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Study on Subcellular Expression Patterns of p62/SQSTM1 in Oral Squamous Cell Carcinomas: An Immunohistochemical Analysis

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Highlights

1.p62 role in normal cell physiology mentioned

2.p62 expression in different layers of normal oral epithelium discussed

3.p62 expression in different grades of OSCCs discussed

4.p62 expression compared between normal oral epithelium and oral carcinoma discussed

ABSTRACT

Background

p62/SQSTM1 is a multifunctional 62 kDa protein that shuttles between the nucleus and cytoplasm to maintain protein homeostasis through the autophagy machinery. Dysregulated p62 acts as an oncogenic signalling hub, activating pathways such as NF-κB, Nrf2, and mTORC1 that promote tumour cell proliferation and resistance to cell death in malignancy.This study aimed to assess the subcellular expression patterns of p62 in OSCCs by an immunohistochemical approach.

Study design

This is an observational in vitro cross sectional study done using a total 45 oral tissue specimens (N=45).

Method

The 45 tissue samples consist of 30 OSCC specimens, and 15 Normal oral mucosal specimens. These samples were sectioned and tissue were stained with H& E stain for histopathological confirmation and IHC staining with p62 marker for assessment.Microscopic evaluation of p62 immunohistochemical stained tissue sections was done by two blinded observers for subcellular p62 staining and a semiquantitative score were calculated. The results were statistically analysed with a significance of p-value at <0.05

Results

Subcellular expression of p62 was significantly upregulated in all grades of OSCC compared to Normal oral mucosal epithelum, where minimal physiological expression was observed. In well-differentiated OSCC, p62 expression was significantly higher in the nucleus compared to controls. Progressive shift towards the cytoplasmic localisation was observed in moderate OSCCs. Poorly differentiated OSCCs exhibited the highest cytoplasmic Q values ($p < 0.001$) and significantly lower nuclear levels ($p = 0.012$).

Conclusion

High nuclear p62 accumulation observed in early stage OSCCs, and medium to high cytoplasmic p62 expression in moderately to poorly differentiated OSCCs**.** Subcellular p62 expression shifts from the nucleus to the cytoplasm during high-grade malignant transformation, serving as a marker for impaired autophagy and abnormal cell proliferation.

Key words

p62, Autophagy, Cell proliferation,Oral squamous cell carcinoma, Nuclear expression, Cytoplasmic expression.

Background

p62/SQSTM1 is a multifunctional 62kDa protein that dynamically shuttles between the cytoplasm and nucleus, contributing to essential cellular processes. [1] It possesses multiple functional domains enabling interactions with autophagy machinery and signaling proteins, thereby mediating selective degradation of ubiquitinated substrates and maintaining protein homeostasis. [2] Through these molecular interactions, p62 regulates stress response, inflammation, and cell survival mechanisms that are crucial for cellular adaptation.[3] Aberrant accumulation or mislocalization of p62 has been implicated in tumor development, supporting its role as an oncogenic signaling hub. [4] In cancer, dysregulated p62 enhances tumor cell proliferation and resistance to cell death by activating oncogenic pathways including NF-κB, Nrf2 and mTORC1.[5] Impairment of autophagic turnover further promotes its accumulation, facilitating metabolic reprogramming and malignant transformation.[6] In oral squamous cell carcinoma (OSCC), altered expression and subcellular localization of p62 correlate with tumor aggressiveness and progression, suggesting its potential utility as a diagnostic and prognostic biomarker even in oral potentially malignant disorders.[7] Therefore, evaluation of p62 through immunohistochemical analysis may provide clinically relevant insights into OSCC pathogenesis and therapeutic targeting. Based on these findings, the present study focused on further investigating the potential of p62 in prediction of OSCC. By comparing expression of p62 in OSCC and normal oral epithelium , this research wanted to stump up the ongoing discussion on the role of p62 in early prediction of OSCC in target population and sites.This study aimed to evaluate immunohistochemical expression of p62 in OSCC through assessing qualitative and quantitative expression of p62 in Oral squamous cell carcinomas and Normal Oral epithelium.

