Original Article

Unexpected additional pathologies at the surgical margins of oral squamous cell carcinoma

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Abstract

Background: There is a scarcity of literature on the presence of additional unexpected pathologies at the surgical margins of oral squamous cell carcinoma (OSCC). It is quite possible that such pathologies might get overlooked because of primary focus on the malignancy at the surgical margins. With this view in mind, a retrospective observational study has been designed to re-visit the surgical margins of OSCC for the possible presence of unexpected pathologies.

Methods: Haematoxylin and eosin-stained sections of 96 cases (four surgical margins in each case) of OSCC were carefully examined under a compound microscope by two oral pathologists for the presence of any additional pathology.

Results: Out of 96 specimens of OSCC, 76 (79.2%) cases showed the presence of accidental pathologies. The surgical margins of 20 (20.8%) cases showed no evidence of any pathology, whereas the margins of 23 (23.95%) cases were associated with more than one pathology. The most commonly observed accidental pathology was oral submucous fibrosis (40.625%), followed by leukoedema (16.675%), retention cysts (10.42%), and calcifications (7.3%). The mucous extravasation phenomenon (6.25%), minor salivary gland (MSG) inflammation (6.25%), and lichen planus (5.21%) were also observed in the surgical margins of OSCC.

Conclusion: A significant number of accidental pathologies exist at the surgical margins of OSCC. This effect could be because of over-emphasis on the tumour status at the surgical margins, which leads to over-looking of minor pathologies.

Keywords: Histopathology, oral cancer, oral pathology, oral squamous cell carcinoma, surgical margins

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) has a significant incidence throughout the world, and it continues to be the chief cause of morbidity and mortality in patients suffering from head and neck cancers.[1,2] Current treatment modalities include surgical excision of the tumour, followed by radiotherapy and chemotherapy.[3] The dosage of radiotherapy and chemotherapy is dependent on the histological status of the surgical margins. The status is usually graded based on the distance of the tumour tissue from the surgical margins into negative, close, or positive margins.[4-6] Sometimes, dysplastic features

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in the epithelium of surgical margins are considered as positive surgical margins.[6] Hence, a pathologist mainly concentrates on the presence of tumour tissues in the stroma of surgical margins or the presence of dysplasia in the epithelium. In doing so, other aspects of tissues are often unnoticed or unattended. We believe that there is a possibility of other lesions at the surgical margins of OSCC. Such findings can be labelled as accidental findings in surgical margins.

There is scarcity of literature on the additional pathologies at the surgical margins. It is quite evident that the margins of OSCC, if studied carefully, might indicate the co-existence of other notable features along with the presence of tumour tissues and the typical epithelial dysplasia. With this view in mind, the present retrospective observational study was designed to re-visit the surgical margins of OSCC for evidence of accidental pathologies.

METHODS

The present study was conducted at the Department of Oral Pathology and Microbiology, Dr. D.Y. Patil Dental College and Hospital, Pune. The archival formalin-fixed and paraffin-embedded specimens of surgical margins from 96 OSCC patients were retrieved. All the cases underwent surgical excision as a part of management of OSCC. The sections obtained from the specimens were stained with routine haematoxylin and eosin stain for detailed examination. There were four to five surgical margins associated with each case. The number of pathologies attributed to each margin was also recorded. The study was approved by the scientific committee of the institute, and the consent was waived off by the ethics committee because of the retrospective nature of the study (DYPDCH/IEC/120/72/19). Only specimens showing adequate tissues for histopathology examination were included in the present study. Three experienced oral pathologists (with an experience of more than 10 years) investigated each surgical margin for unexpected or accidental observation of other pathologies. In the case of disagreement, a fourth oral pathologist was consulted for the opinion.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc. Released 2008, SPSS Statistics for Windows, Version 17.0 Chicago: SPSS Inc.). Mean and standard deviation were used to find out the differences between two quantitative values. Chi square test was used to compare the presence or absence of pathology at the surgical margins of different groups. A *P* value less than 0.05 was considered as statistically significant.

RESULTS

Demographic details

The study included a total of 96 patients. Most of the patients were male (n = 57) compared to female (n = 39), with a male to female ratio of 19:13. The age group of the patients ranged from 21 to 80 years, with a mean of 54.292 (± 12.648). The maximum number of cases was reported in the mandibular gingivo-buccal complex (GBC) (n = 41), followed by mandibular alveolar mucosa (n = 16) and buccal mucosa (n = 12). Out of 96, 51 cases were well-differentiated OSCC (WDSCC) [Table 1].

