Section: Pathology

Original Research Article

THE MORPHOLOGICAL SPECTRUM OF SQUAMOUS CELL CARCINOMA VARIANTS

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ABSTRACT

Background: Squamous cell carcinoma (SCC) is a malignant epithelial neoplasm characterized by squamous differentiation, evident through the formation of keratin and/or the presence of intercellular bridges. It remains a major cause of morbidity and mortality globally, including in the Indian population. SCC is more common in males and typically occurs in the fourth to fifth decades of life. Known etiological factors include cigarette smoking, use of smokeless tobacco, alcohol consumption, betel nut chewing, advancing age (over 40 years), prolonged exposure to radiation, HIV infection or other immunosuppressive states, and genetic predisposition. The aim of this study is to analyze the spectrum and incidence of SCC cases in our institution and to classify them based on morphological grading and histopathological variants.

Materials and Methods: This is an observational study conducted in the Department of Pathology, Index Medical College Hospital and Research Centre (IMCHRC), Indore. A total of 20 histopathologically confirmed cases of SCC were evaluated over a two-month period from December 2022 to January 2023. Morphological features and variant classification were studied.

Results: Among the 20 cases, the most common histological subtype was well-differentiated keratinizing SCC. The buccal mucosa was the most frequent site, followed by the esophagus and cervix. The majority of patients were above 40 years of age and predominantly male. A strong association with tobacco chewing was noted.

Conclusion: The study highlights the significance of clinical features, morphological differentiation, and histopathological analysis in the accurate diagnosis and classification of SCC. Tobacco chewing emerged as a key risk factor, especially in males.

Keywords: Squamous cell carcinoma, histopathology, keratinization, buccal mucosa, tobacco chewing, grading, morphological varians.

INTRODUCTION

Squamous cell carcinoma (SCC) is a malignant epithelial neoplasm exhibiting squamous differentiation, typically evidenced by intercellular bridges and keratin pearl formation. As one of the most frequently diagnosed cancers worldwide, SCC carries a substantial disease burden, particularly among Indian males in their fourth and fifth decades of life.[1] This carcinoma primarily arises from squamous epithelium lining various anatomical sites, including the skin, oral cavity, cervix, esophagus, lungs, and other mucosal surfaces. Cutaneous SCC, originating in the stratum spinosum of the epidermis, often manifests as non-healing, ulcerated or crusted nodules on sun-exposed regions such as the face, neck, and limbs.[2,3]

The histological spectrum of SCC is diverse and clinically significant. Based on the depth of invasion, SCC can be classified as in situ, superficially invasive, or deeply invasive. Furthermore, it is stratified into well-, moderately-, and poorly differentiated subtypes, often with associated keratinization.[4] Beyond these conventional classifications, SCC encompasses a wide array of morphological variants that together account for 10–15% of all cases. These include spindle cell SCC,

desmoplastic SCC, basaloid SCC, acantholytic SCC, verrucous carcinoma, clear cell SCC, pseudovascular SCC, adenosquamous carcinoma, metaplastic SCC, pigmented SCC, and others.[5]

Each histological variant of squamous cell carcinoma (SCC) and adenocarcinoma (Ac) possesses unique clinicopathological characteristics that can impact both prognosis and therapeutic decisions. Immunohistochemistry plays a pivotal role in accurately subclassifying these tumors. Among all markers evaluated, P63 was identified as the most sensitive indicator for SCC, followed by high molecular weight cytokeratins such as CK, CK5/6, SOX2, Thrombomodulin, Desmocollin-3, S100A7, and Glypican-3. Desmocollin-3 emerged as the most specific marker for SCC, with other markers like CK5/6, SOX2, Glypican-3, S100A2, and Thrombomodulin also demonstrating notable specificity. Additional markers including HMCK and S100A2 proved valuable in differentiating SCC from adenocarcinoma, especially in poorly differentiated or histologically ambiguous cases. Given the diverse histological presentations, immunohistochemical profiling is essential for accurate tumor identification. Among all evaluated markers, CK5/6 consistently proved to be the most reliable for distinguishing SCC from Ac, regardless of histologic grade. As a result, the combination of CK5/6 and TTF-1 is considered the most effective immunohistochemical panel for differentiating between SCC and adenocarcinoma across various anatomical sites and grades.[6,7]