Method

Study Design

The study was designed as an analytical cross-sectional in vitro study done in the Department of Oral

Pathology, Government Dental College and Hospital for a period of 6 months from March 2025 to October 2025.Institutional ethical committee approval was taken with No17/D001/IEC/GDC&H/2023-24. Materials utilized for the study were formalin-fixed tissue specimens of OSCC and Normal oral mucosa in the department, processing solutions Leica microtome,the primary antibody-SQSTM1/p62 Rabbit Mab (A19700) at 1:1000 dilution (AB clonal company).

The secondary antibody-HRP Goat Anti-Rabbit IgG (H+L) (AS014) at 1:10000 dilution (ABclonal company), Haematoxylin and Eosin stains , Triconocular research microscope, glass slides, coverslips, beakers, staining jars, forceps, gloves, tissue processing equipment (slide warming table hot air oven). [8]The study was carried out step by step as follows[8]

1.Sample collection and Preparation 2.Tissue Sectioning and Staining with Hematoxylin & Eosin,and p62 IHC marker

3. Evaluation of H&E-stained sections and p62 IHC stained sections

4 . Statistical Analysis

1. Sample Collection And Preparation

Sample selection was based on inclusion criteria of histopathologically diagnosed cases of OSCC (graded according to WHO criteria) and normal oral mucosa from the willing participants were taken with a consent form, preferably from the extraction sites of the 3rd molar in healthy individuals. Exclusion criteria include any diseased oral mucosa.

Sample size was calculated as 45 samples using the Chi-square analysis with G* power 3.1.9.7 software.Thirty formalin-fixed tissue specimens of diagnosed OSCC cases were obtained from the Department of Oral Pathology and 15 normal Oral normal mucosal tissues were collected from the Dept of Oral surgery taken during surgical impactions and jaw fracture management. Tissue blocks were prepared after routine tissue processing of normal oral mucosa specimens. 45 study samples /

specimens (N=45) were grouped into 2 groups as follows

Group A : Tissue specimens of OSCC cases- 30no

Group B: Tissue specimens of Normal healthy oral mucosa-15no

2.Tissue Sectioning , Staining Tissue Sections With Hematoxylin & Eosin, And P62 Ihc Marker

Each specimen was sectioned into two equal pieces , 2 serial sections (4 µm thick) were taken.First Section was stained with Hematoxylin and Eosin (H&E) for confirmatory histopathological diagnosis.Second Section Stained Immunohistochemically for p62 protein Primary antibody: *p62* (ABclonal company). [8]

3. Evaluation Of H&E-Stained Sections And P62 IHC Stained Sections

The H&E-stained sections were independently evaluated by two blinded observers using a Trinocular research microscope under 4x, 10x, and 40x magnifications for confirmatory histopathological diagnosis of OSCCs.The parameters like cytoplasmic p62 expression , nuclear p62 expression , and both nuclear and cytoplasmic p62 expression were evaluated qualitatively and quantitatively in normal mucosal epithelium (Figure 1),well differentiated squamous cell

carcinoma (Figure 2), moderately differentiated squamous cell carcinoma (Figure 3),and poorly differentiated squamous cell carcinoma (Figure 4). Blinding Evaluation done by 2 blinded investigators.Two pathologists independently evaluated the results of immunohistochemical staining without knowing of clinicopathologic features. The interobserver agreement of the two pathologists was high (α=0.94 and α=0.97). The intraobserver agreement of the scoring also showed high concordance (α=0.96). Any difference of opinions were resolved using a multiheaded microscope. Representative histological sections from each case were evaluated for p62 expression [8]. For each section, five random high-power fields were selected and analyzed. A semi-qualitative immunohistochemical Q-score was employed to assess p62 expression separately in the nucleus, cytoplasm, and combined nuclear and cytoplasmic compartments. Quantitative analysis was performed using ImageJ software. The Q-score was

calculated as the product of staining intensity and the percentage of positively stained cells, as described by Mariotti et al.[8]The percentage of positive cells was scored on a scale of 0 to 4, where 0 indicated no positive cells, 1 indicated up to 20% positive cells, 2 indicated 21–50%, 3 indicated 51–70%, and 4 indicated more than 71% positive cells. Staining intensity was graded on a scale of 0 to 3, with 0 representing no staining, 1 representing low intensity, 2 representing moderate intensity, and 3 representing high intensity. The final p62 expression score was obtained by multiplying the percentage score by the intensity score. Based on the final Q-score, p62 expression was categorized as low (scores 1–2), intermediate (scores 3–4), and high (scores >5). [8]

4.Statistical Analysis

All quantitative data were compiled and analysed using SPSS version 26. The results were expressed as mean ± standard deviation (SD) for continuous variables. The Q values of p62 expression in the nucleus, cytoplasm, and combined compartments were assessed across different histopathological grades of oral squamous cell carcinoma (OSCC) and compared with the control group.

