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Original Article

Expression of p53 in Squamous Cell Carcinoma of Oral Cavity: A Cross-Sectional Study

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ABSTRACT

Introduction: Oral squamous cell carcinoma (OSCC) is the most prevalent oral cavity tumor. We aimed to see if the expression of p53 in oral mucosal biopsies can be used as a diagnostic aid for evaluating malignancy. Biopsies are small and only a scant amount of material is required, hence this study could help in early detection of disease and prompt treatment.

Methodology: This cross-sectional study has been conducted on a statistically calculated representative sample size of a total of 90 patients.

The study comprised biopsies and resection samples from individuals with squamous cell carcinoma of the oral cavity and patients of both sexes and all ages (from 13 to 90) with high-grade oral squamous cell carcinoma. The slides were examined under light microscope by the Pathologist and diagnosis was recorded. Immunohistochemistry was applied for p53 expression and further evaluation.

Results: Mean age of the patients was 55.1±12.4 years. There were 54 males (60%) while 36 females (40%). Histopathological sub-types were as follows: conventional squamous cell carcinoma (71.1%), basaloid squamous carcinoma (14.4%), verrucous carcinoma (8.9%), adeno-squamous carcinoma (3.3%) and acantholytic cell carcinoma (2.2%).

The most common grade of tumor was well-differentiated squamous cell carcinoma (45.6%) followed by: moderately differentiated squamous cell carcinoma (34.4%), poorly differentiated squamous cell carcinoma (16.7%) and nonkeratinizing squamous cell carcinoma (3.3%). p53 expression was found to be positive in 65.6% of patients. Stratification for age, gender, histopathological subtype and grade of tumor was also carried out.

Conclusion: In conclusion, p53 expression was positive in oral squamous cell carcinomas in 65.6% cases. It is a significant marker of carcinogenesis and can be considered as an important marker for clinical evaluation, diagnosis as well as prognosis of disease.

Keywords: Squamous cell carcinoma of oral cavity, Expression of p53, Immunohistochemistry, human, cancer.

Introduction

Head and neck cancers are the seventh most common cancers occurring worldwide. Squamous cell carcinoma accounts for 95 percent of all head and neck tumors.[1] The incidence of oral squamous cell carcinoma has tremendously increased in last 10 years.[2] Hence the term oral cancers automatically refer to oral squamous cell carcinoma.[3] Even though several innovative methods have been suggested for the treatment of OSCC, surgery is still the most successful option, while radiation and chemotherapy are advised for malignancies. Chemotherapy has been regularly used as an important part of comprehensive OSCC treatment. The most frequent all-encompassing treatment for OSCC is surgery along with neoadjuvant chemotherapy. Post chemotherapy p53 positivity may result in a brief clinically disappearance of tumors while decreasing the size of the primary tumor, enhancing the rate of tumor resection and the negative rate of the resection edge, blocking tumor metastasis, minimizing postoperative tissue defects, and enhancing patient quality of life in general and in those needing dental and oral surgery in particular.[4]

According to 2012 statistical analysis 145,000 deaths have occurred worldwide because of oral squamous cell carcinoma (OSCC). In United States there is dramatic increase in the incidence of oral squamous cell carcinoma. In India it is the leading cancer in men and 5th most common cancer among women.[5] Its incidence is even higher in Pakistan and other South Asian countries.[6] According to a cancer survey done in Karachi in the

year 2006, squamous cell carcinoma of the oral cavity was the leading carcinoma of head and neck cancers. It can be promptly treated if diagnosed at the right time. But unfortunately, many cases reach hospitals at an advanced stage which leads to poor prognosis of the disease.[7]

The most common sites for oral squamous cell carcinoma are lips, hard palate, buccal mucosa, tongue, trigone, floor of mouth.[8] The two most common risk factors for OSCC are tobacco and betel nut chewing.[9] Drug addiction and alcohol consumption plays a synergistic role in causing squamous cell carcinoma of oral cavity.[10] According to the WHO guidelines oral squamous cell carcinoma is classified into 3 categories: well-differentiated, moderately differentiated and poorly differentiated.[5] This classification is based on Broder's system of grading for oral squamous cell carcinoma developed ink the year 1920.[11] It has classified the OSCC on the basis mitotic activity and pleomorphism, degree of differentiation and keratinization. [12]

Regional arterial infusion may increase the apoptotic impact on tumor cells without obvious damage and achieve a high concentration of anticancer medications surrounding the tumor. As a result, this treatment plan offers a precise, straightforward, long-term, low-toxicity, and very effective way to administer medications. Eckardt et al. effectively treated patients with advanced head and neck squamous cell carcinoma by using regional arterial infusion chemotherapy. Carboplatin and 5-fluorourcil (5-Fu) are an effective therapy combination for oral squamous cell carcinoma (OSCC). The combination of 5-fluorouracil