Etiologically, SCC is multifactorial. Well-known risk factors include tobacco (smoked and smokeless), alcohol, betel nut chewing, chronic radiation exposure, immunosuppressive states (e.g., HIV), and genetic susceptibility. Viral oncogenesis, especially by HPV and EBV, plays a pivotal role in oropharyngeal and nasopharyngeal SCC respectively.[8] Moreover, chromosomal alterations, particularly on 3p, have been implicated in aggressive behavior in head and neck SCC.[9]

Clinically, the presentation of SCC is site-dependent. Head and neck SCC may present with non-healing oral ulcers, dysphagia, or cervical lymphadenopathy; esophageal SCC commonly causes progressive dysphagia; thyroid involvement results in neck masses with voice changes; pulmonary SCC often manifests with persistent cough or hemoptysis; and genitourinary SCC may present with bleeding or painful micturition.[10-12]

Given the histomorphological diversity and varying biological behavior of SCC variants, this study aims to analyze and classify the morphological spectrum of SCC observed in our institution, contributing to enhanced diagnostic precision and individualized patient care.

Table 1: Clinical and histologic features of squamous cell carcinoma variants

Feature	Verrucous	Papillary/Exophytic	Spindle Cell (Sarcomatoid)	Basaloid	Adenosquamous
Gender	M > F, except oral	M > F	M > F	M > F	M slight > F
Location	Oral > Larynx	Larynx > Oral > Nasal	Larynx > Oral > Nasal	Base of tongue > supraglottic larynx	Tongue > Floor of mouth > Nasal
Frequency	<1%	1%	3%	Unknown	<1%
Aetiology Agent	HPV	HPV	Radiation	Unknown	Unknown
Macroscopic	Broad-based, warty, fungating, up to 10 cm	Polypoid, exophytic, bulky, fungiform	Polypoid mass	Firm to hard with central necrosis	Indurated submucosal nodule
Microscopic	Pushing border of infiltration, blunt rete pegs, no pleomorphism, no mitoses	>70% exophytic/papillary architecture, koilocytotic atypia, difficult to demonstrate malignancy	Biphasic: SCC + atypical spindle cells; pleomorphism; increased mitoses	Biphasic: invasive lobular basal cells; high N:C ratio; keratin pearls; necrosis; hyaline material	Biphasic: SCC + adenocarcinoma or undiff. carcinoma; intermixed glandular/SCC; increased mitotic rate
Special Studies	HPV identified	None	70% positive with epithelial markers	Keratin, EMA, CK7, 34βE12	Mucin-positive adenocarcinoma cells
Differential Dx	Verrucous hyperplasia; SCC	In-situ SCC; squamous papilloma; reactive hyperplasia	Benign mesenchymal processes; melanoma; synovial sarcoma	Adenoid cystic carcinoma; small-cell carcinoma	BSCC; mucoepidermoid carcinoma; adenocarcinoma with squamous metaplasia
Treatment	Surgery	Surgery + Radiation	Surgery + Radiation	Surgery + Radiation ± Chemotherapy	Surgery + Neck Dissection
Prognosis	75% 5-year survival	70% 5-year survival	80% 5-year survival	40% 2-year survival	55% 2-year survival
Pitfalls	Inadequate biopsy; tangential sectioning	Orientation, adequacy of specimen	No surface; sarcomatoid may be missed; biopsy inadequate initially	May be mistaken for second primary tumor; high nodal metastasis risk	Can be confused with adeno or SCC depending on biopsy site

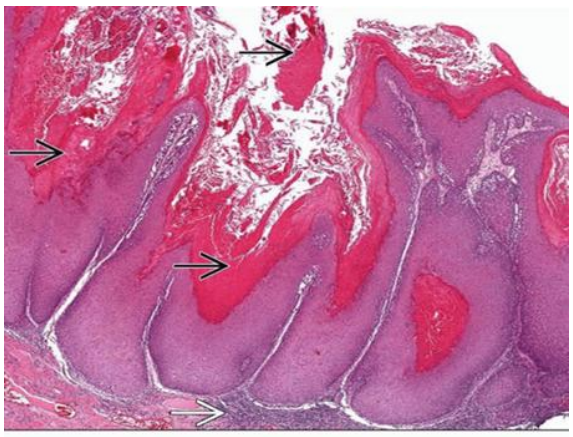

Figure 1a: Verrucous variant 0f squamous cell carcinoma)