Data normality was confirmed using the Shapiro–Wilk test, followed by parametric tests for further analysis. An Independent Samples t-test (both Student's t and Welch's t) was employed to compare mean Q values between each OSCC grade (well-, moderately-, and poorly differentiated) and controls.

In addition, a * Chi-square test-was performed to compare mean Q values among all SCC grades to identify intergroup differences in p62 expression patterns. Where significant differences were observed.

Both p-values and mean differences were recorded to determine statistical significance. A p-value < 0.05 was considered statistically significant.

Results

A total of 45 tissue samples (Groups A and B)were evaluated for p62 staining and the results were as

follows.Table 1 showed cells exhibiting p62 expression in cytoplasmic,nucleus and combined cytoplasmic and nucleus of OSCC tissues (Group A) , whereas cells in normal oral mucosal epithelium (Group B) exhibited no p62 expression in cytoplasm, nucleus and combined cytoplasmic and nucleus and the difference observed was highly statistically significant ($p < 0.001$) .Table 2 showed significantly higher proportion of cells exhibiting p62 expression in nucleus (≥70%) , less cytoplasm (≤10%) and combined cytoplasmic and nucleus (≤ 20%) in well differentiated OSCC cases compared to normal oral mucosal epithelium controls (0%) ($p < 0.001$).Table 3 showed in moderately differentiated OSCC, predominant cells expressed cytoplasmic (≥ 50%) and combined p62 expression were markedly elevated (≤35%) compared to controls ($p < 0.001$), while nuclear expression remained statistically insignificant (≤15%) ($p > 0.05$) . Table 4 showed poorly differentiated OSCC cells demonstrated the highest cytoplasmic (≥ 70%) and combined p62 expression (≤ 20%)($p < 0.001$) ,. nuclear p62 levels were significantly lower (≤ 10%) ($p = 0.012$) than controls. Table 5 showed highly statistically significant association between histopathological grading of OSCC and the pattern of p62 expression ($\chi^2 = 67.09$, $p < 0.001$).Well differentiated squamous cell carcinomas predominantly exhibited nuclear p62 expression, whereas moderately and poorly differentiated carcinomas exhibited cytoplasm expression followed by combined expression.

Tables

Table 1-Comparison of Subcellular p62 Expression in Oral Squamous Cell Carcinoma (Cases Group A) with Normal oral Mucosal epithelium (Control Group B) Based on Subcellular Localization

Parameter Location of p62 expression	OSCC (MTean ± SD)	Normal Mucosa (Mean ± SD)	Mean Difference	t value	p value
p62 in nucleus	106.17 ± 17.38	5.67 ± 1.95	100.50	31.28	< 0.001
p62 in cytoplasm	84.33 ± 9.44	0.00 ± 0.00	84.33	48.93	< 0.001
p62 in nucleus &cytoplasm Combined expression	58.97 ± 15.58	0.00 ± 0.00	58.97	20.73	< 0.001

Student's Samples T-Test , *p- Value <0.05 Statistically significant

The present analysis demonstrates a statistically significant difference in p62 expression between oral squamous cell carcinoma (OSCC) tissues and normal oral mucosa with respect to its subcellular localization.Nuclear expression of p62 was markedly elevated in OSCC (106.17 ± 17.38) compared to normal mucosa (5.67 ± 1.95), with a mean difference of 100.50. This difference was found to be highly statistically significant ($t = 31.28$, $p < 0.001$).Similarly, cytoplasmic expression of p62 was observed exclusively in OSCC tissues (84.33 ± 9.44), whereas no cytoplasmic expression was detected in normal mucosa (0.00 ± 0.00). The difference between the two groups was highly significant, as evidenced by a t-value of 48.93 ($p < 0.001$).Furthermore, combined nuclear and cytoplasmic expression of p62 was significantly higher in OSCC (58.97 ± 15.58) compared to normal mucosa, where no expression was observed. This difference was also statistically significant ($t = 20.73$, $p < 0.001$).

