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Histologic Variants of Cutaneous Squamous Cell Carcinoma Diagnosed in a Tertiary Health Facility in Southeast Nigeria

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ABSTRACT

Cutaneous squamous cell carcinomas are tumours originating from cutaneous keratinocytes and they are among the most commonly encountered skin cancers. This study analysed the various histologic variants of cutaneous Squamous Cell Carcinoma (cSCC) diagnosed in the hospital. The study was a descriptive retrospective study that involved the evaluation of all the skin biopsies histologically diagnosed as cutaneous squamous cell carcinoma in the tertiary health institution between 2012 and 2018. Archival formalin fixed paraffin embedded (FFPE) blocks were retrieved alongside relevant clinical data. Hematoxylin and eosin (H&E) staining was performed on fresh 4µ sections of tumor specimens. The H&E stained slides were interpreted under a light microscope. A total of 55 cases of cutaneous SCC were histologically diagnosed accounting for 36.6% of skin tumours within the study period. Amongst the cSCC subtypes observed, squamous cell carcinoma NOS (not otherwise specified) recorded 29(53%), adenosquamous variant 9(16%), acantholytic SCC 6(11%), keratoacanthoma SCC 6 (11%) and verrucous squamous cell carcinoma 5(9%) cases. There was no significant relationship between cancer prevalence and anatomical sites of occurrence ($p>0.05$). The commonest variant of cSCC recorded in this study was SCC NOS which accounted for more than half of the total number of cSCC present. The 60-69 years age group was the age with the highest prevalence of squamous cell carcinoma (32.7 %). Knowledge of the prevailing subtypes of squamous cell carcinoma would guide interventions in the management of the disease.

Keywords: cutaneous squamous cell carcinoma, histological variants, adenosquamous, acantholytic, keratoacanthoma, verrucous.

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most prevalent cancer, with its frequency often underestimated and rising [1-2]. Over the past 30 years, the number of cSCC cases has surged by 50% to 300% [3]. By 2030, its incidence in European countries is expected to double [4]. There is ongoing debate about whether this increase is due to an actual rise in cases or improved early detection [5].

Cutaneous squamous cell carcinoma (cSCC) is the second leading cause of death from skin cancer after melanoma and is responsible for most skin cancer deaths in individuals over 85 years old [3]. In some parts of the United States, cSCC mortality rates are similar to those of renal carcinoma, oropharyngeal carcinoma, or melanoma [3]. The disease most commonly develops

in sun-exposed areas, with the head and neck having the highest incidence [6]. The rising rates of cSCC may be linked to increased sun exposure, ozone layer depletion, longer life spans, and changes in clothing styles that allow more skin exposure [7-9].

Most patients are men, with an average age of onset at 66 years [6]. The economic burden of skin cancer exceeds $29 billion in direct medical costs, with an additional $10 billion lost in productivity [10].

The true prevalence of SCC in Nigeria is still debated. Various center-based studies report that 7% to 20% of all histologically diagnosed malignancies are SCCs, with regional and geographic differences in statistics [11]. For instance, Lagos has reported a 22% prevalence, while Oshogbo has reported 32.7% of all cutaneous malignancies as SCCs [12]. The high frequency of cutaneous SCC significantly impacts the health system, making it a public health issue despite its low mortality rates and rare occurrence of metastases [13-14].

Given the common nature of cSCC, clinicians must remain vigilant in surveillance and diagnosis. This study therefore, examined the histologic variants of cutaneous squamous cell carcinoma diagnosed through routine biopsies at a tertiary healthcare center between 2012 and 2018.

MATERIALS AND METHODS

Study design

This is a cross-sectional retrospective study, conducted over a seven-year period (from January 1, 2012, to December 31, 2018), investigated the histological variants of cutaneous squamous cell carcinoma. The research was carried out in the Department of Anatomical Pathology at the Federal Medical Center in Umuahia, Abia State, South East Nigeria. The hospital has a 327-bed capacity and a functional Anatomical Pathology Department, which processes approximately 850-1000 patient tissue samples annually.

Study population

All histologically diagnosed cases of cutaneous squamous cell carcinoma at the Department of Anatomical Pathology in the hospital from January 1, 2012, to December 31, 2018, were included in the study.

Inclusion and exclusion criteria

The study utilized formalin-fixed paraffin-embedded (FFPE) tissue blocks and Hematoxylin and Eosin (H&E) slides of histologically diagnosed cases of cutaneous squamous cell carcinoma from the Department during the study period. Cases with blocks that were missing or damaged were excluded from the study.

Ethical approval

Approval for this research was obtained from the institutional Health Ethics Research Committee (HREC), with the approval number: FMC/QEH/596/Vol.10/421.

Data collection

The list of all histologically diagnosed cutaneous squamous cell carcinomas registered in the department from January 1, 2012, to December 31, 2018, was retrieved from the patients' database. Relevant histology numbers and their corresponding clinical information, including age, sex, specimen nature, and tumor location, were extracted. This information was used to retrieve the archival H&E slides and corresponding FFPE tissue blocks for review. For cases where the slides were faded, fresh sections were cut from the FFPE tissue blocks of histologically diagnosed cutaneous squamous cell carcinoma and processed.

