Stomatologija. Baltic Dental and Maxillofacial Journal, 28: 40-6, 2026

Multinucleated giant cells: Do they have an impact on prognosis and overall survival in oral squamous cell carcinoma?

Kuldeep Singh[*], *Priya Kumar*[*], *Aadithya B. Urs*[*]

SUMMARY

Background. Multinucleated Giant Cells (MGCs) are akin to immune cells that play a crucial role in the tumor microenvironment. MGCs have been shown to have both tumor-promoting and tumor-suppressing effects. This study explores the role of MGCs in OSCC and their prognostic value.

Material and methods. 100 proven cases of OSCC were retrieved with complete clinicopathological data. Haematoxylin-eosin sections were reviewed independently by three pathologists and grouped into two, with and without MGCs. The distribution, and average number of MGCs per 5 high-power fields per case were examined. All clinicopathological parameters and prognosis based on Bryne's grading were compared between groups. The overall survival with follow-up period of >36 months was analysed.

Results. 34 cases with MGCs were found, out of which 21 patients are alive. Cases with MGCs had pTNM stage III whereas majority of cases without MGC's had stage IV. Significant correlation was found for lympho-vascular invasion only. Cases with MGC's showed good prognostic score according to Bryne's grading, while without MGC's showed moderate to poor prognostic score. Cases of alveolar mucosa, including gingiva and ridge SCC with MGCs, showed poor survival.

Conclusions. This study highlights the potential role of MGCs in OSCC, suggesting an association with earlier tumor stages and favorable prognostic scores. Further research is needed to assess their prognostic and therapeutic relevance.

Keywords: Bryne's grading system, clinico-pathological parameters, multinucleated giant cell, oral squamous cell carcinoma, overall survival, prognosis.

INTRODUCTION

Head and Neck Squamous Cell Carcinoma (HNSCC) includes oral cavity tumors, oropharynx, hypopharynx, nasopharynx, and larynx. In India, Oral Squamous Cell Carcinoma (OSCC) is leading malignancy, with most patients presenting at a locally advanced stage at the time of diagnosis. OSCC represents approximately 80-90% of all malignant neoplasms of the oral cavity. The risk factors for the development of OSCC include cigarette smoking, alcohol consumption, betel quid chewing, inadequate nutrition, poor oral hygiene, HPV and Epstein-Barr virus infections, and Candida albicans infections (1, 2).

The complex milieu of extracellular matrix elements and non-cancerous cells known as the Tumor Microenvironment (TME) surrounds solid tumors, and it is the reciprocity of these relationships that ultimately determines the malignant behavior of the tumor (3).

In the TME, there are both innate cells (macrophages, dendritic Cells (D. C), lymphocytes, and Natural Killer (NK) cells) and adaptive (T and B cell) immune cells, with CD8+T cells, NKs, and DCs playing the most efficient anti-tumor roles (4).

Among the many inflammatory cells seen in the TME, macrophages are one of the most prominent components in many cancers, including OSCC (4). Macrophages have two distinct cell populations because of a mechanism known as macrophage polarisation, in which the macrophage expresses different functional programmes in response to microenvironmental signals, acquiring a specific phenotype such as M1 or M2. The pro-inflammatory cytokines interleukin IL-1, IL-6, IL-12, and Tumour Necrosis Factor alpha (TNF-α) are produced by M1 macrophages (classically activated macrophages), and these M1 macrophages can exhibit an antitumoral response in cancer. However, M2 macrophages (alternatively activated mac-

[*]*Department of Oral Pathology, Maulana Azad Institute of Dental Sciences, New Delhi, India*

Address correspondence to Priya Kumar, Department of Oral Pathology, Maulana Azad Institute of Dental Sciences, New Delhi, India. E-mail address: drpri_kumar@yahoo.com

rophages) may exhibit a pro-tumoral response by secreting IL-4, IL-10 cytokines, Transforming Growth Factor-beta (TGFβ-), Vascular Endothelial Growth Factor (VEGF),

Matrix Metallo-Proteinases (MMP) and CD163 antigen (5-7).

Th1 and Th2 cytokines induce the fusion of macrophages and result in their differentiation into Multinucleated Giant Cells (MGCs). This has been characterised as a host response to tumoral cells in numerous forms of carcinomas, although the prognostic implications remain unclear (8-12).