(5-Fu) and carboplatin (cisplatin) for regional arterial infusion chemotherapy in the treatment of oesophageal squamous cell carcinoma.[11,12] p53 gene plays an important role in DNA repair and cell death. It favors the apoptosis of abnormal cells. It has a very short half -life of 6 to 20 mins making it very difficult to detect in cells.[13] The mutation in p53 gene impairs the cell ability to repair DNA aid apoptosis of abnormal cells leading to carcinogenesis. Mutated p53 has a prolonged half-life of 6 hours so it can be detected in cancer cells by using immunohistochemistry.[14] A study conducted in Iraq in the year 2013 by Intisar et al showed that 63.2% of oral squamous cell carcinoma showed positivity for p53. In 85.7% of those cases, p53 positivity was found in poorly classified cancer of the oral cavity. This suggests that p53 expression is associated with a poor prognosis for the underlying disease.

Physical and/or chemical stimuli that damage DNA enhance p53 gene transcription and increase wild type p53 protein, which causes the cell cycle to be arrested at the G1/S phase and causes apoptosis of malignant cells. When the p53 gene is altered, the mutant p53 protein loses its ability to prevent cancer and encourages the conversion of healthy cells into cancerous ones. Nearly every form of human tumor has mutant p53, and this is directly connected to the emergence of OSCC. No research on the impact of neoadjuvant chemotherapy on mutant p53 expression has been identified yet. This research aimed to assess mutant p53 expression in OSCC patients before and after intra-arterial chemotherapy to better understand the disease and find novel ways to treat it.[14]

- The goal of our research is to look at p53 expression in oral mucosal biopsies as a diagnostic aid for evaluating oral cancer.
- As the biopsies are small and a scant amount of specimen is required so this study will prove beneficial in early detection of disease and prompt treatment in smaller biopsies.
- This will free patient from undergoing through the process of re-biopsy.
- Therefore, understanding the molecular mechanisms involved in the initiation and progression to malignancy of oral cancer will help to improve its prognosis and in the elaboration of new forms of treatment.

Methodology

Following approval from the hospital's ethics board, this cohort study was conducted from Aug-Dec 2022 in the Combined Military Hospital's Department of Surgery in Rawalpindi, Pakistan. Using a Rao soft calculator with a 95% confidence interval and a 5% margin of error, researchers analyzed data from 470 patients in a study published in 2013.[5] A convenient sampling method was used.

The STROCSS 2021 standards have been strictly followed throughout our research.[6] As a helpful addendum, we've included the whole STROCSS 2021 checklist. Our investigation is registered in Research Registry with the identifier

researchregistry8268.[7] All of our studies strictly follow the guidelines of the Helsinki Declaration.

All participants and/or their legal guardians provided written informed permission. Gallstone-related acute or chronic cholecystitis patients hospitalized through the outpatient Department were considered. Patients who had gallbladder cancer, as determined by clinical symptoms and imaging tests (ultrasound and/or CT scan), were not included. Additionally, gallbladders that showed obvious anomalies during surgery that were consistent with localized or infiltrative cancer were not included.

Prior to surgery, a patient's right hypochondrium was carefully examined and their medical history recorded with meticulous care. Looking for comorbidities was another goal of the systemic review. All patients underwent initial and follow-up examinations, including abdominal sonography.

The histology of all gallbladder samples was performed, including those with no visible gross abnormalities. The collected data were entered into a premade proforma. SPSS 26.0 was used for the statistical analysis.

Ethics approval obtained from Combined Military Hospital, dated 8th Sep 2022. Informed consent" was obtained from all the participants as well as the guardians (for participants below 16 years of age).

Results

Mean age of the patients was 55.1±12.4 years. 31 (34.4%) patients were categorized into 25-50 years age group while 59 (65.6%) fall into 51-90 years age group. There were 54 males (60%) while 36 females (40%). Histopathology results showed that 71.2% were diagnosed as conventional squamous cell carcinoma, 14.4% as basaloid squamous carcinoma, 8.9% as verrucous, 3.3% as adeno-squamous, and 2.2% as acantholytic. Most tumors (i.e., 45.6%), were classified as well-differentiated squamous carcinoma, followed by moderately differentiated squamous cell carcinoma (34.4%), poorly differentiated squamous cell carcinoma (15.7%), and non-keratinizing squamous cell carcinoma (3.3%).

p53 expression was found to be positive in 59 patients (65.6%) whereas 31 patients (34.4%) were found to negative. 45.16% patients in the 25-50 years old age group and 76.27% patients in the 51-90 years old age group showed positive p53 expression after age stratification having a significant p value of 0.003. p53 expression was found to be positive in 61.11% males and 72.22% females as shown in table. I

Table 1: p53 expression in oral squamous cell carcinoma stratified according to age and gender; p-values in bold signify statistically significant values