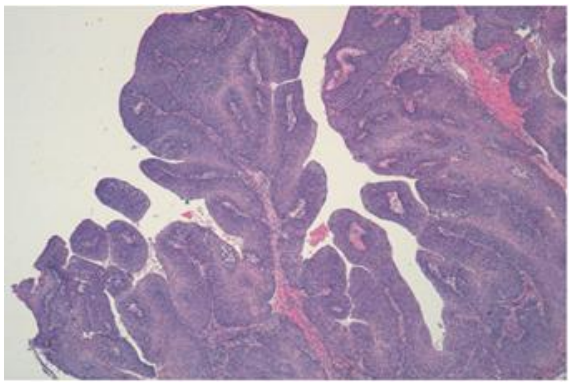

Figure 1b: Papillary squamous cell carcinoma

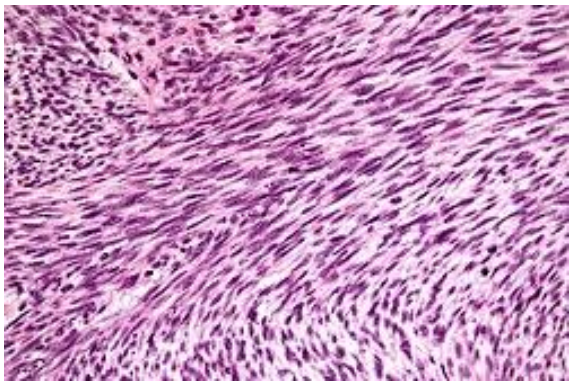

Figure 1c: Spindle cell carcinoma

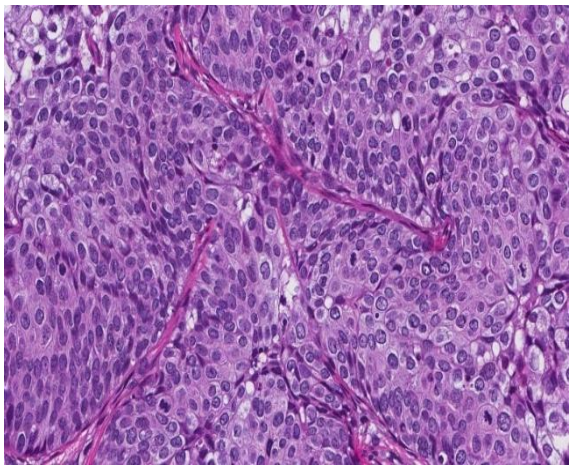

Figure 1d: Basaloid squamous cell carcinoma

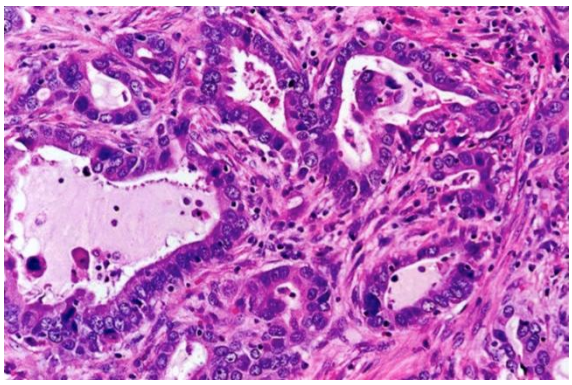

Figure 1e: Adenosquamous

MATERIALS AND METHODS

After obtaining ethical approval from the Institutional Ethics Committee (IEC) of Index Medical College Hospital and Research Centre (IMCHRC), Indore, this observational cross-sectional study was conducted in the Department of Pathology from December 2022 to January 2023.A total of 20 histopathologically confirmed cases of squamous cell carcinoma were analyzed. All patients included were either referred from the surgery outpatient department (OPD) or admitted under the Department of Surgery and subsequently sent for histopathological diagnosis. Informed written consent was obtained from all participants. Patient identity and confidentiality were preserved. The study adhered to the principles of the Declaration of Helsinki and was approved by the IEC of IMCHRC.

Inclusion Criteria

- Patients clinically suspected of malignancy and confirmed histologically as squamous cell carcinoma.
- Samples referred for biopsy and histopathological examination during the study period.

Exclusion Criteria

- Patients with malignancies other than squamous cell carcinoma.
- Samples with inadequate tissue or poor fixation.

Methodology

Tissue Processing and Histopathological Evaluation

Specimens were fixed in 10% neutral buffered formalin, processed, and embedded in paraffin wax. Sections of 4–5 µm thickness were cut and stained with Hematoxylin and Eosin (H&E). Tumor morphology was evaluated for architectural pattern, degree of differentiation, nuclear pleomorphism, mitotic activity, and keratin pearl formation.

