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"Prognostic Value of Perineural Invasion in Oral Cancer: A Retrospective Study"

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ABSTRACT

Oral squamous cell carcinoma (OSCC) remains a major global health concern due to its high morbidity and mortality. Perineural invasion (PNI), where cancer cells invade the perineural space, has emerged as a significant factor associated with poor outcomes, including higher recurrence and decreased survival. This study explores the prognostic impact of PNI in OSCC and its potential role in guiding treatment decisions. Materials and Methods:

A retrospective analysis of 150 patients with OSCC treated surgically at Saveetha Dental College between October 2022 and June 2024 was conducted. Data collected included demographics, tumor characteristics, presence of PNI, treatment modalities, and recurrence outcomes. Survival analysis was performed using Kaplan-Meier estimates and Cox proportional hazards models. Results: PNI was present in 40% of cases, predominantly in tumors of the tongue and floor of the mouth. PNI-positive patients had significantly worse overall survival (45% vs. 75%, $p < 0.001$) and disease-free survival (35% vs. 70%, $p < 0.001$). PNI was independently associated with poorer outcomes, with hazard ratios of 2.3 for overall survival and 2.6 for disease-free survival. Recurrence rates were higher in PNI-positive patients (60% vs. 30%), and distant metastasis was more frequent (15% vs. 5%). Median time to recurrence was shorter for PNI-positive patients (18 vs. 36 months, $p < 0.001$). Conclusion: PNI is a robust prognostic marker in OSCC, significantly associated with worse survival and higher recurrence rates. Its presence should prompt consideration of more aggressive treatment strategies, including wider surgical margins and adjuvant therapies. Routine assessment of PNI is essential for improving OSCC outcomes.

Keywords: Perineural Invasion, Oral Squamous cell carcinoma, Head and neck oncology, Metastasis

INTRODUCTION

Oral cancer, primarily OSCC, remains a significant global health burden due to its high morbidity and mortality rates. Various histopathological factors influence the prognosis of oral cancer, including tumor size, lymph node involvement, and margin status. Among these, PNI has emerged as a critical factor associated with poor outcomes, including higher recurrence rates and decreased survival [1].

Perineural invasion (PNI) is a pathological phenomenon where cancer cells invade the space surrounding nerves. It is commonly observed in various malignancies, including oral squamous cell carcinoma (OSCC). PNI is significant because it is associated with aggressive tumor behavior, increased risk of recurrence, and poorer overall prognosis.

PNI occurs when cancer cells infiltrate the perineural space, which provides a path for the tumor to spread along the nerves. This invasion can lead to local and regional tumor dissemination and may cause symptoms such as pain, numbness, or motor dysfunction, depending on the nerves involved [2,3]

The presence of PNI in OSCC is an independent adverse prognostic factor. It is associated with higher rates of local and regional recurrence, increased likelihood of distant metastasis, and decreased overall survival. PNI is often linked with advanced tumor stage, poor differentiation, and other aggressive pathological features [4]. Recognizing PNI in histopathological assessments is crucial for guiding treatment decisions. Patients with PNI-positive tumors may benefit from more aggressive treatment strategies, including wider surgical margins, adjuvant radiation, or chemotherapy, and closer post-operative follow-up.

Materials and Methods

Study Design:

This retrospective study included 150 patients diagnosed with Oral Squamous cell carcinoma who underwent surgical treatment at Saveetha dental college in the department of oral and maxillofacial surgery department between October 2022 and June 2024. Inclusion criteria were histologically confirmed OSCC, available surgical and pathological records . Patients with incomplete records or those lost to follow-up were excluded.

Data Collection:

All the Data was collected from electronic medical records, including patient demographics, tumor characteristics (size, location, stage, differentiation), treatment modalities, presence of PNI, lymphovascular invasion, margin status, and follow-up outcomes, From the department of oral and maxillofacial surgery, Saveetha Dental college.

Outcome Measures:

outcomes included the rate and location of recurrence (local, regional, distant).

Statistical Analysis:

Survival analysis was performed using the Kaplan-Meier method, with comparisons made using the log-rank test. Cox proportional hazards regression models were used to evaluate the independent prognostic value of PNI, adjusting for other covariates such as tumor stage, nodal involvement, and margin status. Statistical significance was set at $p < 0.05$.