Table 2- Comparing of Subcellular p62 Expression Between Well-Differentiated OSCC and (Cases Group A) Normal oral Mucosal epithelium (Control Group B)

Parameter Location of p62 expression	Description- Group	N	Mean	Median	SD	SE	P value Student's t	P value Welch's t
p62Nucleus expression	Well-differentiated OSCC-A	12	8.50	9.00	2.50	0.723	0.003	0.004
	Normal oral Mucosal epithelium-B	15	5.67	6.00	1.95	0.504		
p62 Cytoplasn expression	Well-differentiated SCC-A	12	3.42	4.00	1.62	0.468	< 0.001	< 0.001
	Normal oral Mucosal epithelium-B	15	0.00	0.00	0.00	0.000		
p62 Nucleu + Cytoplasn combined expression	Well-differentiated SCC-A	12	2.08	2.00	1.24	0.358	< 0.001	< 0.001
	Normal oral Mucosal epithelium-B	15	0.00	0.00	0.00	0.000		

P value <0.05 Statistically significant

Well-differentiated OSCC cases showed significantly higher p62 expression in both nucleus and cytoplasm compared with controls ($p < 0.001$). The elevated Q values reflect increased cellular stress and disturbed autophagic regulation, though the overall rise was moderate compared to higher tumour grades. As prognosis is inversely related to the Q value, the relatively lower Q values in well-differentiated SCC indicate a comparatively favourable prognosis. Early lesions thus show p62 upregulation but retain partial autophagic control.

Table 3 - Comparing of Subcellular p62 Expression Between Moderately Differentiated OSCC (Cases Group A) and Normal oral Mucosal epithelium (Control GroupB)

Location of p62 expression	Description-Group	N	Mean	Median	SD	SE	P value Student's t	P value Welch's t
p62 Nucleus expression	Moderately differentiated OSCC-A	11	5.17	6.00	2.44	0.705	0.559	0.570
	Normal oral Mucosal epithelium-B	15	5.67	6.00	1.95	0.504		

p62 Cytoplasm expression	Moderately differentiated OSCC-A	11	6.08	6.00	3.34	0.965	< 0.001	< 0.001
	Normal oral Mucosal epithelium-B	15	0.00	0.00	0.00	0.000		
p62 Nucleus Cytoplasm combined expression	Moderately differentiated OSCC-A	11	4.92	4.00	3.23	0.933	< 0.001	< 0.001
	Normaloral Mucosal epithelium-B	15	0.00	0.00	0.00	0.000		

*p- Value <0.05 Statistically significant

In moderately differentiated OSCC, cytoplasmic and total p62 expression were markedly elevated compared with controls ($p < 0.001$), while nuclear expression remained

statistically insignificant ($p > 0.05$). Higher Q values, particularly in the cytoplasm, indicate a worse prognosis than in the well-differentiated group. This redistribution from nuclear to cytoplasmic localisation suggests progressive autophagic blockade, leading to p62 accumulation. The moderate differentiation stage, therefore, represents a transitional phase where p62 overexpression begins to correlate strongly with disease advancement and poorer outcomes.

Table 4.Comparing Subcellular p62 Expression Between Poorly Differentiated OSCC (Cases Group A) and Normal oral Mucosal epithelium (Control GroupB)

Location of p62 expression	**Description-Group**	**N**	**Mean**	**Median**	**SD**	**SE**	**P value Student's t**	**P value Welch's t**
p62 Nucleus expression	Poorly differentiated OSCC-A	7	3.29	4.00	1.70	0.644	0.012	0.012
	Normal oral Mucosal epithelium-B	15	5.67	6.00	1.95	0.504		

p62 Cytoplasm expression	Poorly differentiated OSCC-A	7	9.43	9.00	2.70	1.020	< 0.001	< 0.001
	Normal oral Mucosal epithelium-B	15	0.00	0.00	0.00	0.000		
p62 Nucleu & + Cytoplasn combined expression	Poorly differentiated OSCC-A	7	6.00	6.00	2.24	0.845	< 0.001	< 0.001
	Normal oral Mucosal epithelium-B	15	0.00	0.00	0.00	0.000		

*p- Value <0.05 Statistically significant

Poorly differentiated SCC demonstrated the highest Q values for cytoplasmic and combined p62 expression ($p < 0.001$), indicating a strong correlation with poor prognosis. Nuclear p62 levels were significantly lower ($p = 0.012$) than controls, suggesting loss of nuclear function and predominant cytoplasmic retention of p62 in advanced tumours. The marked cytoplasmic accumulation aligns with aggressive tumour behaviour, reflecting disrupted autophagic clearance and enhanced malignant potential. The higher the Q value, the worse the prognosis, making cytoplasmic p62 over expression a potential indicator of tumour aggressiveness.