Immunohistochemistry

Immunoperoxidase staining was performed on representative tissue sections using the following antibodies to support diagnosis and identify variants:

- P63
- Cytokeratin 5/6 (CK5/6)
- MNF116
- Epithelial Membrane Antigen (EMA)

These markers were especially helpful in confirming poorly differentiated SCC and classifying histological subtypes.

Histopathological Grading Systems

The SCC cases were evaluated and graded using multiple established grading systems. The following systems were referenced for morphological grading:

1. Broder's System: One of the earliest grading methods, this system classifies SCC into well, moderately, and poorly differentiated based solely on the percentage of keratinization.

2. Jacobsson's System: Expands grading to include tumor cell anaplasia and invasiveness in addition to keratinization and mitotic figures.

3. Fisher's System: Emphasizes nuclear pleomorphism, mitotic activity, and host inflammatory response in grading.

4. Lund's System: Focuses on tumor size, depth of invasion, and degree of keratinization for staging and prognosis.

5. Willén's System: Incorporates nuclear polymorphism, mitoses, and pattern of invasion, providing a detailed cellular morphology assessment.

6. Crissman's System: Used primarily for head and neck SCC, includes grading of tumor-host interaction and depth of invasion.

7. Anneroth's System: Assesses six parameters: degree of keratinization, nuclear polymorphism, number of mitoses, pattern of invasion, stage of invasion, and lymphoplasmacytic infiltration.

8. Bryne's System (Most widely accepted): A modification of Anneroth's system; it considers the invasive front of the tumor and gives importance to tumor-host interface, making it a powerful tool for predicting prognosis.

Statistical Analysis: All data were compiled in Microsoft Excel and analyzed using SPSS version 25.0. Descriptive statistics (frequencies, percentages, mean ± standard deviation) were used to summarize demographic and histopathological features. Association between variables such as tumor site, age group, grade, and variant subtype were tested using Chi-square or Fisher's exact test. A p-value <0.05 was considered statistically significant.

RESULTS

Based on the observations from the present study comprising 20 histologically confirmed cases of squamous cell carcinoma (SCC), the data revealed a distinct male predominance, with 75% of cases occurring in males and only 25% in females. This gender distribution highlights the higher exposure of males to recognized risk factors such as tobacco, smoking, and alcohol consumption, which are more prevalent in male populations, particularly in socioeconomically active groups.

Age-wise analysis showed that the maximum number of cases occurred in the 50–60 years age group (50%), followed by the 40–50 years group (30%), indicating a peak incidence in the fifth and sixth decades of life. This aligns with the natural history of carcinogenesis, where cumulative exposure to carcinogens and delayed cellular repair mechanisms contribute to malignant transformation with increasing age.

With regard to anatomical distribution, the lung was the most frequently affected site (25%), followed closely by the breast (20%) and colorectal region (20%), suggesting a significant burden of SCC in internal organs as well, not just the mucocutaneous surfaces. These findings underscore the heterogeneity in SCC presentation and the necessity for site-specific awareness in clinical and diagnostic practice.

Analysis of etiological factors revealed that tobacco chewing and smoking were the leading contributors, with tobacco alone accounting for nearly 50% of all cases. This supports existing literature that implicates chronic exposure to carcinogenic agents in tobacco as a major driver of squamous differentiation and malignant transformation. Alcohol use and other contributing factors such as chronic irritation and viral infections played a relatively lesser, but still important, role.

Table 2: Distribution of Study Subjects based on Gender, Age, Site and etiology (N = 20)

Parameters	Frequency	Percentage
Gender		
Male	15	75%
Female	5	25%
Age		
40–50	6	30%
50–60	10	50%
60–70	2	10%
>70	1	5%
Primary Sites of SCC		
Lung	5	25%
Breast	4	20%
Colorectal	4	20%
Prostate	3	15%
Skin	2	10%
Stomach	2	10%
Risk Factor		
Tobacco	10	50%
Smoking	4	20%
Alcohol	3	15%
Others	4	25%

DISCUSSION

Squamous cell carcinoma (SCC) is a malignant epithelial neoplasm defined by squamous differentiation, including features such as keratinization and intercellular bridges. It can arise in a wide array of anatomical locations including skin, oral cavity, esophagus, lung, cervix, and less commonly in sites such as the breast, prostate, and colon. Histologically, SCC demonstrates considerable heterogeneity and presents in several morphological variants with differing prognostic and therapeutic implications. The present study aimed to analyze the clinicopathological patterns and morphological spectrum of SCC cases diagnosed over a defined period.