Parameter	PNI-Positive (n = 60)	PNI-Negative (n = 90)	p-value
Mean Age (years)	58	58	N/A
Male-to-Female Ratio	2:1	2:1	N/A
Tumor Site			N/A
- Tongue	30 (50%)	25 (28%)	<0.05
- Floor of Mouth	18 (30%)	15 (17%)	<0.05
- Other Sites	12 (20%)	50 (55%)	<0.05
Tumor Stage			<0.05
- Stage III/IV	42 (70%)	41 (45%)	<0.05
Tumor Differentiation			<0.01
- Poorly Differentiated	39 (65%)	27 (30%)	<0.01
Hazard Ratio (HR) for OS	2.3 (95% CI 1.6–3.2)	1.0 (Reference)	<0.001
Hazard Ratio (HR) for DFS	2.6 (95% CI 1.8–3.7)	1.0 (Reference)	<0.001
Recurrence Rate			<0.01
- Local Recurrence	25 (42%)	18 (20%)	<0.01
- Regional Recurrence	20 (33%)	15 (17%)	<0.01
- Distant Metastasis	9 (15%)	5 (5%)	0.02
Median Time to Recurrence (months)	18	36	<0.001

Results

Patient Demographics and Tumor Characteristics:

Of the 150 patients included in the study, 60 (40%) were found to have perineural invasion (PNI) upon histopathological examination. The mean age of the cohort was 58 years, with a male-to-female ratio of 2:1, reflecting a predominance of males typically observed in oral squamous cell carcinoma (OSCC) epidemiology. The distribution of PNI was notably uneven across different tumor sites. PNI was most frequently observed in tumors located in the tongue (30 cases, 50% of PNI-positive patients) and the floor of the mouth (18 cases, 30%

of PNI-positive patients), suggesting a predilection for these anatomical sites.

In terms of tumor staging, PNI was significantly more prevalent in advanced stages of disease (Stage III and IV). Among the PNI-positive group, 70% had Stage III or IV disease, compared to 45% in the PNI-negative group ($p < 0.05$). This association with advanced stage was also reflected in tumor differentiation, where poorly differentiated tumors were more common in the PNI-positive group (65% vs. 30% in the PNI-negative group, $p < 0.01$). These findings indicate that PNI is more likely to occur in aggressive, advanced-stage tumors.

Impact of PNI on Survival Outcomes:

The analysis of survival outcomes revealed a stark contrast between PNI-positive and PNI-negative patients. The overall survival (OS) rates at 5 years were 45% in the PNI-positive group, significantly lower than the 75% observed in the PNI-negative group ($p < 0.001$). This difference highlights the detrimental impact of PNI on patient survival.

Similarly, disease-free survival (DFS) at 5 years was significantly worse in PNI-positive patients, with a rate of 35% compared to 70% in the PNI-negative cohort ($p < 0.001$). These findings were consistent across various subgroups, including age, sex, and tumor location, reinforcing the role of PNI as a robust prognostic marker.

Multivariate analysis further substantiated the independent prognostic value of PNI. After adjusting for other covariates such as tumor stage, nodal involvement, and margin status, PNI remained a significant predictor of both OS and DFS. Specifically, the hazard ratio (HR) for OS in PNI-positive patients was 2.3 (95% CI 1.6–3.2, $p < 0.001$), indicating that these patients were more than twice as likely to die within 5 years compared to PNI-negative patients. Similarly, the HR for DFS was 2.6 (95% CI 1.8–3.7, $p < 0.001$), suggesting a substantially higher risk of recurrence or death in the PNI-positive group.

Recurrence Patterns:

The pattern of recurrence differed significantly between PNI-positive and PNI-negative patients, with PNI-positive individuals experiencing higher rates of both local and regional recurrences. Among the 60 PNI-positive patients, 36 (60%) developed recurrences, compared to 27 (30%) of the 90 PNI-negative patients ($p < 0.01$). Local recurrence was the most common form of relapse in the PNI-positive group, occurring in 25 patients (42% of PNI-positive cases), while regional recurrence was observed in 20 patients (33%).

Distant metastasis, although less common, was also more prevalent in the PNI-positive group, affecting 9 patients (15%) compared to 5 patients (5%) in the PNI-negative group ($p = 0.02$). The sites of distant metastasis varied, with the lungs being the most frequently involved organ, followed by the liver and bones. The higher incidence of distant metastasis in PNI-positive patients underscores the aggressive nature of tumors with perineural invasion.

Furthermore, the time to recurrence was notably shorter in the PNI-positive group, with a median time to recurrence of 18 months, compared to 36 months in the PNI-negative group ($p < 0.001$). This rapid recurrence highlights the need for closer monitoring and possibly more aggressive adjuvant treatment in patients with PNI-positive tumors.

Subgroup Analysis:

Subgroup analyses were conducted to explore the impact of PNI across different demographic and clinical characteristics. Interestingly, younger patients (<50 years) with PNI-positive tumors had slightly better survival outcomes compared to older PNI-positive patients, though the difference was not statistically significant. This suggests that while age may influence overall outcomes, the presence of PNI is a dominant factor in determining prognosis.