MGCs are commonly associated with keratin scavenging. Recent studies suggest that they have a more complex role in tumor biology. MGCs have been detected within tumor islands and in chemotherapy-treated cases, indicating their possible association with tumor microenvironment changes rather than solely as a reaction to keratin. Some cases even exhibit true tumor giant cells expressing epithelial markers, suggesting a distinct oncogenic behavior (13).

Gessain G. *et al.* identified MGCs in HNSCC tumors, associating them with a favorable prognosis in both treatment-naive and preoperative chemotherapy-treated patients. Their increased density post-therapy suggests a role in the antitumoral response. Spatial transcriptomic and proteomic analysis revealed an MGC-specific signature resembling TREM2-expressing macrophages in keratin-rich tumor niches. These findings position MGCs as a potential prognostic biomarker (14).

While the role of tumor-associated macrophages (TAMs) in OSCC progression is well-established, with M2-polarized macrophages linked to poor prognosis, the prognostic significance of MGCs remains unclear. Some studies suggest MGCs may not contribute to tumor progression, yet emerging evidence indicates a potential link between MGC presence and aggressive tumor behavior, irrespective of histological grade. If further validated, MGCs could be incorporated into histological grading and explored as potential therapeutic targets for improving patient outcomes (13).

The nature and importance of MGC reactions in intraoral SCC is poorly understood. Data available implies that MGC reactions are likely the result of M2 macrophages and indicate a foreign body reaction to keratinized SCC cells (15, 16).

A recent study explored the potential relationship between MGC reactions and tumor progression in Oral Tongue Squamous Cell Carcinoma (OTSCC), which suggest that the absence of MGC reactions may serve as an indicator of more aggressive tumor behavior and progression in OTSCC, underlining the potential prognostic value of MGCs in assessing the aggressiveness of the disease (17).

The current study was undertaken to evaluate the role of MGCs in the tumor micro-environment and to further assess their role in the prognosis.

MATERIAL AND METHODS:

One-hundred cases of OSCC obtained from the archives of Maulana Azad Institute of Dental Sciences, New Delhi, India were selected for the study. This study included OSCC cases that had undergone complete surgical resection and had paraffin blocks with sufficient tissue for histological examination. Histological diagnosis of OSCC was performed according to the criteria outlined in the 5th Edition of the World Health Organization Classification of Head and Neck Tumours (2022) (18). In addition, tumors were histologically graded into well-differentiated, moderately differentiated, and poorly differentiated squamous cell carcinomas as per WHO guidelines.

Patients' that had received radiation, chemotherapy, or any other sort of treatment prior to surgery were excluded. Cases with inadequate/or incomplete data of clinicopathological parameters (patient's sex, age, clinical and pathological stages, and less than 3 years of follow-up) were also excluded. This study was approved by the institutional ethical research committee wide No.F./18/81/MAIDS/Ethical Committee/2023/1290 dated 16th June, 2022.

We examined the H&E-stained sections of all cases for the presence (Group I) or absence (Group II) of MGCs under a light microscope (Nikon, Eclipse Ci-L, Tokyo, Japan) and identified these cells according to the criteria described by Brooks *et al.* (11) (Figure 1).

I. Located within, adjacent to the neoplastic cells and/or associated with foreign body material i.e, keratin in connective tissue.

II. The cytoplasm should be glossy dense eosinophilic.

III. Presence of at least three regularly scattered nuclei in the cytoplasm.

For quantitative analysis, we examined 5 high-power fields (HPFs; 400×) containing maximum number of MGCs, and then calculated the average number of MGCs per 5 HPF per case. Further, the overall average MGCs per case was calculated by averaging the values obtained for each case. The MGCs cells also classified as "superficial" or "deep" based on their microscopic localization. MGCs near the epithelial-stromal interface were considered superficial, while those associated with deeper tumor nests adjacent to skeletal muscle fibers were classified as deep, following the criteria described by Sánchez-Romero *et al.* (2018) (19). The eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system was used for tumor staging. Histopathological prog-

