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Expression of PD-L1 in Head and Neck Squamous Cell Carcinoma

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KEYWORDS

Head and neck squamous cell carcinoma, PD-L1, immunohistochemistry, combined positive score.

ABSTRACT:

BACKGROUND AND OBJECTIVES

Head and neck squamous cell carcinoma (HNSCC) is a cancer that ranks as the 7th most common globally, characterized by a poor prognosis and decreased overall survival. In recent times, tumor immunotherapy has emerged as the most promising antitumor treatment, gaining widespread acceptance. One reliable method for identifying patients who may benefit from anti-PD-L1 immunotherapy is through the expression of Programmed death ligand-1 (PD-L1) using immunohistochemistry.

The aim of this study is to investigate the Immunohistochemical (IHC) expression of PD-L1 in head and neck squamous cell carcinomas and to examine its correlation with histopathological factors.

METHODS

It is a retrospective and prospective study done at a tertiary care hospital from 01/02/2023 to 31/01/2024. A total of 60 cases of HNSCC were selected, histopathological features studied and PD-L1 expression was evaluated using a combined positive score (CPS). The statistical significance was evaluated to study the correlation between different histopathological features and PD-L1 expression.

RESULTS

PD-L1 immunopositivity was seen in 44 cases (73.34%) using CPS, of which 24 cases (40%) showed low expression (CPS 1-49) and 20 cases (33.3%) showed high expression (CPS > 50). A statistically significant correlation (0.011) was noted between the PD-L1 score and tumor grade. No other statistically significant correlation was noted with patient demographics, tumor site or tumor stage.

CONCLUSION

Higher amounts of PD-L1 are commonly connected to more aggressive tumors in head and neck squamous cell carcinoma (HNSCC), and it plays a crucial role in evading the immune system. To make an informed decision about therapy, it is important to understand the significance of PD-L1 expression in various types of cancer. Immunohistochemistry can be used to detect PD-L1 status in patients with HNSCC, which can help identify those who may benefit from targeted immunotherapy in the future.

INTRODUCTION

Head and neck carcinoma includes tumors arising from distinct locations in the upper aerodigestive tract, including the nasal cavity, oral cavity, pharynx, and larynx. [1] Most of the head and neck tumors are squamous cell carcinoma which are termed head and neck squamous cell carcinomas (HNSCC). It ranks seventh in the worldwide cancer cases. [2] It is the most common malignancy of the head and neck and arises from the mucosal epithelium.

According to GLOBOCAN, the incidence of HNSCC is rising and is expected to increase by 30% by 2030, or 1.08 million new cases annually. [3,4] High rates of oropharyngeal HPV infection have contributed to the high prevalence of HNSCC in the USA and Western Europe, while consumption of particular carcinogen-containing products such as tobacco, smoking, alcohol, etc. is linked to the high prevalence of HNSCC in regions like Southeast Asia and Australia. [9]

PD-L1, also known as B7-H1 or CD274, is the first functional characteristic ligand co-inhibited by PD-1. [5] It is a cell surface glycoprotein that serves as the physiological ligand for PD-1. It is expressed by immune effector cells as well as various tumor cells.

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PD-1 is a transmembrane receptor of the immunoglobulin superfamily that is expressed on activated T lymphocytes, natural killer cells and B lymphocytes upon induction. [2]

The tumor cells in HNSCC overexpress PD-L1, which causes an interruption in anti-tumor activity and evades the host's autoimmunity. [1] Solid tumors can be immune response-evading, which contributes to their aggressive nature. Both intrinsic and extrinsic regulatory mechanisms, such as immune cells secreting interferon-gamma (IFN-γ), can cause tumor cells to overexpress PD-L1. [14] One approach to do this is by having tumor-specific T cells express programmed cell death ligand 1 (PD-L1), which binds to and inhibits the antitumor activity of tumor-specific T cells through interaction with its receptor (PD-1). [11] This interaction is blocked by novel PD-1/L1 targeting drugs, allowing effector function and lymphocyte proliferation to get back to normal. [12] Evaluating PD-L1 expression levels in HNSCC is essential for gaining insights into the tumor's behavior, response to treatment, and overall clinical outcomes. [13]

Anti-PD-L1 antibodies such as pembrolizumab and nivolumab have been approved for the treatment of recurrent or metastatic HNSCC and can also be used in the prevention of recurrence.