Table 5-Comparison of p62 Expression in various grades of Oral Squamous Cell Carcinomas (Group A) Based on Subcellular Localization

Location of p62 expression	**Histopathological Grade**			
	Well differentiated OSCC	Moderately differentiated OSCC	Poorly differentiated OSCC	P- value
p62 Nucléus expression	102	56	23	< 0.001
p62 Cytoplasm expression	41	73	66	< 0.001

p62 Nucleus & Cytoplasm combined expression	23	66	42	< 0.001

*p-Value <0.05 Statistically significant

Statistically significant * Chi-square value (χ^2): 67.09,Degrees of freedom: 4, p-value: < 0.001

CHI square analysis revealed a highly statistically significant association between histopathological grading of OSCC and the pattern of p62 expression (χ^2 = 67.09, p < 0.001).Well differentiated squamous cell carcinomas predominantly exhibited nuclear p62 expression, whereas moderately and poorly differentiated carcinomas exhibited cytoplasm expression followed by combined expression.

Figures

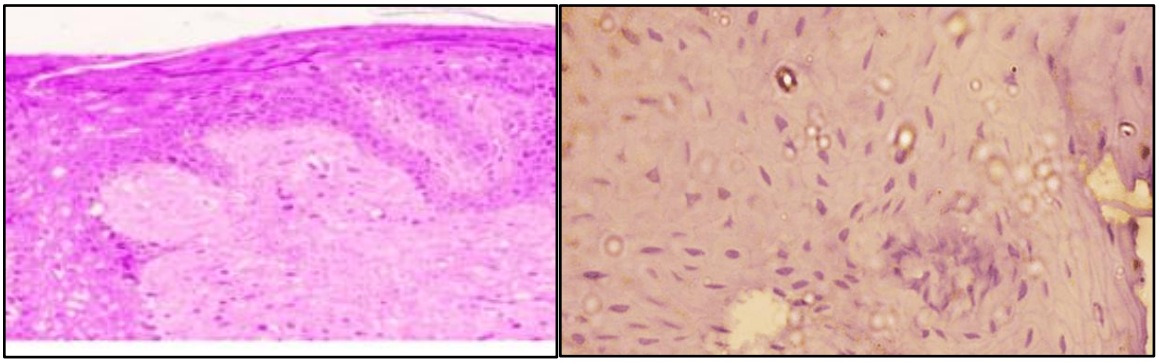


Figure 1. A Showed Normal oral mucosal epithelium (H&E stain 10X Magnification)

Figure 1. B Showed no Cytoplasmic and no Nuclear expression of p62 in Normal oral mucosal epithelium (20X Magnification)

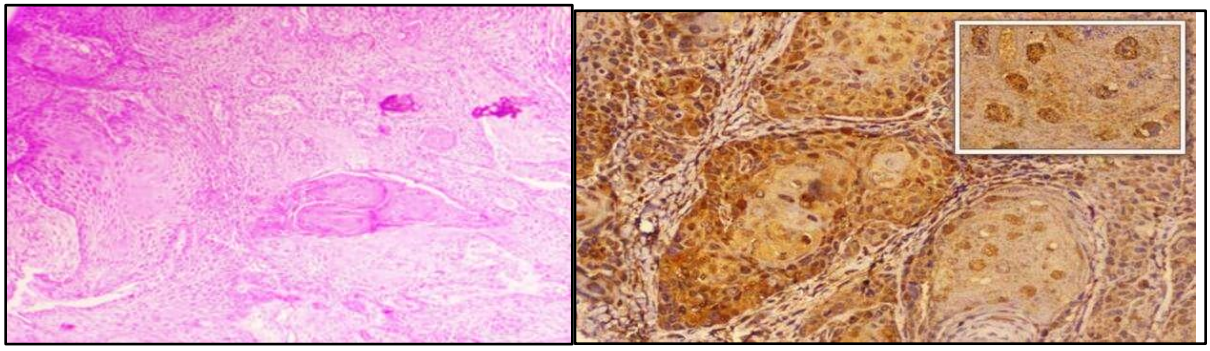


Figure 2. A Showed Well Differentiated Squamous Cell Carcinoma (H& E stain 10X Magnification)