Pathologies detected at surgical margins

The surgical margins of 96 specimens of OSCC were observed under a compound microscope. A total of 76 (79.2%) cases showed the presence of pathologies at the surgical margins. The surgical margins of 20 (20.8%) cases showed no evidence of any pathology, whereas the margins of 23 (23.95%) cases were associated with more than one pathology. The most commonly encountered accidental pathology was oral submucous fibrosis (OSMF) (40.625%), followed by leukoedema (16.675%), retention cysts (10.42%), and calcifications (7.3%). The pathologies such as the mucous extravasation phenomenon (6.25%), minor salivary gland (MSG) inflammation (6.25%), and oral lichen planus (OLP) (5.21%) were also observed in the surgical margins of OSCC [Figure 1]. More details of other unexpected pathologies detected at surgical margins are shown in Table 2.

Table 1: Demographic details of included oral squamous cell carcinoma patients

Parameter	Total Number (%)	Pathology *n* (%)
Age		
21-40 years	18 (18.75%)	16 (88.89%)
41-60 years	48 (50%)	36 (75%)
61-80 years	30 (31.25%)	24 (80%)
Gender		
Male	57 (59.38%)	44 (77.19%)
Female	39 (40.62%)	32 (82%)
Site		
Mandibular GBC + alveolar mucosa	57 (59.375%)	47 (82.456%)
Retro-molar triangle	5 (5.21%)	4 (80%)
Maxillary GBC + alveolar mucosa	6 (6.25%)	2 (33.33%)
Buccal mucosa	12 (12.5%)	12 (100%)
Tongue	5 (5.21%)	5 (100%)
Palate	2 (2.08%)	No evidence
Lip	2 (2.08%)	2 (100%)
Multiple sites	7 (7.29%)	4 (57.14%)
Histopathology Grade		
Well-differentiated	51 (53.125%)	40 (78.43%)
Moderately differentiated	42 (43.75%)	34 (81%)
Poorly differentiated	3 (3.125%)	02 (66%)

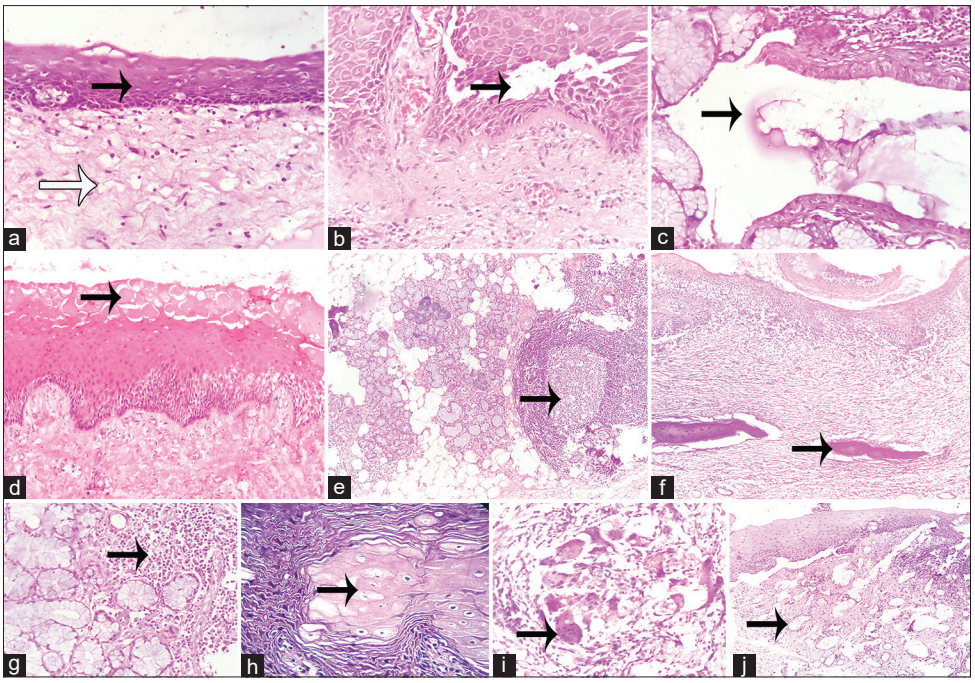

Figure 1: Photomicrographs showing various pathologies observed at the surgical margins of OSCC. (a) Oral submucous fibrosis with an atrophic epithelium (black arrow) and fibrosis (white arrow); (b) supra-basilar split (black arrow); (c) mucocele with cystic cavity (black arrow); (d) totos bodies in the surface layer of the epithelium (black arrow); (e) mucosa-associated lymphoid tissue with the germinal centre (black arrow); (f) non-specific calcifications in the stroma (black arrow); (g) chronic non-specific inflammation in the minor salivary glands (black arrow); h) ghost cells devoid of a nucleus (black arrow); (i) foreign body giant cells (black arrow); (j) hemangionma with irregular vascular spaces (black arrow). (Haematoxylin and eosin stain; total magnification 400X)