Age (n)		p53 expression		Total	p-value
	Negative		Positive		
25-50 (31)	17 (54.84%)		14 (45.16%)	31	0.003
51-90 (59)	14 (23.73%)		45 (76.27%)	59	0.003
		Gender (n)			
Male (54)	21 (38.89%)		33 (61.11%)	54	0.277
Female (36)	10 (27.78%)		26 (72.22%)	36	0.277

After stratifying for histopathological sub-type, we found that 65.62% patients with conventional squamous cell carcinoma, 76.92% patients with basaloid squamous cell carcinoma, and 37.50% patients with verrucous carcinoma, 66.67% patients with adeno-squamous carcinoma and 100% patients with acantholytic cell carcinoma had a positive p53 expression in their aforementioned cancers but the p-value remained non-significant at 0.33.

Results from tumor-grade stratification showed that p53 gene expression was positive in 39.02% patients with well-differentiated squamous carcinoma, 80.65% patients with moderately differentiated squamous cell carcinoma, and in all patients with either poorly differentiated squamous cell carcinoma or nonkeratinizing squamous cell carcinoma with a significant p-value of 0.001 as shown in table 2.

In short, the clinician should be more suspicious of malignant oral squamous cell carcinoma if samples from the oral mucosa tests are positive for p53 and shows signs of malignancy. This should prompt the clinician to begin anti-cancer treatment as soon as possible with the proper modality and dosage so that the patient is able to follow the clinical path to recovery.

Table 2: p53 expression in oral squamous cell carcinoma stratified according to histopathological subtype and grading of tumor; p-values in bold signify statistically significant values.

Histopathological subtype (percent out of all subtypes)	p53 expression			p-value
	Negative (%)	Positive (%)	Total	
Conventional squamous cell carcinoma (71.11%)	22 (34.38%)	42 (65.62%)	64	0.333
Basaloid squamous carcinoma (14.44%)	3 (23.08%)	10 (76.92%)	13	
Verrucous carcinoma (8.90%)	5 (62.50%)	3 (37.50%)	8	
Adeno-squamous carcinoma (3.33%)	1 (33.33%)	2 (66.67%)	3	
Acantholytic cell carcinoma (2.22%)	0 (0%)	2 (100%)	2	
Grade of Tumor (percent out of all grades)	Negative (%)	Positive (%)	Total	
Well differentiated squamous carcinoma (45.56%)	25 (60.98%)	16 (39.02%)	41	0.001
Moderately differentiated squamous cell carcinoma (34.44%)	6 (19.35%)	25 (80.65%)	31	
Poorly differentiated squamous cell carcinoma (16.67%)	0 (0%)	15 (100%)	15	
Nonkeratinizing squamous cell carcinoma (3.33%)	0 (0%)	3 (100%)	3	
No squamous cell carcinoma	0 (0%)	1(100%)	1	

Discussion

Oral cancer is the most common cancer and constitutes a major health problem in developing countries, representing the leading cause of death.[17] Although representing 2-4% of the malignancies in the West, this carcinoma accounts for almost 40% of all cancers in the Indian subcontinent.[18] A key factor in the lack of improvement in prognosis over the years is the fact that a significant proportion of oral squamous cell carcinoma (OSCC) are not diagnosed or treated until they reach an advanced stage. The prognosis for patients with OSCC that is treated early is much better, with 5-year survival rates as high as 80%.[18] In addition; the quality of life also improves after early treatment.

In accordance with our findings, a study carried out in 2020 found that expression of p53 increased with the progression of OSCC from well-differentiated squamous cell carcinoma (WDSCC) to poorly differentiated squamous cell carcinoma.[19] In our study, males were more affected than females because traditionally males are more likely to display oral habits such as tobacco smoking and betel quid chewing. which is consistent with the report of Langdon et al.[20] According to research from Chongqing Medical University published in 2015, patients with higher pathological grades had mutant p53 positive rates that were much greater than those with lower pathological grades, which is consistent with our findings.[21]

A study conducted by Rowley et al. analysed p53 expression in oral dysplasia and oral SCC. Positive p53 expression was seen in 77% of SCC compared to our study having 65.55%.[22] In another study by Verma et al found p53 expression in 66.6% cases of squamous cell carcinoma.[23] Consistent with our findings, wherein more patients were seen in Conventional squamous cell carcinoma and Basaloid squamous cell carcinoma, a 2018 study concluded that a significant incidence of p53 disruption was detected in both variants (84.4% of 32—SCC and 81.2% of 16— BSCC; p = 0.78).[24]

Conclusion

In conclusion, 65.6% of oral squamous cell carcinomas showed positive p53 expression. Malignancy can be assessed through the examination of p53 expression in oral mucosal biopsies. This research has the potential to aid in the diagnosis and treatment of disease at an early stage because biopsies are inexpensive and only require a small sample of tissue.

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