Figure 2. B showed predominant Nuclear (≥70%) ,combined expression (≤ 20%) and (≤10%) Cytoplasmic expression of p62 in Well Differentiated Squamous Cell Carcinoma cell

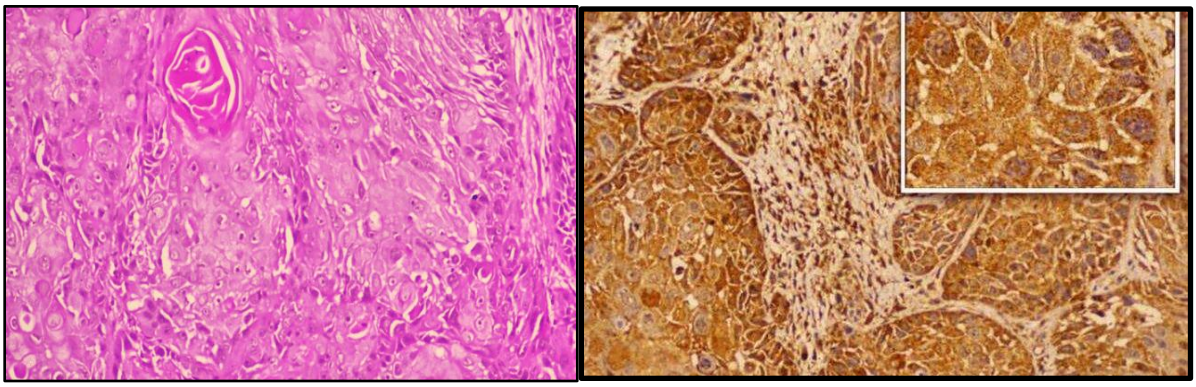


Figure 3. A Showed Moderately Differentiated Squamous Cell Carcinoma (H&E staining-20X Magnification)

Figure 3. B Showed cells with (≥ 50%) predominant Cytoplasmic expression , (≤35%) predominant combined expression and (≤15%)Less Nuclear expression in Moderately Differentiated Squamous Cell Carcinoma (p62 IHC staining-20X and 40X inlet Magnification)