MATERIALS AND METHOD

This is a retrospective and prospective study done in the Department of Pathology at tertiary care hospital, from 01/02/2023 to 31/01/2024 over a period of 12 months. After getting ethical clearance from the IEC committee, vide no. MMCH & RI, IEC/PG/61/JUNE/23. A total of 60 patients who underwent surgery at the tertiary care hospital, and were diagnosed with head and neck squamous cell carcinoma on either biopsy or specimen were taken.

INCLUSION CRITERIA:

- All cases of head and neck squamous cell carcinomas, irrespective of grade and stage of carcinoma were included.
- Both biopsies and specimens are included.
- Availability of adequate tissue material in paraffin blocks.

EXCLUSION CRITERIA:

- Tissue blocks of preoperative chemotherapy or radiotherapy patients.
- Not enough tissue material in the paraffin embedded block.

Patient demographic and clinicopathological data were collected from the medical records department of the hospital by reviewing histopathological and cancer registers. The data collected included age, sex, tumor site, histopathological grading, lymphovascular invasion, and TNM classification. To ensure the accuracy of the results, the formalin-fixed paraffin-embedded blocks and hematoxylin and eosin (H&E) stained slides of the retrospective cases were retrieved and examined. The H&E slides were graded as well, and 20 cases of each category (well-differentiated, moderately differentiated, and poorly differentiated) were randomly selected without any bias. The most representative areas were selected for immunohistochemistry (IHC) analysis of PD-L1.

Along with the positive control from the tonsils, each batch was also stained. To evaluate the immunohistochemistry (IHC), the combined positive score (CPS) was used. Any degree of partial or complete membrane staining of tumor cells and any degree of cytoplasmic or membrane staining in immune cells (lymphocytes and macrophages) was considered positive. Only the immune cells that had infiltrated the tumor or were surrounding it (peritumoral stroma) were taken into account. The CPS was calculated by dividing the number of PD-L1 positive tumor cells and immune cells by the total number of tumor cells multiplied by 100. The cutoff for the CPS was set at ≥1, which was considered positive, and <1 or no expression in tumor or immune cells was negative. Cases with a CPS of ≥1 were further classified as low expression if the CPS was 1-49 and high expression if the CPS was ≥50.

Data was entered in MS Excel worksheet, compared and analysed for statistical significance using SPSS version 27 software. Quantitative data was presented as mean and range. Pearson Chi square test was used to test the significance of difference between groups in qualitative variables. P value of < 0.05 was considered significant for statistical analysis.

RESULT

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In this study, out of 60 cases, 40 were male (66.67%) and 20 were female (33.33%). The median age was 60.5 years (range 38-87). There were 14 cases (23.33%) of age group <50years and 46 cases (76.67%) in age group >50years.

Table 1 summarizes the clinicopathological factors, PDL1 expression, and patient characteristics.

TABLE 1: PATIENT CHARACTERISTICS AND PD-L1 EXPRESSION

VARIABLE	FREQUENCY	PERCENTAGE
AGE		
<50	14	23.33
>50	46	76.67
GENDER		
MALE	40	66.67
FEMALE	20	33.33
TYPE OF SPECIMEN		
BIOPSY	48	80
WIDE EXCISION	8	13.33
RESECTION	4	6.67
TUMOR SITE		
Oral cavity	38	63.34
Pharynx	8	13.33
Larynx	14	23.33
Tumor grade		
Well differentiated	20	33.33
Moderately differentiated	20	33.33
Poorly differentiated	20	33.33
Tumor stage		
T1	44	73.33
T2	16	26.67
PD-L1 EXPRESSION		
POSITIVE	44	73.33
NEGATIVE	16	26.67
BASES ON CPS SCORE		
<1(NEGATIVE)	16	26.67
1-49(LOW EXPRESSION)	24	40
≥50(HIGH EXPRESSION)	20	33.33

Among the 60 cases, 38 cases (63.34%) were from the oral cavity, 08 cases (13.33%) were from the pharynx and 14 (23.33%) cases were from the larynx. Out of the 38 cases from the oral cavity, the majority were of the tongue 26/38cases (68.42%), followed by the buccal mucosa 6/38 cases (15.79%) and the palate 6/38cases (15.79%).

The samples included 48 biopsy (80%), 8 wide excision (13.33%) and 4 resection (6.67%) specimens. Figure 1 shows a gross specimen of a hemiglossectomy case.