Microtomy and tissue preparation for staining

This process followed the method of Carson [15]. Representative thin sections, 4 µm thick, of the paraffin-embedded tissue blocks of the selected cSCC cases were cut with a microtome. These sections were floated on charged slides and incubated for ten minutes at 55°C to melt the wax. The sections were then de-paraffinized in two changes of xylene, each lasting ten minutes, to completely remove the wax. To prevent residual wax artifacts, the xylene volume was limited to 50 ml per fifty slides. The tissue sections were then passed through two changes of 100% ethyl alcohol, each for three minutes, to remove the xylene. Following this, the sections were passed through 95% and 70% ethyl alcohols, each for three minutes, and then placed in an aqueous wash buffer for five minutes. Staining was performed using Hematoxylin and Eosin (H&E). The slides were subsequently observed using a light microscope.

Data analysis

IBM SPSS Statistical software for Windows version 25.0 (IBM Corp., Armonk, N.Y., USA) was used for data entry and validation. The chi-square test was employed to examine the relationship between categorical variables at a 95% confidence interval.

RESULTS

Age and sex distribution of cutaneous SCC variants

The age range of individuals diagnosed of squamous cell carcinoma (SCC) was 22 to 95 years with a mean age of 51.8 ± 17.1 years. Out of the 55 cases of SCC, 35 (63.6%) were diagnosed in males while 20 (36.4%) were from females (Table 1). The highest number of cases of SCC occurred at 60-69 year age group (sixth decade) with a frequency of 18 (32.7%) followed by 15 (27.3%) at 40-49 year age group (fourth decade), while the least prevalence was noted in the 90-99 year age (ninth decade) with a frequency of 2 (3.6%) and ages 80-89 recorded no case. The most common variant of SCC found was SCC NOS which had 29 cases (53%) accounting for more than half of the SCC population and were mostly found at fourth and sixth decades. The least variant of SCC was verrucous SCC with 5 (9.0%) cases which was predominant at the sixth decade.

Table 1: Age and sex distribution of histologic variants of cutaneous squamous cell carcinoma

Age (years)	Male	Female	Adenosquamous	Acantholytic	SCC NOS	Verrucous	KA	**Total number of cases (%)**
20-29	3	3	2	-	4	1	-	7(12.7)
30-39	5	1	-	2	2	-	1	5(9.1)
40-49	11	4	2	2	9	-	2	15(27.3)
50-59	4	-	1	-	2	1	-	4(7.3)
60-69	9	9	4	1	8	2	3	18(32.7)
70-79	3	1	-	1	2	1	-	4(7.3)
80-89	-	-	-	-	-	-	-	-(0)
90-99	-	2	-	-	2	-	-	2(3.6)
Total.	**35**	**20**	**9**	**6**	**29**	**5**	**6**	**55**(100)

