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SHORT PAPER

Analysis of Cervical Node Metastasis in Oral Cavity Squamous Cell Carcinoma Patients

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ABSTRACT

Background/Objective: Oral Cavity Cancer is a frequent type of Head and Neck Cancer, associated with high mortality rates worldwide. One of the main prognostic factors for the disease is regional lymph node metastasis that is associated with survival rate reduction by 50%. Reported tumour sites more frequently associated with regional node metastasis vary throughout literature. Therefore, we aimed to conduct a retrospective study that would allow us to identify the relationship between patient and SCC tumour factors with the rate of neck metastasis and compare our data with the conclusions from similar studies.

Methods: A retrospective study was conducted in the Oral Medicine and Oncology Consultation of the Stomatology Department from Centro Hospitalar Universitário Lisboa Norte, comprehending patients diagnosed with Squamous Cell Carcinoma between January 2015 and April 2021. As eligibility criteria we considered patients which had clinical charts with complete information including sociodemographic variables, tumour site and disease staging at diagnosis. We excluded tumour sites with only two diagnosed cases, considering bias risk. Three groups were defined according to a clinical/pathological reason. The current research was approved by an independent ethics committee.

Results: The sample includes 151 cases, the majority of which were males (≈59%) and with average age at diagnosis (± standard deviation) of 65 ± 13 years-old. Oral tumour sites with highest percentage of cases with clinical positive lymph nodes (cN+) by the time of diagnosis were inferior gingiva (72.7%, n=16), mouth floor (66.7%, n=22), oropharynx (64.7%, n=11), retromolar trigone (58%, n=11) and ventral tongue (57%, n=16). Sites with fewer cases of cN+ were inferior lip (31%, n=4) and superior lip (n=0). Similar results were found in our sample when operated tumors (pN+) were considered: floor of the mouth (65%, n=13), retromolar trigone (63.6%, n=7), inferior gingiva (46.2%, n=6) and ventral tongue (45%, n=9). Tumour sites with fewer pN+ cases were hard palate (25%, n=1), superior gingiva (16.7%, n=1) and inferior lip (0 out of 7 cases). According to Fisher's exact test there is no statistically significant association (p-value=0.1506) between primary tumour site and cervical node disease (either cN+ or, whenever available, pN+).

Conclusions: Our data seem to indicate an association between primary tumour site and N+, being cervical metastasis more frequent when tumour site was posterior and caudally located. Lower lip had the fewer positive lymph nodes, probably correlated with the inclusion in the same group of oral mucosa and skin cancers. Despite these findings, the association was not statistically significant.

Introduction

Oral Cavity Cancer is a frequent type of Head and Neck Cancer and is in sixteenth position worldwide [1]. Squamous Cell Carcinoma (SCC) accounts for more than 90% of the cases in this region [2]. Oral cavity cancer is a malignant neoplasia that includes subsites buccal mucosa, floor of mouth, anterior tongue, alveolar ridges, retromolar trigone, hard palate, and inner part of lips. About 90% of the cases are attributable to tobacco and alcohol use as well as deleterious chewing habits (including tobacco chewing, betel quid, areca nut, pan masala, gutka and others) [1]. Although the incidence rates are higher in men, diagnosis in females seems to be increasing in some parts of the world [3].

This disease is associated with high mortality rates [4] and the presence of lymphatic metastases is thought to be the most relevant prognostic factor [5]. When present, it is associated with survival rate reduction by almost 50% [4] – early stage cancers (stages I and II) have about a 80% 5-year survival rate,

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compared with a 50% 5-year survival rate in cases with locoregional metastasis (stages III, IVA and IVB) and only 25% for cancers with distant metastasis (stage IVC) [3]. Cervical node metastasis are directly related to tumour T staging as well as depth of invasion and tumour thickness [6]. Other factors that negatively influence the outcome of oral cavity cancer patients include presence of extracapsular spread and number of involved lymph nodes [5].

Metastasis is not an early finding in oral cavity SCC (OSCC) patients, but delay in diagnosis increases the likelihood of it being present in initial evaluation [3]. Reported tumour sites more frequently associated with regional node metastasis vary throughout literature and it is thought that the dissemination behaviour may be influenced by barriers it encounters, namely bone and the lymphatic drainage [7]. With this in mind, tumours that arise more posteriorly in the oral cavity are usually more prone to cervical metastasis [3].