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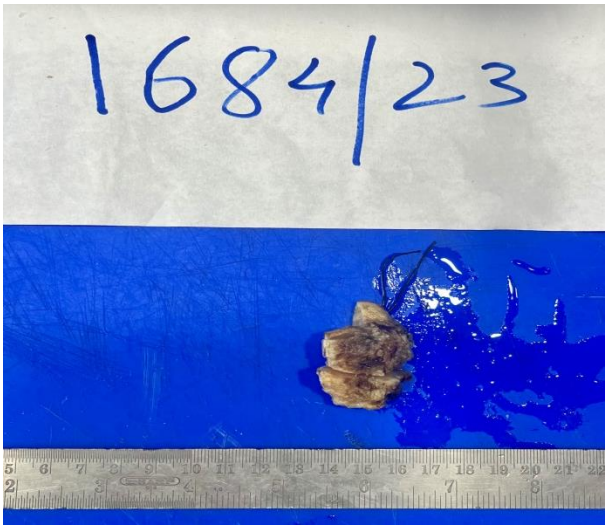


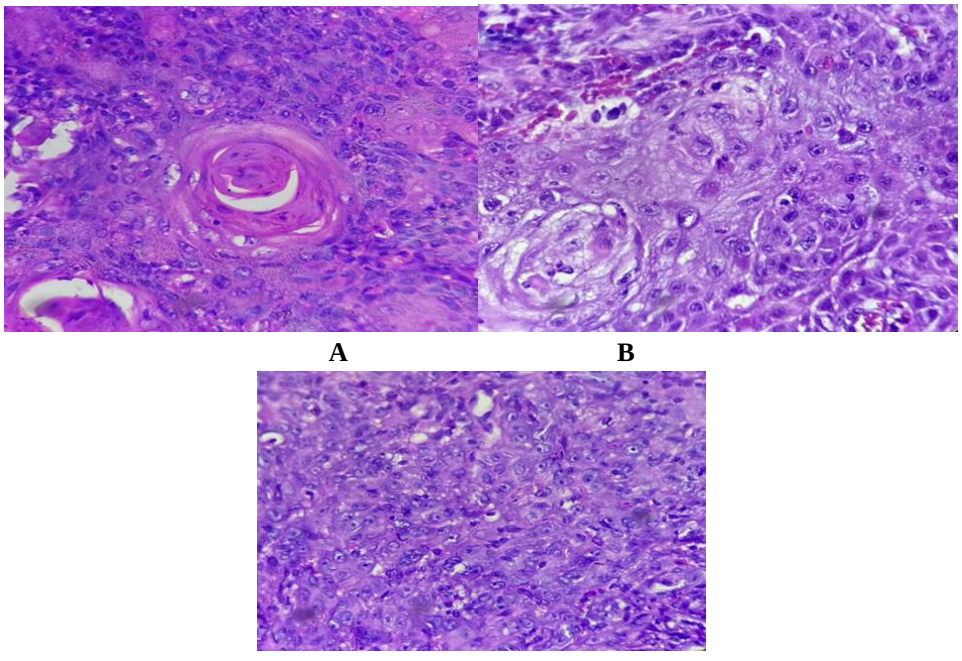
Figure 1: Gross image of hemiglossectomy specimen showing an ulceroproliferative growth.

Based on the histological grading, there were 20 cases of well differentiated, 20 cases of moderately differentiated and 20 cases of poorly differentiated cases. Figure 2 shows H & E images of different grades of head and neck squamous cell carcinoma.

According to the TNM classification, there were 44 cases of T1 stage and 16 cases of T2 stage. There were no cases in our study that belonged to stage T3 or T4. None of the cases showed any nodal involvement or the presence of distant metastasis.

CPS <1 was seen in 16 cases while 44 cases had CPS ≥ 1 of which 24 cases showed low expression (CPS 1-49) and 20 cases showed high expression (CPS ≥ 50) as depicted in figure 3.

Figure 4 shows PD-L1 IHC staining patterns.



A **B**

C

Figure 2: Photomicrograph depicting H&E staining in (A) well differentiated HNSCC showing keratin pearls, (B) moderately differentiated HNSCC and (C) poorly differentiated HNSCC.