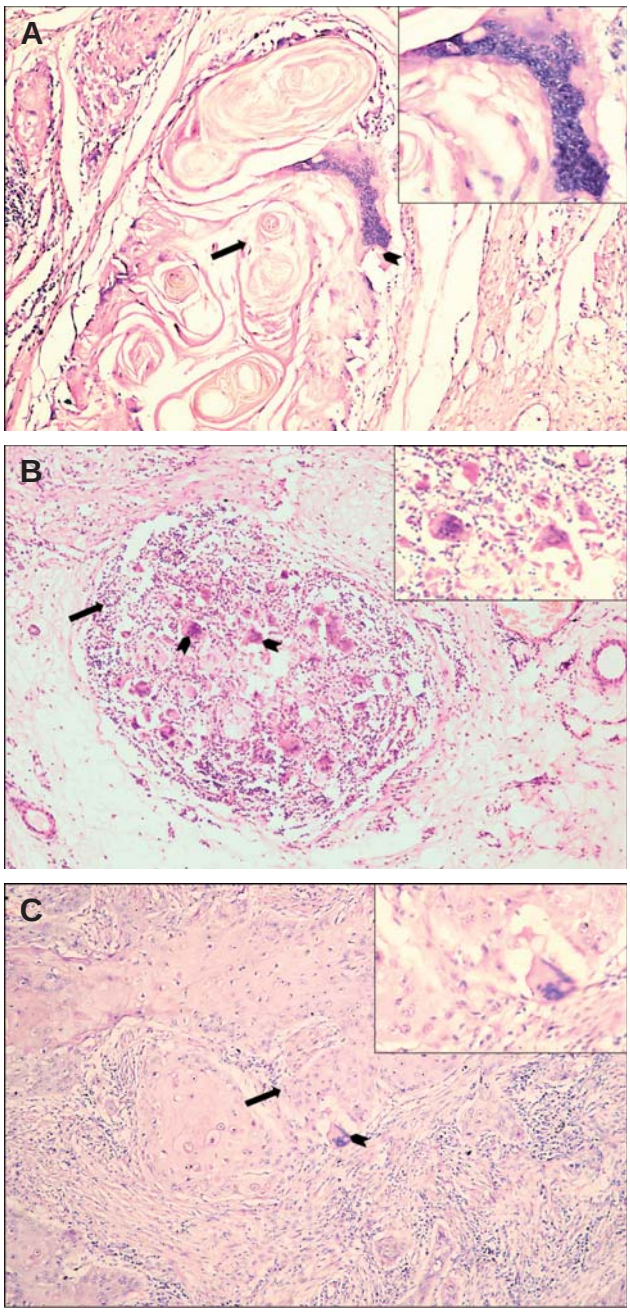

Fig. 1. MGCs associated with keratin pearls (A), tumor cells (B), and inflammatory cells (C) in oral squamous cell carcinoma (OSCC). Images at 10×; insets at 40×. Straight arrows indicate MGCs; arrowheads mark keratin pearl in (A), tumor islands in (B), and inflammatory cells in (C).

nostic score was evaluated using the system proposed by Bryne *et al.* (20, 21). Histologic variables like Worst Pattern Of Invasion (WPOI), Depth Of Invasion (DOI), Lymphatic/Vascular Invasion (LVI), and PerineuralInvasion (PNI) were also assessed by adapting the criteria used by Margaret Brandwein-Gensler *et al.* (22).

To assure interobserver reliability, Cohen's Kappa coefficient was calculated between the two independent oral pathologists who evaluated the presence of MGCs. The Kappa values were interpreted according to the Landis and Koch scale (23).

For statistical analysis, chi-square test or Fisher's exact test was used to determine possible associations between the two groups (with and without MGCs) with all clinicopathological parameters. Furthermore, we also evaluated the association between these two groups with the prognosis of OSCC patients according to Bryne's histopathological grading system. Lastly, the overall survival with a follow-up period of 36 months was analysed by the Kaplan-Meier survival curve in the two groups. Differences were considered significant if p-value <0.05 for all tests.

RESULTS

All hundred diagnosed cases of OSCC were examined based on clinico-pathological parameters, comparing two distinct groups: those with MGCs and those without MGCs. The study included 34 cases with MGCs and 66 cases without MGCs. The interobserver agreement for MGCs identification between the two oral pathologists was substantial, with a Cohen's Kappa coefficient of 0.78, indicating good reliability. The age range of cases with MGCs was between 29 to 91 (average-60 years) years, while those without MGCs ranged from 28 to 84 (average-56 years) years. In terms of sex, the group with MGCs comprised 27 males and 7 females (M : F=3.8 : 1), whereas the group without MGCs had 53 males and 13 females (M : F=2 : 1) (Table 1).

Based on histological differentiation, 46 cases were well-differentiated, 39 were moderately differentiated, and 15 were poorly differentiated OSCC. No statistically significant correlation was observed between tumor grade and the presence of MGCs (p=0.284).