Therapeutic management of clinically node negative neck is defined by calculated risk of occult metastases or undetectable micro metastases [5], and primary subsite of cancer lesion may play a relevant role in this estimates [8].

Therefore, we aimed to conduct a retrospective study that would allow us to identify the relationship between patient and SCC tumour factors with the rate of neck metastasis. For this, we included the patients diagnosed with oral SCC between January 2015 and April 2021 in our Department. Afterwards, we proceeded to compare our data with the conclusions from other similar studies.

Methods

A retrospective study was conducted in the Oral Medicine and Oncology Unity of the Stomatology Department of Centro Hospitalar Universitário Lisboa Norte, comprehending patients diagnosed with SCC between January 2015 and April 2021. A convenience sample was considered accordingly with the clinical information available. As eligibility criteria we considered patients which had clinical charts with complete information including sociodemographic variables, tumour site and disease staging at diagnosis. We excluded tumour sites with only two diagnosed cases, considering bias risk. Because the study sample dimension is small to assess a big number of tumour sites, were defined three groups according to a clinical/pathologic reason: i) anterior region - upper maxilla: upper lip, maxillary gingiva and alveolar ridge, upper vestibule, jugal mucosa, hard palate; ii) anterior region - lower jaw: lower lip, lingual border, lingual dorsum, lingual belly, floor of the mouth, mandibular gingiva and alveolar ridge, lower vestibule; iii) posterior region: retromolar trigone, oropharynx.

For continuous variables, the average ± standard deviation or median values and corresponding interquartile range were presented, according to data underlying distribution. Data distribution normality was evaluated with Kolmogorov-Smirnov test, with Lilliefors correction. For categorical variables, results were presented as frequency and percentage - n (%). For continuous variables, comparison with two independent samples, t-test or Mann-Whitney U test was performed, when suitable. When more than two independent samples were present, Kruskal-Wallis test was applied. For categorical variables, Qui-Square or exact Fisher test were performed, when applicable.

Qui-Square test seeked to assess possible associations between following variables: tumoral location, staging/growth, and differentiation degree. For the implementation of said test, Cochran criteria were verified; (ii) when Cochran criteria were violated, Fisher exact test and its extension (Fisher-Freeman-Halton test) were applied [9]. For each statistical test performed, when suitable, inherent test statistics (TS), degree of freedom (df) and p-value were presented in brackets. Significance level was established at 5% and all statistical processing and graphic representation were performed using R language [10].

The current research was approved by an independent ethics committee. The study was performed in a retrospective fashion, with only patient charts consulted and personal data completely anonymised, and therefore informed consent was not collected.

Results

The sample included 151 patient cases, the majority of which were males (n=87, ≈58%) with a medium age at diagnosis of 65 ± 13 years-old (Table I). The minimum age registered was 24 years-old and the maximum 100. Elder patients were females (male: 62.38 years-old vs. female: 69.25 years-old; p=0.002). In our sample, 43% of the patients were active smokers, 45% were alcohol abusers (45 (30.8%) simultaneously consume alcohol and tobacco) (Table I). No cases of deleterious chewing habits were detected in our sample. The three groups have the following percentages: i) anterior region - upper maxilla: upper lip (0.83%), maxillary gingiva and alveolar ridge (4.17%), upper vestibule (0.83%), jugal mucosa (7.92%), hard palate (3.33%); ii) anterior region - lower jaw: lower lip (5.42%), lingual border (24.17%), lingual dorsum (3.75%), lingual belly (11.67%), floor of the mouth (13.75%), mandibular gingiva and alveolar ridge (9.17%), lower vestibule (0%); iii) posterior region: retromolar trigone (7.92%), oropharynx (7.08%). The proportions of primary tumor location with cervical metastization were found to be distinct (Chi-square test for proportions, p-value<0.001). Oral tumour sites with highest percentage of cases with