Table 2: Accidental pathologies observed at the surgical margins

Accidental Pathologies	*n* (%)	Association with more than one pathology (*n*)
Oral submucous fibrosis	39 (40.625%)	19
Leukoedema	16 (16.675%)	02
Retention cyst	10 (10.42%)	10
Calcifications	07 (7.3%)	01
Mucous extravasation	06 (6.25%)	03
Salivary gland inflammation	06 (6.25%)	06
Lichen Planus	05 (5.21%)	01
Non-specific Giant Cell reaction	02 (2.08%)	01
Hemangioma	02 (2.08%)	01
Suprabasilar split	02 (2.08%)	01
Toto bodies	02 (2.08%)	00
Mucosa-associated Lymphoid Tissue	02 (2.08%)	02
Lymphangioma	01 (1.04%)	01
Muscle inflammation	01 (1.04%)	00
Chronic non-specific inflammation	01 (1.04%)	01
Ghost cells in the oral epithelium	01 (1.04%)	00

Analysis of pathologies with different parameters

Pathologies co-existed in the surgical margins of 44 male and 32 female patients. There were no statistically significant differences between males and females regarding the presence of unexpected pathologies at the surgical margins. The age group of the cases ranged between 21 and 80 years, and the group 41–60 years included 48 (50%) patients, out of which 75% cases exhibited pathologies in their surgical margins. OSCC occurring in the mandibular GBC showed the presence of pathologies in the greatest number of cases (n = 37), followed by buccal mucosa (n = 12) and mandibular alveolar mucosa (n = 10). All the specimens of OSCC at the sites of buccal mucosa, the lip, and the tongue had the existence of pathologies in their surgical margins. None of the OSCC cases of palatal mucosa showed any evidence of pathologies. A total of 51 out of the 96 cases were WDSCC. 41.67% of the total cases were WDSCC, which had the presence of pathologies in the margins, followed by moderately differentiated OSCC (MDSCC) (35.42%) and poorly differentiated OSCC (PDSCC) (2.08%). Table 3 describes the evidence of accidental pathologies in relation to the different parameters of OSCC. The presence of accidental pathologies in the surgical margins of OSCC specimens was found to be statistically significant when compared in the different sites of OSCC.

DISCUSSION

Malignant tumours are often associated with the enigma at their resected margins.[7] The assessment and evaluation of the surgical margins of a resection specimen is a major part of pathological examination. Examining the histopathological status of these margins serves as an important tool to determine the outcome of the

Table 3: Accidental pathologies in different parameters of oral squamous cell carcinoma

Parameter of OSCC	Accidental pathology *n* (%)		Chi square value and *P*
	Present	Absent	
Gender			
Male	44 (45.83%)	13 (13.54%)	Chi-square value: 0.3314
Female	32 (33.33%)	7 (7.3%)	*P*-value: 0.564 (Not significant)
Grade			
Well-differentiated (WD)	40 (41.67%)	11 (11.46%)	WD vs MD: Chi-square value: 0.09 (*P* : 0.764)
Moderately differentiated (MD)	34 (35.42%)	8 (8.33%)	WD vs PD: Chi-square value: 0.2269 (*P*: 0.634
Poorly differentiated (PD)	02 (2.08%)	01 (1.04%)	MD vs PD: Chi-square value: 0.3571 (*P*: 0.55)
Site			
Mandibular (Mand)	51 (53.125%)	11 (11.46%)	Mand vs Max: Chi-square value: 7.6163; *P* value: 0.005784
Maxillary (Max)	02 (2.08%)	04 (4.2%)	Mand vs BM: *
Buccal mucosa (BM)	12 (12.5%)	00	Mand vs T: *
Tongue (T)	05 (5.21%)	00	Mand vs L: *
Lip (L)	2 (2.08%)	00	
Multiple sites	4 (4.12%)	3 (3.125%)	

* Due to zero values, the statstical analysis was not possible

treatment.[8] The margins are usually classified as clear, close, and involved based on the presence or absence of malignant tumour cells within the margins.[6] The presence of dysplasia, peri-neural, and vascular invasions are also looked for, and the status of the margins is then classified accordingly.[6] The evidence of these features is usually examined and routinely reported, but there is limited literature on the evidence of other pathologies in the surgical margins. These lesions are usually unnoticed but can provide valuable data regarding the cause and effects of carcinogenesis. In the present study, we observed such unnoticed pathologies in 79.2% of the cases.

