European countries.[41]

The studies included in the systematic review mentioned about the investigation techniques which included biopsy, CT scans, contrast-enhanced CT, ultrasound, MRI, PET/CT scans and FDG-PET/CT scans. PET/CT is frequently used during follow-up of the cancer patients. WT demonstrates high FDG uptake leading to the misdiagnosis of cervical lymph node metastases. In such cases, fine-needle aspiration cytology (FNAC) is useful to evaluate salivary gland tumor.

The diagnostic accuracy of FNAC for detecting salivary gland neoplasms, especially WT is good (74-100%).[42] WT is a benign slow growing.[43] Therefore, surgeons can take a risk to manage such cases conservatively after diagnosis with FNAC.

To detect the synchronous coincidence of WT and OSCC is a real diagnostic challenge leading to difficulties for the radiologists as well as surgeons. Cervical lymph nodes and tail of parotid are one of the most conventional sites for metastasis from primary OSCC. On the other hand, the incidence of 1.3% was found to be with extra-parotid WTs in neck specimen of OSCC patients. Thus, these tumors can lead to inaccurate staging of OSCC. Moreover, false positive results of FDG-positive WT add to the misdiagnosis. Therefore, CT/ultrasonography guided FNAC may be helpful in such situations to distinguish WT from OSCC metastasis.

The treatment of synchronous WT and OSCC requires careful planning and consideration of various factors, including the location and extent of the lesions, the stage of the cancer, and the patient's overall health. The available literature shows that the most common treatment modality for synchronous WT and OSCC is surgical removal of the primary tumor and involved lymph nodes. The extent of dissection of neck varies according to the location and extent of the tumor, with supraomohyoid neck dissection and modified radical neck dissection being the most performed procedures. In some cases, adjuvant radiotherapy may be required to reduce the risk of recurrence.[14,16-18,19-26] The follow-up period for patients with synchronous WT and OSCC is critical, and close monitoring is necessary to detect any signs of recurrence. The prognosis for patients with synchronous WT and OSCC is generally favorable if the lesions are detected and treated early. However, the prognosis may be poor in advanced stages of the disease or if there are underlying comorbidities. It is important to note that the available literature on synchronous WT and OSCC is limited, and there is a need for further studies to determine the most effective treatment strategies and the long-term outcomes of patients with this rare combination.

Limitations and future scope

Rarity of the synchronous occurrence of WT with OSCC is one of the major limitations, which does not allow performing any meta-analysis on the topic. Moreover, the results can not be generalized due to limited number of the included cases. We also declare the possibility of

selection bias due to inclusion of only case report and case series. Case report and case series presentations often show heterogeneity in terms of presentation of clinic-pathological, radiological, management and prognostic data limiting the comparability of the data. There is need for original research on larger sample sizes on this rare pathology to get meaningful results. This also should involve the genetic and molecular characterization of the WT with OSCC and development of targeted therapy. Since, there is a diagnostic challenge, future studies should also focus on finding accurate imaging techniques.

Conclusions

The rare finding of synchronous occurrence of WT at a different site from the primary tumor can mimic a metastatic lesion from primary OSCC. It is a serious diagnostic challenge and can lead to mismanagement of the case with consequent complications. Accurate diagnosis of such cases is essential for proper management, otherwise, it can alter the entire treatment strategy and affect the quality of life of the individual. The team of specialists (radiologists, surgeons, and pathologists) involved in managing such cases should be well versed of the existence of such synchronous neoplasms. Awareness about this coexistence can avoid the overtreatment of such condition. If diagnosed correctly using techniques like FNAC, the condition can be managed conservatively using non-surgical techniques especially in elder individuals.

Authors' Contribution

Study conception and design was done by GS and SaS. SM, ShS and NS contributed to the data collection. Data analysis was performed by VM and RA. The results were interpreted by GS, SaS and VM. All authors were involved in manuscript preparation and editing. All authors approved the final version of the manuscript.