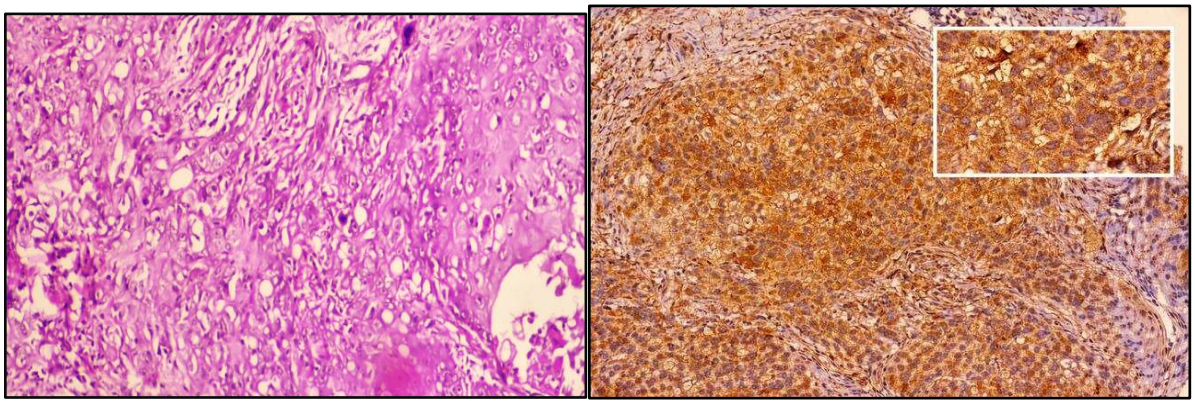
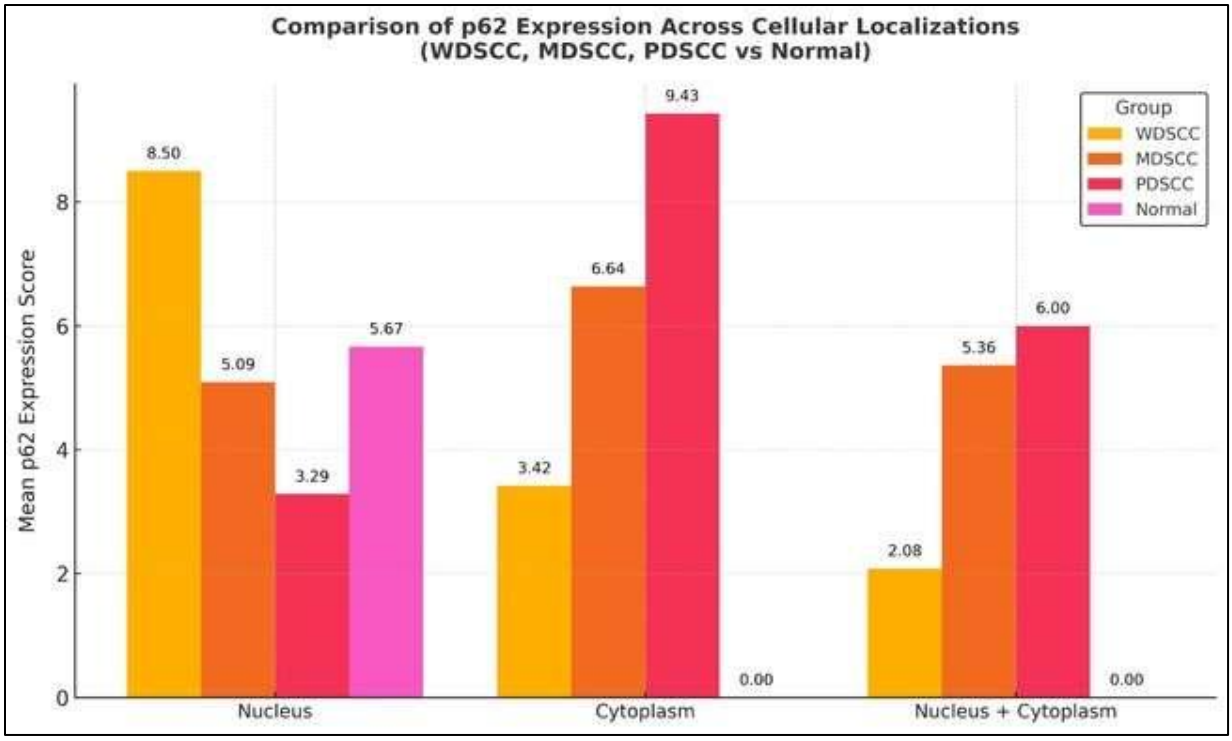


Figure 4. A showed Poorly Differentiated Squamous Cell Carcinoma (H&E staining-20X Magnification)

Figure 4. B Showed more (≥ 70%) Cytoplasmic expression, Least (≤ 10%) Nuclear expression, and Least (≤ 20%) combined expression in Poorly Differentiated Squamous Cell Carcinoma (p62 IHC staining-20X and 40X inlet Magnification)

Figure 5-Graphical representation of p62 subcellular Expression in grades of OSCC and Normal Oral Mucosa



Discussion

The study findings (Table 1) indicated that p62 expression is significantly upregulated in OSCC irrespective of its sub cellular localization compared to normal oral mucosal epithelium , which exhibited only minimal physiological staining (Figures 1A and 1B) The consistently significant results suggested a potential role of p62 in the pathogenesis of OSCC and support its utility as a biomarker.[9] These results agreed with the observations of Liang L et al.study in 2022 who concluded that high cytoplasmic expression of p62 may serve as a poor prognostic marker for OSCC patients. [10]

The present study results of well-differentiated OSCC cases showed significantly increased p62 expression in the nucleus , high combined nucleus and cytoplasm p62 expression compared to controls (Table 2, Figures 2A and 2B). These elevated levels reflect increased cellular stress and disturbed autophagic regulation. Early lesions thus showed p62 upregulation but retained partial autophagic control. These results were in accordance with the study done by Eva Philipson on pancreatic cancers in 2022 and Cheng Lei on