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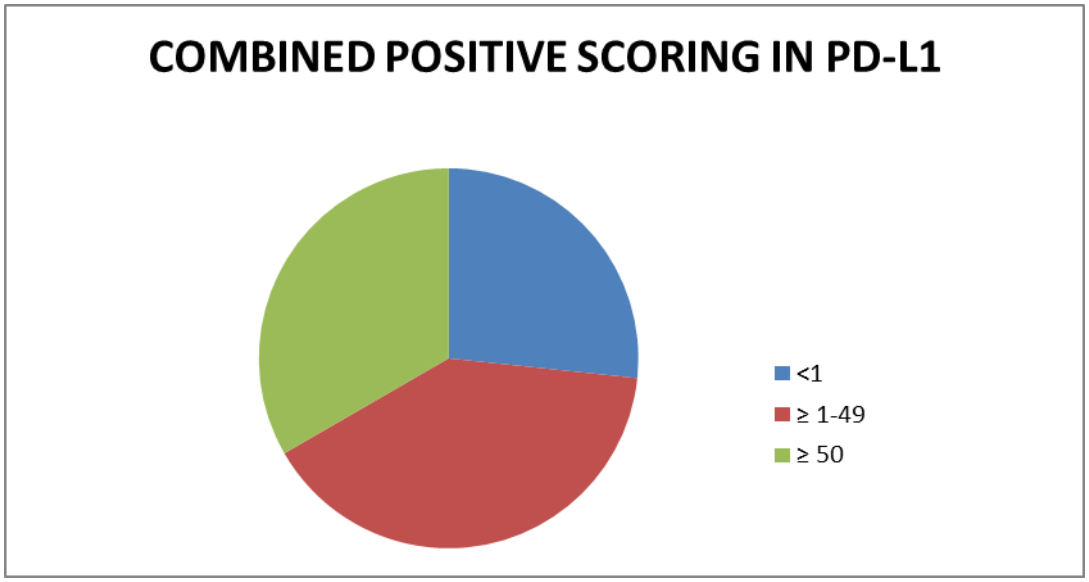
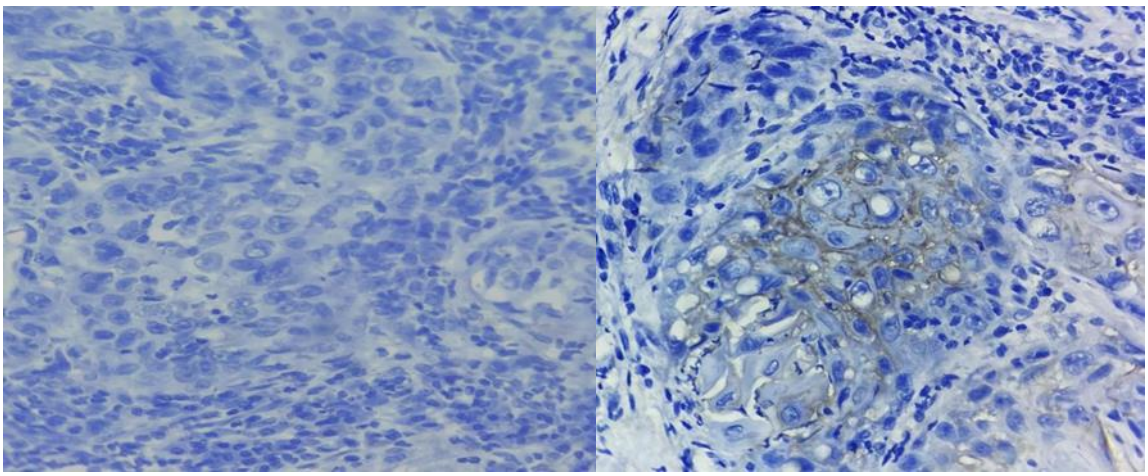
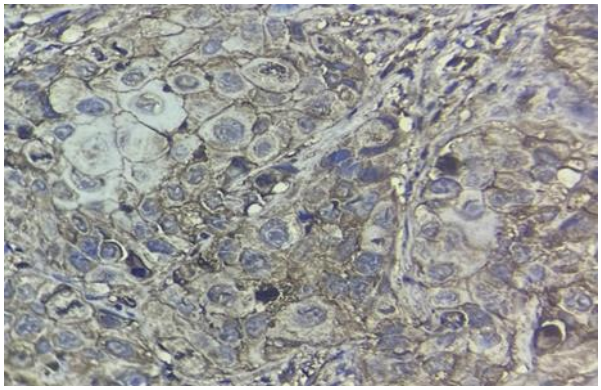


Figure 3: Distribution of PD-L1 expression in head and neck squamous cell carcinoma.