Medical literature has reported the presence of concealed thyroid carcinomas in resection specimens of patients who had undergone surgeries for head and neck cancers.[9,10] Gilbert *et al*.[9] in 2012 observed 2538 neck dissections and identified the existence of thyroid cancer in 28 cases, which were of head and neck squamous cell carcinomas. In 2016, Olthof *et al*.[10] similarly diagnosed thyroid carcinomas in resection specimens of 0.3 to 1.9% patients, who had been operated for head and neck cancers. Keshet *et al*.[11] indicated the development of mucoceles in cancer patients after radiation therapy because of irradiation damage of the minor salivary glands. In line with the present study, the most common pathology reported at the surgical margins was OSMF (40.625%), followed by leukoedema (16.675%) and retention cysts (10.42%).

Minor salivary glands (MSGs) are usually found to be adjacent to the oral mucosal tissue and are very much susceptible to get affected by the process of carcinogenesis. Sarode *et al*.[12] have reported the presence of superficial mucoceles in the surgical margins of OSCC. The advancement of OSCC gradually leads to the loss of adhesion and cohesion between cells and can have the same effect on the ductal systems of the minor salivary glands. As a result of this, there is leakage and spillage of mucous secretory products into the surrounding connective tissue. Hence, the mucous extravasation phenomenon can be found in the surgical margins of OSCC. In our present study, 6.25% of the OSCC cases showed the mucous extravasation phenomenon in the surgical margins, whereas 10.42% cases exhibited retention cysts. Because of the close proximity to oral mucosa, MSGs are quite evident to get affected by carcinogenesis.

Oral potentially malignant disorders (OPMDs) often pave the path towards the development of OSCC. OSMF is one such pre-cancerous condition with a 7.6% rate of malignant transformation.[13] The malignant transformation of OSMF is usually attributed to areca nut-induced carcinogenesis.[14] A study by Siriwardena *et al*.[15] reported the presence of histopathological features of OSMF in 130 (48%) out of 273 specimens of OSCC. Similar studies designed by Chourasia *et al*.[16] and Singh *et al*.[17] reported 25.77% and 66% of OSMF cases in the specimens of OSCC examined. The result of our present study is in concordance with the results of the literature and has found the existence of OSMF in the surgical margins of OSCC in 40.625% of the cases. Intriguingly, the previous status of these patients about association with OSMF was not known and noted in the records. Hence, surgical margin assessment can help in distinguishing and diagnosing this unique type of OSCC, which will help in passing this information to the surgeon so that proper post-operative management and follow-up can be designed.

Many studies in the literature support the theory that OSCC associated with OSMF is clinicopathologically distinct and has better prognosis than OSCC without OSMF.[14,18,19] In OSMF, there are alterations occurring in the submucosa,

which include excessive collagen fiber synthesis leading to abnormal fibrosis, reduction in vascularity, and hypoxia.[15] These changes facilitate the carcinogenic mediators to express their actions for a prolonged duration.[20,21] Hence, the process of carcinogenesis in OSCC associated with OSMF might vary from OSCC arising in the absence of OSMF. OSCC in the background of OSMF has been found to exhibit a better grade, less chances of lymph node metastasis, early detection, and better oncologic results than OSCC without OSMF.[18,19] Thus, evidence of OSMF in the surgical margins of OSCC might be an indicator of good prognosis and treatment outcome. In this study, out of the 39 cases which exhibited OSMF in the surgical margins, 21 (53.85%) were WDSCC. The 39 OSMF cases were distributed among 27 male and 12 female patients. Most of the OSCC cases (n = 31) associated with OSMF in their surgical margins were in the mandibular GBC site.