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During the preparation of this work the authors used ChatGPT in order to refine the language of the paper in a few sections. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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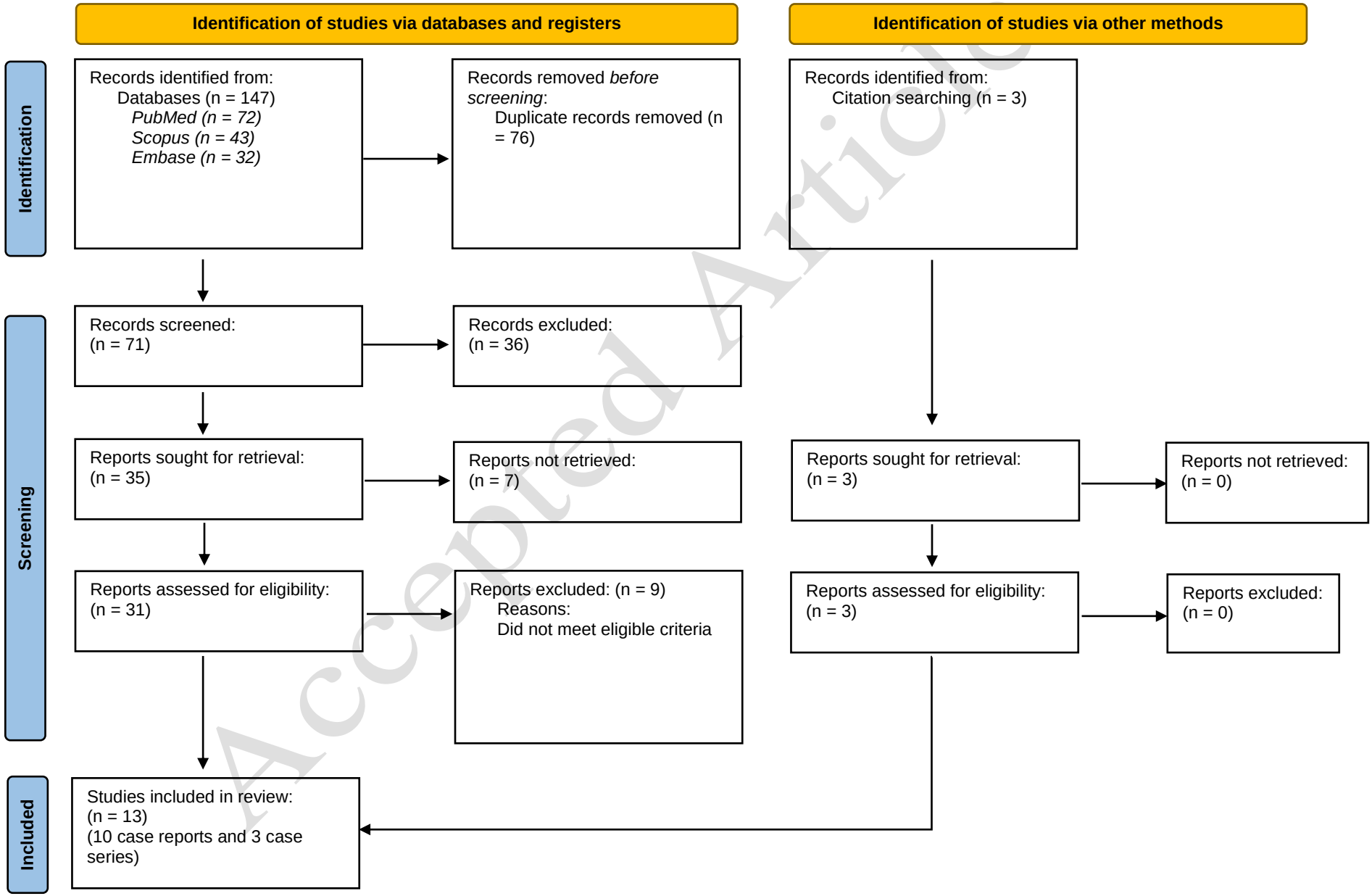
Figure 1: PRISMA 2020 flow diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Table 2: Site wise distribution of oral squamous cell carcinoma and Warthin's tumor