The clinical TNM stage distribution showed no significant correlation between the two groups (p=0.623). Notably, the group without MGCs had a higher proportion of cases at stage IV (a+b). There was a significant correlation in the pathological TNM stage distribution between the two groups (p=0.037). The group with MGCs consisted primarily of cases in earlier stages (I and II), whereas the group without MGCs had a higher representation in later stages (stage IV). The average DOI did not show any significant correlation between the two groups (p=0.284). The distribution of invasive patterns according to the criteria used by Margaret Brandwein-Gensler *et al.* for WPOI and PNI showed no significant correlation, (p=0.134) & (p=0.288) respectively. LVI was significantly correlated (p=0.038).

The distribution of cases across different prognostic scores according to the Bryne's prognostic score system showed a significant correlation (p=0.033), with a higher number of cases of "Good" prognoses

in the group with MGCs. There was no significant correlation in overall survival between the two groups (p=0.217, Table 1, Figure 2A).

We also investigated 34 cases of the group OSCC with MGCs (Table 2) based on clinical site and microscopic location of MGCs and correlated it with overall survival. The distribution of cases with MGCs according to clinical site of lesion, alveolar mucosa including gingiva and ridge, buccal mucosa, and tongue, showed a significant correlation with overall survival (p=0.001, Figure 2B). Notably, all cases of OSCC with MGCs at alveolar mucosa including gingiva and ridge exhibited poor overall survival, contrasting with the better overall survival mortality rates observed for OSCC cases with MGCs in buccal mucosa and tongue. The microscopic location of MGCs (superficial, deep, or both) in OSCC cases did not show a significant correlation with overall survival (p=0.581), indicating that the location alone may not impact prognosis.

However, when considering the distribution of MGCs based on their depth within the TME (superficial, deep, and superficial + deep), no significant correlation with overall survival was found (p=0.581, Figure 2C). The majority of cases exhibited superficial MGC involvement, with comparable survival rates across different depth.

The overall average of MGCs for 34 cases ranged from 0.2 to 6, with a mean of 2.012 and a standard deviation of 1.247. Despite this variation, the correlation between the overall average of MGCs (for all, alive and death cases) and overall survival was not statistically significant (p=0.265, Figure 2D).

Also we further observed that most of the MGCs tended to be associated with keratin pearls and may function to engulf tumor cells and inflammatory cells within the tumor microenvironment.

DISCUSSION

OSCC presents a significant challenge due to its aggressive behavior and limited treatment options. In recent years, the tumor microenvironment's role, including immune cell infiltration, has acquired increasing attention in understanding OSCC pathogenesis, prognosis and survival. Among various immune cells, MGCs have come to prominence as a novel, poorly understood component of the OSCC environment (1-7).

In this study, MGCs were observed in approximately 1/3rd of the OSCC cases, indicating their presence as a distinct histological feature within OSCC tumors. This finding is consistent with previous studies emphasising the heterogeneous nature of OSCC histopathology (17). Notably, this study revealed a significant correlation between the presence of MGCs and earlier pathological TNM stages (I and II) compared to cases without MGCs, which were predominantly observed in later stages (stage IV). This observation suggests the presence of MGCs reduces tumor aggressiveness or invasiveness (4).

We also found that LVI was significantly correlated with the presence of MGCs (p=0.038). However, PNI did not show a significant correlation with MGCs presence (p=0.288). These findings suggest that the

Table 1. Sample distribution: Group I – premenopausal women within the age group of 30-45 years (Pre-M); Group II – postmenopausal women within the age group of 45-60 years (Post-M)

Clinico-pathological parameters	Cases		p-value
	with MGCs % (N=34)	without MGCs % (N=66)	
Age range (in yrs)	29-91	28-84	
Sex			
Male	79.4 (27)	80.3 (53)	
Female	20.6 (7)	19.7 (13	
Pathological TNM stage			0.037*
Stage I	14.7 (5)	4.5 (3)	
Stage II	20.6 (7)	19.7 (13	
Stage III	38.2 (13)	19.7 (13)	
Stage IV (a+b)	26.5 (9)	56.1 (37)	
DOI			0.161
<10 mm	61.8 (21)	47 (31)	
≥10mm	38.2 (13)	53 (35)	
WPOI (Grade)			0.134
1	0 (0)	1.5 (1)	
2	2.9 (1)	3.0 (2)	
3	2.9 (1)	1.5 (1)	
4	5.9 (2)	6.1 (4)	
1-4	44.1 (15)	51.5 (34)	
5	44.1 (15)	36.4 (24)	
L-V invasion			0.038*
Present	11.8 (4)	9 (6)	
Absent	88.2 (30)	91 (60)	
PNI			0.228
Present	38.2 (13)	21.2 (14)	
Absent	61.8 (14)	78.8 (52	
Prognostic score			0.033*
Good	82 (28)	56 (37)	
Moderate	14.7 (5)	36.7 (24)	
Poor	2.9 (1)	7.6 (5)	
Overall survival			0.217
Alive	61.8 (21)	54.5 (36)	
Death	38.2 (13)	45.5 (30)	