Table 1 – Patients characteristics

Variable	
Sex, n(%)	
Male	87 (57.6)
Female	64 (42.4)
Age (mean ± SD) years-old	65.39 ± 13.82
Smoking status, n(%)	
Never	60 (40.8)
Active	63 (42.9)
Ex-smoker	24 (16.3)
Alcohol status, n(%)	
Never	72 (49.3)
Active	66 (45.2)
Ex-consumer	8 (5.5)
Immunosuppressive conditions, n(%)	
HIV	4 (44.4)
Primary Immunodeficiency	1 (11.1)
Bone Marrow Transplant	2 (22.2)
Solid organ transplantation	2 (22.2)
Oncological background, n(%)	27 (18.8)
Referencing, n(%)	
Dentist	18 (12.3)
Stomatology consultation	12 (8.2)
Emergency Stomatology	45 (30.8)
FMG	51 (34.9)
Other	20 (13.7)

clinical positive lymph nodes (cN+) by the time of diagnosis were inferior gingiva (72.7%, n=16), mouth floor (66.7%, n=22), oropharynx (64.7%, n=11), retromolar trigone (58%, n=11) and ventral tongue (57%, n=16). Sites with fewer cases of cN+ were inferior lip (31%, n=4) and superior lip (n=0). Regarding operated tumors and respective neck dissection biopsy (pN+) we observed: floor of the mouth (65%, n=13), retromolar trigone (63.6%, n=7), inferior gingiva (46.2%, n=6) and ventral tongue (45%, n=9). Tumour sites with fewer pN+ cases were hard palate (25%, n=1), superior gingiva (16.7%, n=1) and inferior lip (0 out of 7 cases). According to Fisher exact test/ Fisher-Freeman-Halton test, there is no statistically significant association (p-value=0.1506) between primary tumour site and cervical node disease (N+).

Discussion

Studies show different conclusions on which oral subsites are more frequently associated with precocious nodal involvement, differing as much as palate [3], buccal mucosa [11],[12] and tongue [13],[14].

The subsites least likely to metastasize are not so well described, but hypothesis seem to be least divergent, with commissure and lip being the most described in our search [12],[3]. This is in accordance to usual literature that considers that the lip is an anatomic overlap of two separate groups of cancer: cutaneous squamous cell carcinoma (cSCC), with low incidence of nodal metastasis (2.3-5.2%), and oral mucosa squamous cell carcinoma (omSCC), with higher rates of cervical positive nodes (18.6-44%). Therefore, lip cancer patients usually present intermediate rates of nodal spread, mortality, and clinical outcomes between the two [15].

Our data seem to indicate an association between primary tumour site and N+, with cervical metastasis more frequent when tumour site was posterior and caudally located, such as in floor of the mouth and retromolar trigone regions.

On the other hand, inferior lip had the fewer positive lymph nodes, probably because in this group we include without differentiation oral mucosa and skin cancers, but the association was not statistically significant. Some reasons may justify those results: the sample is relatively small (n=151) and therefore, there are few cases for each oral cavity subsite so the association between variables may not be sufficiently strong to prove significance; although separately (different patients for each arm), we considered both positive lymph nodes as defined by radiological examination (cN+) and histopathology / neck dissection biopsy (pN+). This means that we might have not considered some occult metastases or undetectable micro metastases that were probably present in our sample.

Our findings were in accordance with theoretical knowledge, meaning that posteriorly located tumours such as retromolar trigone are more frequently associated with cervical metastasis. The floor of the mouth, that faces few barriers to lymphatic drainage and encounters no bone interposition, was also found to have high metastatic rates in our study.

The same happened when considering the location associated with least nodal metastasis. As the lip presents with intermediate prognosis and outcomes between the cSCC and omSCC, it was expected to present with least metastatic cases. This is also in accordance with the literature we found. We also verified that the proportions of tumours location were related with higher rates of positive lymph nodes.

We believe this is an interesting area to further investigate, as we could not find many large sample recent studies that would directly compare oral cavity primary tumour subsite with nodal metastasis rates. This factor might prove to also have an important influence on the therapeutic management of clinically node negative neck, adding information to the estimation of occult metastases or undetectable micro metastases.

Ethics committee and informed consent:

The current research was approved by an independent ethics committee. The study was performed in a retrospective fashion, with only patient charts consulted and personal data completely anonymised, and therefore informed consent was not collected.

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