SITE OF OSCC	SITE OF WARTHIN'S TUMOR		NO. OF CASES
Tongue	Parotid gland (4 cases)	Peri-parotid lymph node	1
Tongue		Tail of parotid gland	1
Buccal mucosa		Tail of parotid	1
Buccal mucosa		Lower lobe of parotid gland	1
Floor of mouth	Submandibular gland (3 cases)	Sub mandibular gland	1
Retromolar triangle		Sub mandibular gland	1
Maxillary gingiva		Sub mandibular gland	1
Tongue	Cervical lymph nodes (10 cases)	Cervical lymph node	1
Lower lip		Cervical lymph node	1
Buccal mucosa		Level II lymph node	1
Buccal mucosa and gingiva		Cervical lymph node	1
Floor of mouth		Level II lymph node	1
Tongue		Level II lymph node	2
Lower gingiva		Level II lymph node	1
Mandible		Level II lymph node	1
Gingivobuccal complex		Level II lymph node	1
Total cases			**17**

Table 3: Risk of bias assessment

		Synderman et al.1986	Sato et al. 1998	Demir et al.2002	Shehan et al. 2004	Nupehewa et al. 2009	Schwarz et al. 2009	Enomoto et al. 2011	Iwai et al. 2012	Bhatlawande et al. 2019	Sato et al. 2020	Yang et al. 2020	Gontarz et al. 2021	Goh et al. 2022
1	**Selection**													
	1. Does the patient(s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported	NO	YES	YES	NO	YES	YES	YES	NO	YES	NO	NO	YES	YES
2	**Ascertainment**													
	2. Was the exposure adequately ascertained?	NO	YES	NO	YES	YES	YES	NO	NO	YES	NO	NO	YES	YES
	3. Was the outcome adequately ascertained?	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
3	**Causality**													
	4. Were other alternative causes that may explain the observation ruled out?	YES	YES	NO	YES	YES	NO	YES	NO	YES	NO	YES	YES	ye
	5. Was there a challenge/rechallenge phenomenon?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	6. Was there a dose–response effect?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	7. Was follow-up long enough for outcomes to	YES	YES	NO	YES	NO	NO	NO	YES	NO	YES	YES	YES	YES

	occur?													
4	**Reporting**													
	8. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?	YES	YES	NO	YES	YES	NO	TES	NO	YES	YE S	YES	NO	YES

Table 4: Percentage of case reports and case series reporting based on CARE checklist

Item number	Section	Total (n)	Percentage (%)
1	Title	6/13	46.15%
2	Keywords	7/13	53.84%
3a	Abstract	11/13	84.61%
3b	Case representation	13/13	100
3c	Conclusion-What were the main “takeaways” lessons from this case?	12/13	92.30%
4	Introduction	5/13	38.46%
5a	Patient information	13/13	100
5b	Main symptoms of the patient	13/13	100
5c	Medical, family, and psychosocial history-including diet, lifestyle, and genetic information whenever possible and details about relevant comorbidities and past interventions and their outcomes	13/13	100

6	Clinical findings	13/13	100
7	Timeline	6/13	46.15%
8a	Diagnostic assessment	13/13	100
8b	Diagnostic challenges	-	-
8c	Diagnostic reasoning	11/13	84.61%
8d	Prognostic characteristics	8/13	61.53%
9a	Therapeutic intervention	12/13	92.30%
9b	Administration	-	-
9c	Changes in intervention	-	-
10a	Follow-up and outcomes	9/13	69.23%
10b	Important follow-up test results	9/13	69.23%
10c	Intervention adherence and tolerability	-	-
10d	Adverse and unanticipated events	3/13	23.07%
11a	Discussion		
11b	Relevant literature	12/13	92.30%
11c	Rationale for conclusions	11/13	84.61%
11d	Main “take-away” lessons of this case report	12/13	92.30%
12	Patient perspective	-	-
13	Informed consent	2/13	15.83%