OSCC, Oral Squamous cell carcinoma; MGC, Multinucleated giant cell; PNI, Perineural invasion;L-V invasion, Lymphovascular invasion; DOI, Depth of invasion; WPOI, Worst pattern of invasion.

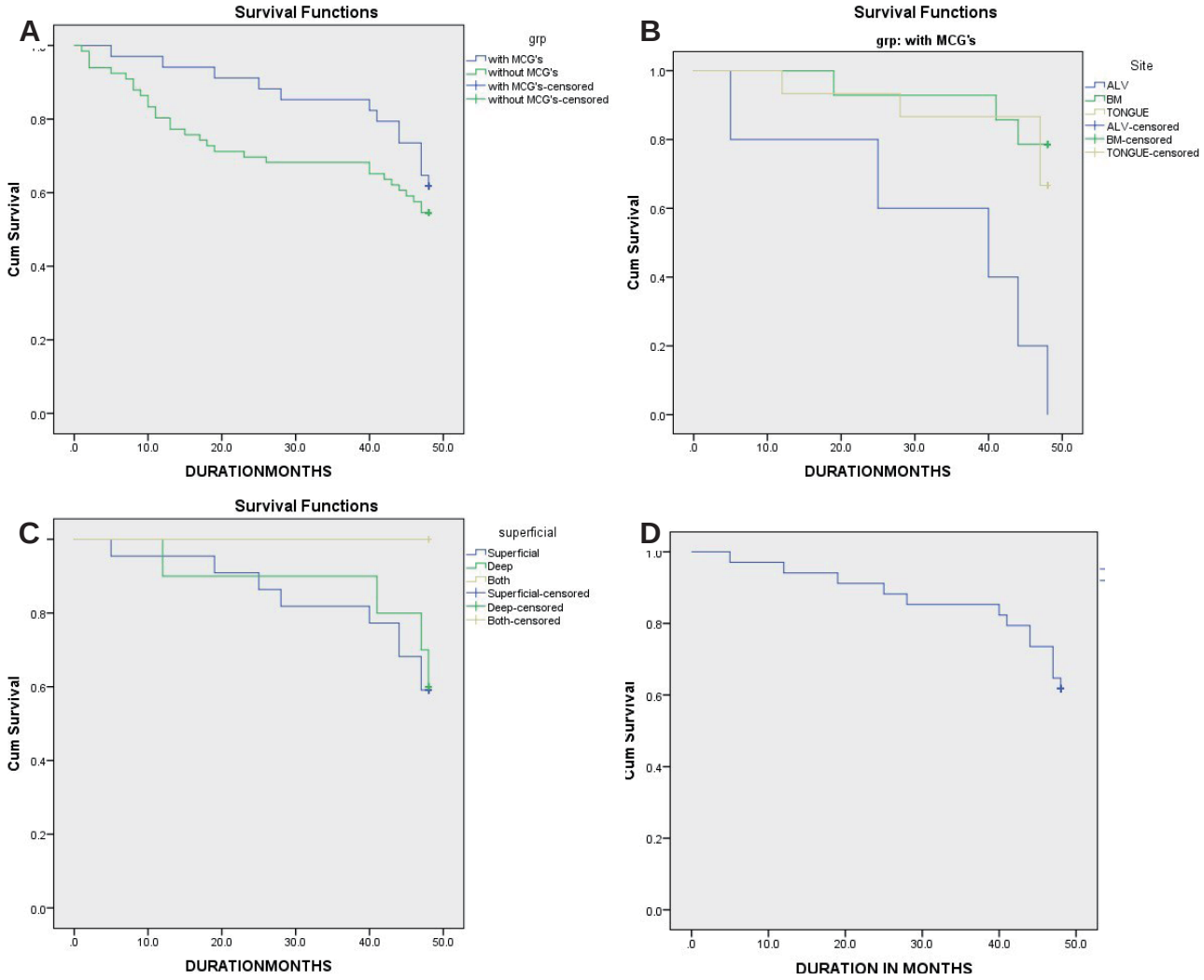

Fig. 2. Kaplan-Meier Survival Analysis showing the correlation of overall survival with—(A) two group, with MGCs and without MGCs, (B) Lesion site distribution, (C) MGCs histologically depth-wise distribution in the tumor microenvironment, and (D) Overall average MGC count.

presence of MGCs in OSCC cases may significantly influence the likelihood of LVI but not PNI.