A B



C

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Figure 4: Photomicrograph depicting PD-L1 immunohistochemistry A) Negative with CPS <1. B) Positive membranous immunostaining with CPS ≥1 –low expression. C) Positive membranous immunostaining with CPS ≥50 –high expression.

A significant correlation (0.011) was seen between tumor grade and the PD-L1 score. The association between PD-L1 expression and clinicopathological features is shown in Table 2.

There was no statistically significant correlation seen between low and high PD-L1 scores as shown in Table 3.

TABLE 2: PD-L1 EXPRESSION IN ASSOCIATION WITH VARIOUS CLINICOPATHOLOGICAL FEATURES

Variables	**PD-L1 Positive n (%)**	**PD-L1Negative n (%)**	**P***
Age			0.853
<50	10 (16.67%)	4 (6.67%)	
>50	34(56.67%)	12 (20%)	
Gender			0.409
Male	28(46.67%)	12 (20%)	
Female	16(26.67%)	4 (6.67%)	
Tumor site			0.198
Oral cavity	26 (43.33%)	12 (20%)	
Pharynx	6 (10%)	2 (3.33%)	
Larynx	12(20%)	2 (3.33%)	
Tumor grade			
Well differentiated	16 (26.67%)	4 (6.67%)	0.011
Moderately differentiated	10 (16.67%)	10 (16.67%)	
Poorly differentiated	18 (30%)	2 (3.33%)	
Tumor stage			0.860
T1	32 (53.33%)	12 (20%)	
T2	12 (20%)	4 (6.67%)	

TABLE 3: LOW AND HIGH EXPRESSION OF PD-L1 IN ASSOCIATION WITH VARIOUS CLINICOPATHOLOGICAL FEATURES

Variables	**PD-L1 score 1-49 (n)**	**PD-L1 score ≥ 50 (n)**	**P***
Age			0.693
<50	6	4	
>50	18	16	
Gender			0.086
Male	18	10	
Female	6	10	
Tumor site			0.630
Oral cavity	18	8	
Pharynx	2	4	
Larynx	4	8	
Tumor grade			0.530
Well differentiated	10	6	
Moderately differentiated	6	4	
Poorly differentiated	8	10	

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Tumor stage			0.322
T1	16	16	
T2	8	4	

DISCUSSION

HNSCC has incidence of high mortality and has a poor prognosis with only 40-50% of cases surviving for five years.

Since IHC is a basic, standardized, and trustworthy diagnostic method, it is frequently used in histopathology labs.

Tumor immunotherapy is now being considered the most promising anti-tumor treatment, having gradually gained acceptance recently. [3, 14] The expression of PD-L1 evaluated by IHC is the most frequently used biomarker of immunotherapy response in clinics. [2] A significant development in the management of HNSCC has been brought about by the use of anti-PD-1 immunotherapy. [15] By destroying and suppressing cancer cells through immune system activation, immunotherapy works to restore and strengthen the body's anti-tumor immunological response. Immunotherapy targeting PD-1 and PD-L1 has demonstrated improved efficacy and raises the probability of long-term survival.

According to a number of studies, cancer patients receiving anti-PD-1 or anti-PD-L1 monoclonal antibodies showed greater therapeutic advantages when their PD-L1 expression was high. [2] Research indicates that PD-L1 expression on tumor cells may have predictive value; hence, pembrolizumab was licensed in 2019 as the first-line treatment for patients with HNSCC who had a CPS of ≥1. [13]

In this study, we used CPS, which is a FDA-recommended scoring system used to determine if PD L1 can serve as a valuable predictive biomarker for HNSCC. [2] There is a difference in expression in various studies which may be because there is no fixed protocol to be used for this scoring system. The results of the KEYNOTE 048 trial, which showed that patients with CPS ≥ 20 responded better to immunotherapy treatment than those with CPS ≤ 1, indicate that this scoring system has a predictive effect. [10, 21]

The overall positivity of PD-L1 was 73.33% in this study. These results are similar to the studies by Downes et al. and Chureemas et al. where PD-L1 positivity was seen to be 67-78% and 72% respectively. Whereas in the study by Mishra PS et al. PD-L1 positivity was seen to be 47.3%, this variation may have occurred as there is no standardised protocol available for using CPS system for PD-L1 scoring .[1, 22, 23]