OLP is another potentially malignant disorder with malignant transformation rates ranging between 0.07 and 5.8%.[22] There exists a dilemma in the medical literature of OLP regarding its malignant transformation. A study by Aghbari *et al*.[22] proved that a small population of OLP (1.1%) transforms into OSCC. The present study has also seen evidence of OLP in the surgical margins of OSCC in 5.21% of the specimens examined. There are high possibilities of ignorance of OLP in the initial stages, which might have led to the development of OSCC. It is believed that OSCC often exhibits features which resemble the primary lesion.[15] The accidental finding of OLP in the surgical margins recommends to keep a regular follow-up of such patients to reduce the risk of OSCC.

Chronic irritation and constant trauma often change the mechanical properties of the local environment, resulting in cancer development. Local trauma can sometimes cause a whitish lesion, leukoedema, of the oral mucosa.[23] Our study observed the presence of leukoedema in the surgical margins of 16 (16.675%) cases of OSCC. It can be concluded that continuous local irritation can be a path to tumourigenesis. Assessment of surgical margins for such unnoticed pathologies may reveal the etiology, benefit the surgeons to design an appropriate treatment strategy, and help patients to take further care for prevention.

Similar to OPMD, chronic inflammation has also been documented in the literature to play a pivotal role in carcinogenesis. It is well-proved that inflammation lasting for a long duration gradually leads to disease progression. Studies say that genetic mutations are the cause of cancer development in a few cases, but in most of the instances, it is initiated by the environmental factors, most of which are linked to some form of chronic inflammation.[24] The existence of inflammation in the microenvironment of the tumour favours many pro-tumoural effects and provides a very suitable background for cancer initiation.[25] Chronic inflammation aids survival and proliferation of tumour cells, invasion, and metastasis and leads to therapy resistance.[24] The present study documented six (6.25%) cases of MSG inflammation and one (1.04%) case of muscle inflammation in the surgical margins of OSCC. Chronic inflammation in the surgical margins can give an overview of the local environment of the tumour, and proper reporting of such unnoticed findings might be of great help to the clinicians in planning an improved management strategy.

The existence of chronic inflammation in the peri-tumoural tissue sometimes leads to fusion of the inflammatory cells. Macrophages merge together forming multi-nucleated giant cells, and it is regarded as a response of the host to malignant tumour cells.[26] The prognostic importance of this finding is however still not clear and requires future studies. This study has observed two (2.08%) cases of OSCC showing giant cell reaction in the surgical margins. Therefore, observing the surgical margins properly for such an unattended phenomenon might help in determining the host response and thus the prognosis.

The malignant tumour cells of OSCC secrete parathyroid hormone-related peptides and can cause cancer-related hypercalcaemia.[27,28] The presence of tumour tissues in the surgical margins of OSCC, high levels of serum calcium, and increased angiogenesis can make the bioavailability of calcium quite high, and non-specific calcifications can be observed in those margins.[27] This finding can be a good indicator of hypercalcaemia associated with cancer and of poor prognosis. Calcifications were found in the surgical margins of seven (7.3%) cases.

Different kinds of studies have been performed on the surgical margins, and various prognostic indicators, optimal surgical margins to reduce local recurrences, and the effects of formalin have been mentioned in the literature. The presence of such accidental pathologies in the surgical margins has not yet been explored properly. Such unexpected lesions demand the observation of these margins in all possible aspects to better understand the mysterious nature of OSCC.

The present study had a few drawbacks. It was performed on a small sample size of 96 OSCC cases and was limited to a single institute. In spite of these limitations, the study has observed a wide range of accidental pathologies in the surgical margins

of OSCC. To validate these results, a multi-institutional study should be carried out, including a large sample size. These kinds of studies will give an overview of the tumour local environment, the effects of carcinogenesis on the adjacent structures, and the body's response to the malignancy. Future studies are required to document and validate such findings in the surgical margins, which might become helpful tools in planning therapies for the tumour.

CONCLUSION

This is for the first time a study has been designed to investigate the co-existence of unexpected pathologies at the surgical margins of OSCC. There is a significant number of pathologies detected at the surgical margins, which have been over-looked during routine day-to-day pathology practice. Future studies are required to document such accidental pathologies in the resected margins that will assist the surgeons to plan additional therapies and achieve better outcomes. Such a study attempted for the very first time will guide pathologists to examine surgical margins of OSCC from all aspects and will change their perspective towards routine practices.

Declaration of patient consent

Due to the retrospective and in-vitro nature of the study, patient informed consent is not applicable. We obtained the waiver of consent from the Institutional Ethics Committee.

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Conflicts of interest

There are no conflicts of interest.

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