Table 2. Comprehensive analysis of OSCC cases with MGCs: Clinical distribution of cases based on lesion site and microscopic location of MGCs correlation with overall survival.

Parameters	% (N=34)	Overall survival		p-value
		Alive (N=21)	Death (N=13)	
Site				0.001*
Alveolar mucosa (gingiva and alveolar ridge)	14.7 (5)	0 (0)		
Buccal mucosa	41.2 (14)	78.6 (11)	100 (5)	
Tongue	44.1 (15)	66.7 (10)	21.4 (3)	
			33.3 (5)	
Location				0.581
Superficial	64.7 (22)	(13)	41 (9)	
Deep	29.4 (10)	(6)	40 (4)	
Superficial + Deep	5.9 (2)	100 (2)	0 (0)	
With MGCs	34	61.76 (21)	38.23 (13)	
Overall Avg. of MGCs	2.012	1.9	2.0	0.265
Min.	0.2	0.6	0.2	
Max.	6.0	6	4	
Mean (S.D)	2.012 (1.247)	1.990 (1.224)	2.046 (1.339)	

OSCC, Oral Squamous cell carcinoma; MGC, Multinucleated giant cell.

Our study aligns with the findings of Gessain *et al.* (2024) (14), who observed that the presence of MGCs in OSCC tumors was linked to earlier pathological TNM stages (I and II), suggesting a less aggressive phenotype. However, Gessain *et al.* also reported a positive correlation between MGC density and improved survival outcomes (overall survival and progression-free interval). In the present study, although a better survival outcomes was seen in cases with MGCs, these findings were not statistically significant (p=0.217). This discrepancy may be due to differences in cohort size or patient demographics.

The presence of MGCs in tongue OSCC was associated with improved overall survival, with 66.7% of cases surviving compared to 33.3% in those without MGCs.

This suggests a more favorable prognosis for patients with MGCs in OSCC of tongue, which aligns with the clinical significance of lesion location. Previous studies have shown that the absence of MGCs in oral tongue SCC is linked to tumor progression, advanced clinical stage, regional lymph node metastasis, and poorly differentiated tumors, all of which correlate with worse prognosis. Hence, the role of MGCs in its TME is further reinforced with its potential prognostication (17). However, few studies have suggested associations between immune cell infiltration, including MGCs or tumor-associated macrophages (TAMs), and tumor invasion in OSCC (4, 6). This disparity could be attributed to differences in study populations, methodologies, or sample sizes. Additionally, in our study, the lack of a significant association may underscore the complexity of the TME and the multifaceted interactions between immune cells and tumor cells.

The association between MGCs presence and different prognostic scores according to Bryne's system suggests a potential prognostic value of MGCs in OSCC. Our study demonstrated a higher proportion of "Good" prognoses in OSCC cases with MGCs, indicating a potential favorable prognostic influence of MGCs. However, further longitudinal analyses are warranted to validate these findings and delineate the precise prognostic significance of MGCs in OSCC.

45% of cases without MGCs were dead within the 36 months of follow-up period in comparison to 29% of cases with MGCs. Although these figures were not statistically significant, the presence of MGCs seems to increase overall survival. Previous studies have demonstrated association between immune cell infiltration, including TAMs, and survival outcomes in OSCC (5, 6, 14). The lack of significant survival differences may be attributed to several factors, including the small sample size and heterogeneity of patient populations.

The distribution analysis depicted in Table 2 provides valuable insights into the presence and impact of MGCs in OSCC, shedding light on their association with overall survival rates across different anatomical sites and depth within the TME.

The data reveals notable variations in the prevalence of MGCs across different anatomical sites, with lesion on the buccal mucosa exhibiting the highest overall survival (78.6%). The high prevalence of MGCs, particularly in cases with better patient survival rates, suggests a potential beneficial role of these cells in OSCC. Conversely, lesion on alveolar mucosa inlcuding gingiva and alveolar ridge presents a striking scenario with 100% mortality, suggesting aggressive tumor behavior and potential challenges in therapeutic management because of early involvement of bone.