The mean age of the cases that were presented in the current study was 60.5 years. The majority of the cases fell within the sixth decade. PD-L1 positivity was found in 22.7% of patients younger than 50 years and 26.1% of those older than 50 years. With respect to gender, 22.2% of males and 30% of females tested positive for PD-L1. There was no statistically significant correlation seen in the distributions of PD-L1 scores between age groups (P = 0.693) and gender (P = 0.086). These results are similar to other research that found no significant demographic influences on PD-L1 expression, suggesting that PD-L1 expression in HNSCC is not affected by these demographic characteristics. [1, 2] Nevertheless, PD-L1 expression and older age were found to be significantly correlated (P<0.001) by Ngamphaiboon N et al. [17] Variations in tumor features, patient demographics, and sample sizes between studies may be the cause of this disparity. Consequently, more studies including bigger, more varied populations are required to definitively ascertain the association between age and gender with PD-L1 expression in HNSCC.

The most common tumor location was seen in the oral cavity (63.34%), which was similar to the study by Unnikrishnan et al. as well as Chen SW et al. [1, 13] On the contrary, the study by Wusiman et al. showed larynx and hypopharynx as the predominant tumour location. [2] The tumor site did not significantly correlate with PD-L1 positivity (P = 0.198) or PD-L1 expression levels (P = 0.630). PD-L1 positivity was higher in the oral cavity (31.6%) compared to the pharynx (25%) and larynx (14.3%). There was no significant difference in low versus high PD-L1 expression across different

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tumor sites. According to these findings, there was some variation in PD-L1 expression between various tumor locations, but it wasn't statistically significant. This finding is in line with earlier research that indicates PD-L1 expression may be more significantly influenced by tumor microenvironment factors than by the original tumor location. [2, 10]

The correlation between tumor grade and PD-L1 positivity was statistically significant ($p = 0.011$), but there was no significant correlation seen between tumor grade and PD-L1 expression (low / high). Poorly differentiated tumors had a markedly higher PD-L1 positivity rate (90%) compared to moderately differentiated (50%) and well-differentiated tumors (80%). This suggests that poorly differentiated tumors show higher PD-L1 expression, which could indicate more aggressive tumor biology with enhanced immune evasion capabilities through PD-L1 expression. The significant difference in PD-L1 positivity among poorly differentiated tumors suggests that these tumors might be more responsive to PD-1/PD-L1 inhibitor therapies, making PD-L1 expression a potential marker for identifying patients who could benefit from immunotherapy. [18, 19, 20] similar conclusion was also seen in a meta-analysis by Wu P et al. that suggested higher PD-L1 expression is generally associated with poor prognosis and more advanced tumor stages, reinforcing the potential of PD-L1 as a marker for aggressive disease [24]

There was no significant correlation seen between tumor stage and PD-L1 positivity and/or expression. 27.3% of T1 tumors were PD-L1 positive compared to 25% of T2 tumors ($p=0.860$). This is in agreement with previous studies done by Mishra PS et al. and Gangadhar et al. [1, 10] However, in the study by Wusiman D et al., there was an association found between PD-L1 expression and tumor stage with a P-value of 0.022. [2] This variation may occur because other factors such as the tumor microenvironment, genetic mutations, and treatment history, which can vary significantly across different studies and patient populations, might have influenced PD-L1 expression.

CONCLUSION

The role of the PD-1/PD-L1 pathway in tumor progression is a subject of increasing research, and individuals with recurrent or metastatic HNSCC have shown some initial success with immune checkpoint therapy.

The possible function of PD-L1 as a biomarker for tumor differentiation status is emphasized by the correlation found between PD-L1 expression and tumor grade. These results should help inform treatment choices since cancers that express more PD-L1, especially those that are poorly differentiated, may respond better to immunotherapy. Poorly differentiated cancers have greater levels of PD-L1 expression, which indicates that patients with these malignancies should receive more aggressive and focused treatment.

Understanding the expression of PD-1 and PD-L1 in tumor cells improves our understanding of the biological behaviour of HNSCC. More work needs to be done to find populations that respond to PD-1/PD-L1 suppression and combine it with other molecular targets in order to boost the response rate and increase the overall survival. [14]

Limitations

There are certain limitations to our study. This is a retrospective and prospective study conducted at a single tertiary care centre. There has been no follow up carried out with our selected patients, so we can't assess the prognosis and survival of the patients. The sample size of our study is small and the number of patients in each tumor site is less, thus this may lead to statistical bias. Most of the samples are biopsy specimens and very few resections and wide excision specimens were included in the study. None of the patients in the current study have received anti PD-L1 immunotherapy, thus we cannot determine the effectiveness of the therapy in PD-L1 positive patients.

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