In the current study of 20 histologically confirmed SCC cases, a clear male predominance (75%) was observed, consistent with recent epidemiological data indicating that squamous cell carcinomas occur more frequently in males. A multicentric review by Tan B et al. (2022) confirmed that SCC affects men disproportionately due to higher lifetime exposure to carcinogens like tobacco and occupational hazards.[13] Similarly, gender-based disparities in cutaneous SCC were also highlighted in a 2023 population-based analysis from United states, indicating behavioral and occupational risk factors as key contributors.[14] This finding mirrors earlier studies, such as those by Gupta et al. (2013),[15] and Hashibe et al. (2009),[16] which linked higher SCC rates in males to greater exposure to tobacco and alcohol. Thun M et al. (2017),[15] also confirmed that over 90% of lung SCC cases occurred in males with a history of chronic smoking

The peak incidence in the 50–60-year age group in our study aligns with findings from a recent study bySantos HB et al. (2021), which reported that the majority of SCC patients fall within the fifth and sixth decades of life, a pattern attributed to the cumulative effect of environmental and genetic insults over time [18].This age-related trend is consistent with previous findings by Thomas et al. (2015),[19] Shah JP et al. (2012),[20] and Alam M et al. (2001),[21] all of whom reported that SCC predominantly affects individuals above the fifth decade due to cumulative carcinogen exposure and impaired cellular repair mechanisms with age. Singh MP et al. (2016),[22] also noted that most SCC patients presented between 50 and 70 years.

In terms of anatomical distribution, the lung (25%) was the most common site in our cohort, followed by the breast and colorectal region (20% each). This is in agreement with GLOBOCAN 2020 statistics, which identified lung SCC as a major global cancer burden, especially among chronic smokers.[23] Recent reports by Chen Z et al. (2022) and Nassar H et al. (2022) have also emphasized the increasing recognition of rare variants like primary SCC of the breast and colorectum, which often carry a poor prognosis and are resistant to conventional therapies.[24,25] These findings align with Travis et al. (2015),[26] who described SCC as a major histologic subtype of non-small cell lung carcinoma (NSCLC), particularly among smokers. Hennessy et al. (2005),[27] emphasized the aggressive and late presentation of primary SCC of the breast, while Kang et al,[28] (2014) highlighted the rarity but poor prognosis of colorectal SCC. Similarly, prostatic SCC, though comprising less than 1% of prostate cancers, was described by Rawla P et al,[29] (2019) as being more aggressive and less responsive to hormonal therapy.

Tobacco chewing (50%) emerged as the most prevalent risk factor, followed by smoking (20%) and alcohol (15%), mirroring observations by Jun S et al. (2024), who emphasized the synergistic carcinogenic effect of tobacco and alcohol, especially in head and neck SCC.[30] The IARC Monograph (2021) continues to classify both smoked and smokeless tobacco as Group 1 carcinogens, strongly associated with oral and pulmonary SCC.[31] The strong correlation between tobacco (both smoked and smokeless) and SCC has been well-established in literature. The IARC Monograph (2012) classified tobacco and areca nut as definitive carcinogens in oral, esophageal, and lung SCC.[32] Gupta et al,[15] (2013) also reported that over 70% of oral cancers in India were associated with smokeless tobacco use. Hashibe et al. (2009) [16] demonstrated a synergistic increase in SCC risk with concurrent tobacco and alcohol use, and Thun M et al,[15] (2017) confirmed tobacco as a principal cause of pulmonary SCC.

From an immunohistochemical standpoint, our findings reaffirm the high sensitivity of P63 and specificity of Desmocollin-3 in SCC. Additionally, CK5/6, SOX2, Glypican-3, S100A2, S100A7, HMCK, and Thrombomodulin were found to aid in differentiating SCC from adenocarcinomas. Among these, CK5/6 combined with TTF-1 remains the most reliable diagnostic panel across tumor grades and sites, as supported by the studies of Gurda GT et al. (2015) and Khayyata S al. (2009).[33,34]

In conclusion, this study reinforces the established clinicopathological features of SCC with updated evidence from contemporary literature, emphasizing the importance of risk factor mitigation, early screening, and immunohistochemical profiling for effective diagnosis and management.

CONCLUSION

In conclusion, the present study reinforces the diverse anatomical distribution and morphological presentation of SCC. A high prevalence of traditional risk factors such as tobacco and alcohol further emphasizes the need for aggressive public health policies. Awareness of site-specific variants, age susceptibility, and gender disparities is essential for timely diagnosis and tailored therapeutic strategies in managing squamous cell carcinoma.

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