These observations are consistent with previous research suggesting that MGCs, possibly originating from tumor-associated macrophages, may contribute to tumor progression. While this study provides a more detailed clinico-pathological analysis and survival data, prior studies focus more on the phenotypic characteristics and variability of MGCs within the tumor microenvironment. Both sets of findings highlight the need for further research to fully elucidate the role of MGCs in the prognosis of OSCC (13).

Analyzing the distribution of MGCs based on depth within the tumor microenvironment reveals intriguing patterns. While the majority of cases exhibit superficial MGCs involvement, both superficial and deep locations showed comparable survival rates. This could be attributed to the intricate interplay between tumor-stroma interactions and immune responses, as well as the heterogeneous nature of MGC distribution within the tumor mass. Notably, cases with MGCs present in both superficial and deep location demonstrated a trend toward decreased mortality rate, indicative of the synergistic impact of multifocal MGCs infiltration on patient overall survival outcomes.

Although the presence of MGCs alone does not exhibit a significant association with survival, variations in the average number of MGCs per case between surviving and deceased patients underscore the potential prognostic value of MGCs burden quantification. These differences may reflect variations in tumor aggressiveness, immune responses, and treatment responses among patients with OSCC (1, 12). Understanding the distribution and impact of MGCs in OSCC holds significant implications for risk stratification and therapeutic decision-making.

Gessain *et al.* also noted that TILs correlated with MGC density and prognosis, which was not assessed in our study but could be an area for future exploration to understand the immune-related mechanisms behind MGCs in OSCC (14).

While our study provides novel insights into MGCs presence in OSCC and its clinicopathological correlations, several avenues for future research warrant exploration. A key limitation of this study is the lack of immunohistochemical confirmation of the cellular lineage of MGCs. Although morphological features suggest histiocytic origin, CD68 immunostaining is strongly recommended in future studies to confirm their macrophage derivation and better understand their immunobiological role in the tumor microenvironment. Longitudinal studies with larger patient cohorts are needed to validate our findings and elucidate the underlying mechanisms governing MGCs presence and its impact on OSCC progression and patient outcomes. Additionally, further investigations into the origin, functional roles, and therapeutic implications of MGCs in OSCC are essential for comprehensive understanding and clinical translation.

CONCLUSION

In conclusion, this study underscores the emerging significance of MGCs as a distinctive histological feature in OSCC. To the best of our knowledge, no previous studies have fully evaluated MGCs in OSCC in relation to histological parameters and overall survival. Our findings suggest that MGCs in OSCC are associated with earlier tumor stages and favorable prognostic scores, indicating a potentially less aggressive tumor phenotype. However, while no direct link to overall survival was found, the distribution of MGCs in OSCC across anatomical sites suggests their potential influence on tumor progression and patient outcomes.

The question remains: Do MGCs impact prognosis and survival in OSCC? While our study points to a possible association with less aggressive behavior, further research is required to confirm this. Future studies should involve larger, more diverse cohorts and explore the functional roles of MGCs in OSCC progression. Investigating their interaction with immune markers, like tumor-infiltrating lymphocytes (TILs), could provide deeper insights into OSCC's immunological mechanisms. Longitudinal studies are essential to evaluate the prognostic value of MGCs and their potential therapeutic target, ultimately enhancing OSCC management and patient outcomes.

STATEMENT OF CONFLICTS OF INTEREST

The authors state no conflict of interest.