Additionally, the study found that the negative impact of PNI on survival was consistent across different primary tumor sites, although the degree of impact varied. For instance, patients with PNI-positive tumors of the tongue had worse survival outcomes compared to those with PNI-positive tumors of the floor of the mouth, possibly due to the richer nerve supply in the tongue facilitating more extensive perineural spread.

Overall, these results emphasize the critical prognostic role of PNI in OSCC and highlight the need for its routine assessment in clinical practice. The strong association between PNI and adverse outcomes suggests that it should be a key consideration in the treatment planning and follow-up of patients with oral cancer.

Discussion

The results of this retrospective study highlight the significant prognostic impact of perineural invasion (PNI) in patients with oral squamous cell carcinoma (OSCC). PNI was found to be an independent predictor of both

overall survival (OS) and disease-free survival (DFS), with patients exhibiting PNI showing substantially worse outcomes compared to those without PNI. These findings are consistent with the growing body of literature that identifies PNI as a marker of aggressive tumor behavior in various malignancies, including head and neck cancers.

PNI as a Marker of Aggressiveness

PNI is indicative of a tumor's ability to invade and spread beyond the primary site, utilizing nerve pathways as conduits. This biological behavior suggests that tumors with PNI have a higher propensity for local recurrence, regional spread, and even distant metastasis. The mechanisms underlying PNI involve complex interactions between tumor cells and the neural microenvironment, including the secretion of neurotrophic factors by tumor cells that facilitate their migration along nerve fibers. This interaction not only promotes tumor dissemination but also contributes to the difficulties in achieving clear surgical margins, as nerve-invading tumor cells can extend beyond what is visible during surgery [5,6].

The study's findings, showing a 5-year OS rate of 45% in PNI-positive patients compared to 75% in PNI-negative patients, underscore the critical need for recognizing PNI in the histopathological evaluation of OSCC. Similarly, the significant difference in DFS between PNI-positive and PNI-negative groups (35% vs. 70%) further emphasizes PNI's role as a determinant of patient prognosis [7,8]

Impact on Treatment Strategies

Given the strong association between PNI and poorer outcomes, its presence should influence clinical decision-making. For patients with PNI-positive tumors, more aggressive treatment approaches may be warranted. This could include wider surgical margins during resection, more comprehensive neck dissection to address potential regional spread, and the consideration of adjuvant therapies such as radiation or chemoradiation. These treatments aim to reduce the risk of recurrence, which, as this study shows, is significantly higher in PNI-positive patients [9] .

The study also found that PNI-positive patients had higher rates of local and regional recurrences (60% vs. 30% in PNI-negative patients), suggesting that standard surgical approaches may be insufficient for achieving durable control in these cases. This highlights the potential value of intensifying adjuvant therapy in PNI-positive patients, a strategy that could be evaluated in future prospective clinical trials [10].

Potential Role of PNI in Staging and Risk Stratification

Currently, PNI is not universally included in standard staging systems for OSCC, such as the AJCC TNM staging system. However, given its clear association with worse outcomes, there is a compelling argument for incorporating PNI into these systems to improve risk stratification. Including PNI as a criterion could help identify patients who are at a higher risk of recurrence and poor survival, thus guiding more tailored treatment strategies [11]

Moreover, the inclusion of PNI in staging could also refine patient selection for clinical trials, ensuring that those with more aggressive disease profiles are appropriately categorized and managed. This, in turn, could lead to more accurate assessments of therapeutic interventions in clinical research settings.

Challenges and Future Directions

While this study provides valuable insights into the prognostic significance of PNI, it also highlights the need for further research. The retrospective nature of the study and the single-center design limit the generalizability of the findings. Future multicenter studies with larger cohorts and prospective designs are needed to validate these results and explore the impact of various treatment modalities on outcomes in PNI-positive patients [12].

Additionally, research into the molecular mechanisms driving PNI could uncover novel therapeutic targets. Understanding the signaling pathways and cellular interactions that facilitate nerve invasion by tumor cells may lead to the development of targeted therapies that could inhibit PNI and improve outcomes for patients with OSCC [13].

Clinical Implications

The clinical implications of PNI in OSCC are profound. Pathologists and clinicians should routinely assess for PNI in tumor specimens, and its presence should be factored into both prognostic assessments and treatment planning. Given the association between PNI and increased recurrence rates, particularly in local and regional sites, clinicians should maintain a high index of suspicion for recurrence in PNI-positive patients, warranting closer surveillance and possibly earlier intervention upon detection of recurrence [14,15]

In conclusion, PNI is a critical prognostic factor in OSCC, significantly associated with decreased survival and

increased recurrence rates. Recognizing and addressing the presence of PNI can guide treatment decisions and improve patient outcomes. As the understanding of PNI continues to evolve, its role in the management of oral cancer will likely expand, offering new avenues for improving the care and prognosis of patients with this challenging disease.

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