Gastrointestinal Carcinomas in 2019 indicated mild cellular Stress with partial disturbance in autophagy. [10,11]

In moderately differentiated OSCC, p62 levels are much higher in the cytoplasm but show no major change in the nucleus compared to normal oral mucosal epithelium (Table 3, Figures 3A and 3B) . Higher expression particularly in the cytoplasm, indicated a worse prognosis than in the well-differentiated group. This redistribution from nuclear to cytoplasmic localisation suggests progressive autophagic blockade, leading to p62 accumulation.[12] The moderate differentiation stage, therefore, represents a transitional phase where p62 overexpression begins to correlate strongly with disease advancement and poorer outcome.This shift of p62 from the nucleus to the cytoplasm indicates reduced autophagy and increasing tumour progression.[13] These observations were in accordance with the study done by J-L Liu on oral squamous cell carcinoma in 2014.[14]

Poorly differentiated OSCC demonstrated the highest p62 expression values in cytoplasm and combined p62 expression indicating a strong correlation with poor prognosis. Nuclear p62 levels were significantly lower than controls, suggesting loss of nuclear function and predominant cytoplasmic retention of p62 in advanced tumours. The marked cytoplasmic accumulation aligns with aggressive tumour behaviour, reflecting disrupted autophagic clearance and enhanced malignant potential.Cytoplasmic p62 overexpression is a potential indicator of tumour aggressiveness and worse the prognosis.In poorly differentiated OSCC, p62 levels are highest in the cytoplasm, combined and lowest in the nucleus, showing a clear link with poor prognosis (Table 4, Figure 4A and 4B).Therefore, high cytoplasmic p62 indicates advanced disease and greater malignant potential.It is in accordance with Inui T et al., study results on OSCCs in 2015.[15] This strong cytoplasmic buildup means the cells have lost normal control mechanisms, leading to more aggressive tumour behaviour.

The present study results observed well differentiated squamous cell carcinomas predominantly exhibited nuclear and combined p62 expression , whereas moderately and poorly differentiated carcinomas demonstrated a progressive shift toward combined nuclear–cytoplasmic localization and cytoplasmic expression (Table 5, Figure 5).This shift in localization with worsening tumor differentiation suggested dysregulation of autophagy pathways and increased tumor aggressiveness, highlighting the potential role of p62 as a prognostic marker of tumor progression in OSCC. [9,16]

Limitations

The sample size was limited (only 30 cases), which may affect the statistical power and generalisation of results.No normalisation or validation of IHC results with molecular methods like Western blotting or RT-PCR.

Conclusion

The study observed different expression patterns of p62 in normal oral mucosas, and OSCCs.Altered p62 localisation that is p62 expression shifts from the nucleus to the cytoplasm from well differentiated OSCCs to poorly differentiated OSCCs in this study implied that autophagy impairment contributed to cancer progression in the OSCCs . Nuclear and combined p62 accumulation could be a marker for early stage OSCCs and predominant cytoplasmic p62 expression for poorly differentiated OSCC.These results notion that subcellular expression of p62 could be applied to assess the carcinogenic potential of epithelial dysplasias in oral potentially malignant disorders.Larger studies regarding the relationships of autophagy and progression of OSCCs are required to confirm the results.

Abrevations

NOME-Normal Oral Mucosal Epithelium

OSCC-Oral Squamous Cell Carcinoma

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Authors' Contribution -The authors affirm their participation in the work as follows: Bygani Supraja Kumari, Sirigala Lavanya, Mandaloju Mythri -Conception and design of the work, Data collection, Analysis, and interpretation of the results; Sravya Kodati,Venkata Chakrapani Kuncha,Lumbini Y,Mandaloju Mythri - Preparation of the manuscript. All authors reviewed the results, contributed to the discussion, and approved the final version of the manuscript.

Competing Interests- The authors declare no conflict of interest, financial or otherwise.

Ethical Approval-Institutional ethical committee of Government Dental College and Hospital,Vijayawada, Andhra Pradesh, India approval was taken with Ref No17/D001/IEC/GDC&H/2023-24 dated 18.04.2024.

Patient consent forms were signed from willing participants in the study

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