REFERENCES

1. Marur S, Forastiere AA. Head and Neck Squamous Cell Carcinoma: Update on Epidemiology, Diagnosis, and Treatment. Mayo Clin Proc. 2016 Mar;91(3):386-96.
2. Freeman P, Mielgo A. Cancer-Associated Fibroblast Mediated Inhibition of CD8+ Cytotoxic T Cell Accumulation in Tumours: Mechanisms and Therapeutic Opportunities. Cancers (Basel). 2020 Sep 21;12(9):2687.
3. Guillerey C. NK Cells in the Tumor Microenvironment. Adv Exp Med Biol. 2020; 1273:69-90.
4. Costa NL, Valadares MC, Souza PP, Mendonça EF, Oliveira JC, Silva TA, et al. Tumor-associated macrophages and the profile of inflammatory cytokines in oral squamous cell carcinoma. Oral Oncol 2013; 49: 216-23.
5. Hu JM, Liu K, Liu JH, Jiang XL, Wang XL, Chen YZ, et al. CD163 as a marker of M2 macrophage, contribute to predicte aggressiveness and prognosis of Kazakh esophageal squamous cell carcinoma. Oncotarget 2017;8(13):21526–38.
6. Ma J, Liu L, Che G, Yu N, Dai F, You Z. The M1 form of tumor associated macrophages in non-small cell lung cancer is positively associated with survival time. BMC Cancer 2010;10:112.
7. Laoui D, Movahedi K, Van Overmeire E, Van den Bossche J, Schouppe E, Mommer C, et al. Tumor-associated macrophages in breast cancer: distinct subsets, distinct functions. Int J Dev Biol. 2011;55(7–9):861–7.
8. Santos HB, Miguel MC, Pinto LP, Gordón-Núñez MA, Alves PM, Nonaka CF. Multinucleated giant cell reaction in lower lip squamous cell carcinoma: a clinical, morphological, and immunohistochemical study. J Oral Pathol Med. 2017;46:773–9.
9. Helming L, Gordon S. The molecular basis of macrophage fusion. Immunobiology. 2007;212(9–10):785–93.
10. Patil S, Rao RS, Ganavi BS. A foreigner in squamous cell carcinoma! J Int Oral Health. 2013;5(5):147–50.
11. Brooks E, Simmons-Arnold L, Naud S, Evans MF, Elhosseiny A. Elhosseiny Multinucleated giant cells' incidence, immune markers, and significance: a study of 172 cases of papillary thyroid carcinoma. Head Neck Pathol. 2009;3:95–9.
12. Möst J, Spötl L, Mayr G, Gasser A, Sarti A, Dierich MP. Formation of multinucleated giant cells in vitro is dependent on the stage of monocyte to macrophage maturation. Blood 1997; 89: 662-71.
13. Pandiar D, Ramani P, Krishnan RP, Monica K. Multifaceted multinucleated giant cells in oral squamous cell carcinoma. Oral Oncol. 2021 Oct;121:105400.
14. Gessain G, Anzali AA, Lerousseau M, Mulder K, Bied M, Auperin A, et al. TREM2-Expressing Multinucleated Giant Macrophages Are a Biomarker of Good Prognosis in Head and Neck Squamous Cell Carcinoma. Cancer Discov. 2024 Dec 2;14(12):2352-2366.
15. Essa AA, Yamazaki M, Maruyama S, Abé T, Babkair H, Cheng J, et al. Keratin pearl degradation in oral squamous cell carcinoma: reciprocal roles of neutrophils and macrophages. J Oral Pathol Med 2014; 43: 778-84.
16. Essa AA, Yamazaki M, Maruyama S, Abé T, Babkair H, Raghib AM, et al. Tumour-associated macrophages are recruited and differentiated in the neoplastic stroma of oral squamous cell carcinoma. Pathology 2016; 48: 219-27.
17. de Medeiros VA, de Pontes Santos HB, de Brito Monteiro BV, da Paz AR, Alves PM, Nonaka CFW. Absence of multinucleated giant cell reaction as an indicator of tumor progression in oral tongue squamous cell carcinoma. Eur Arch Otorhinolaryngol. 2022 Jun;279(6):3123-3130.
18. WHO Classification of Tumours Editorial Board. Head and Neck Tumours. 5th ed. Vol. 9. Lyon, France: International Agency for Research on Cancer; 2022.
19. Sánchez-Romero C, Carlos R, Dantas Soares C, Paes de Almeida O. Unusual Multinucleated Giant Cell Reaction in a Tongue Squamous Cell Carcinoma: Histopathological and Immunohistochemical Features. Head Neck Pathol. 2018 Dec;12(4):580-586.
20. Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, et al. Head and neck cancers—major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin. jour. 2017 Mar;67(2):122-37.
21. Bryne M, Koppang HS, Lilleng R, Kjaerheim A. Malignancy grading of the deep invasive margins of oral squamous cell carcinomas has high prognostic value. J Pathol 1992; 166: 375-81.
22. Brandwein-Gensler M, Teixeira MS, Lewis CM, Lee B, Rolnitzky L, Hille JJ, et al. Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease free and overall survival. Am J Surg Pathol 2005; 29: 167-78.
23. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977 Mar;33(1):159-74. PMID: 843571.

Received: 08 07 2025
Accepted for publishing: 22 06 2026