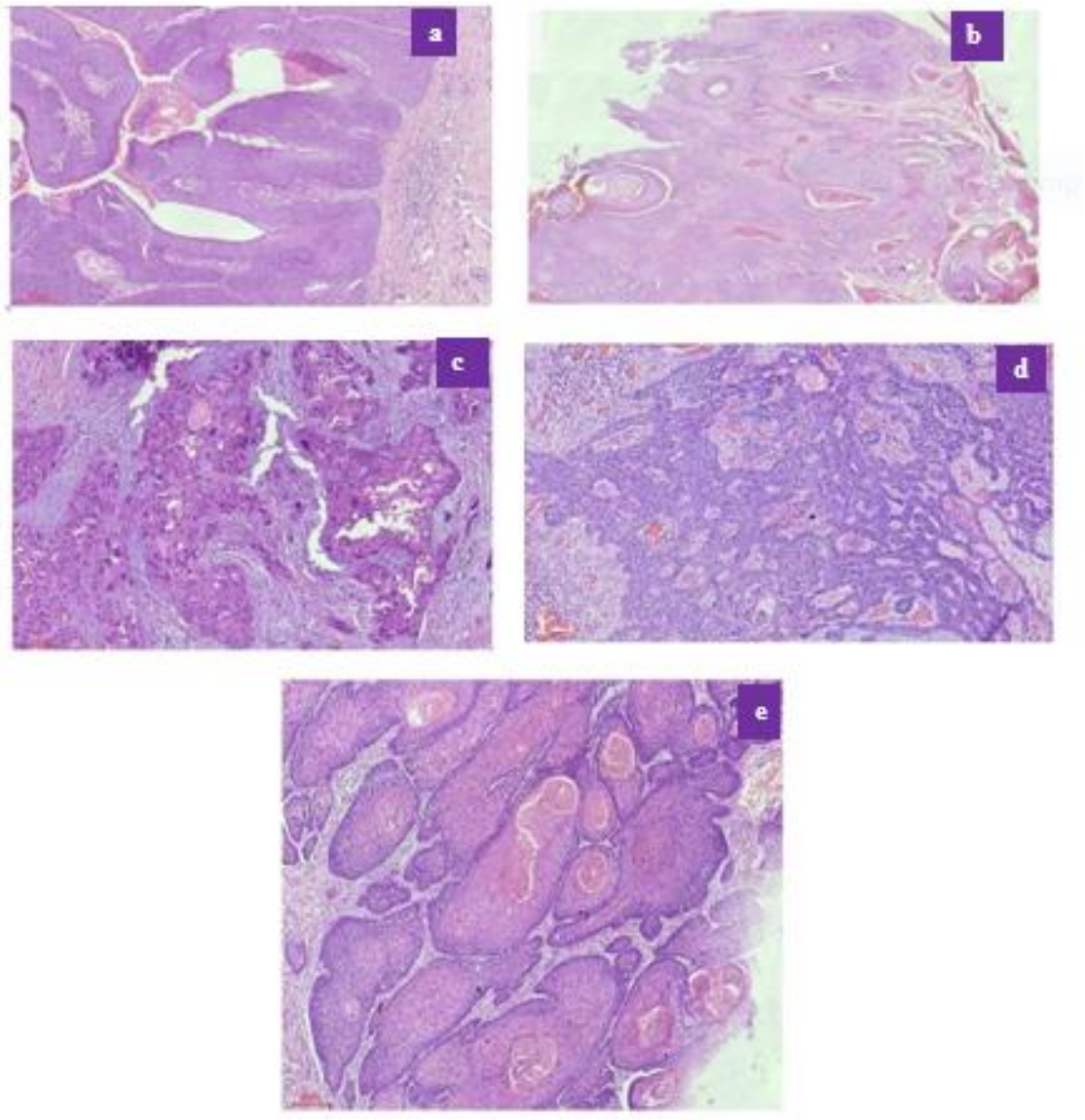

Figure 1: Photomicrographs showing histologic subtypes of cutaneous squamous cell carcinoma: a- verrucous SCC; b- keratoacanthoma SCC; c- acantholytic SCC; d- adenosquamous SCC; e- squamous cell carcinoma NOS. H & E stain x 40 magnifications.

Prevalence of cutaneous squamous cell carcinoma and variants

Squamous cell carcinoma constituted 36.6% (55 of 150 cases) of cutaneous malignancies within the study period**.** The variants of cutaneous squamous cell carcinoma observed in this study were 5 in number including; squamous cell carcinoma NOS constituting more than half (53%) of the population of tumours recorded. Adenosquamous carcinoma (16%), keratoacanthoma and acantholytic variants accounted for 11% of the variants each while verrucous subtype occurred in 9% of the population (Figure 2).

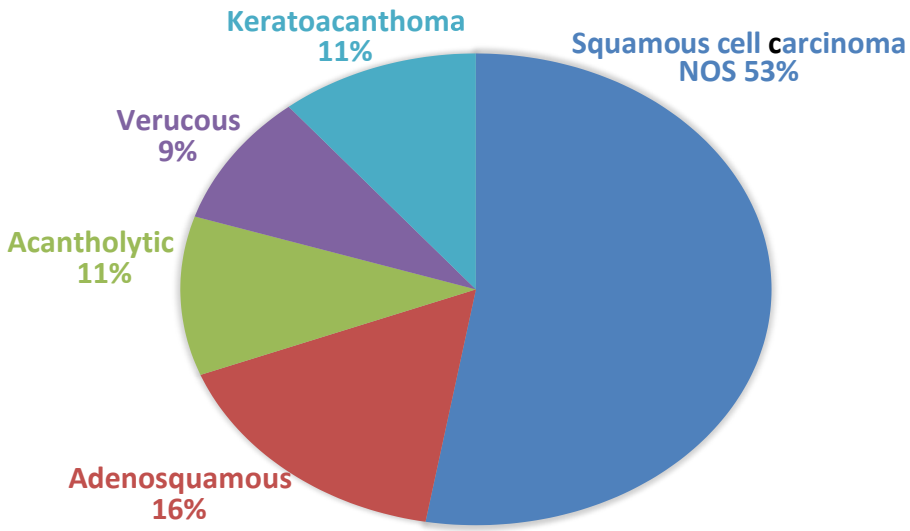

Figure 2: Histologic variants of cutaneous squamous cell carcinoma

Site distribution of cutaneous squamous cell carcinoma variants

More than one-fourth of the 55 cases of squamous cell carcinoma (SCC) observed in this study were found in the head and neck region 16 (29%). The body (trunk) however had a prevalence of (31%) while the remaining 23 cases (40%) of the squamous cell carcinoma were located on the upper and lower limbs (extremities) (Figure 3). Among the variants of cSCC, 1 case of keratoacanthoma, 4 adenosquamous, 2 acantholytic and 9 cases of SCC NOS were found within the head and neck region (Table 2). The face was the most affected part in the head and neck region with a frequency of 50% (8 out of 16). Other sites in the head and neck region affected by SCC were scalp 37.5% (6 out of 16), the pinna and the mandible had 6.3% (1 out of 16) each. On the body, SCC NOS was also the most prevalent tumour 52.3% (9 of 17 cases). Next to this was keratoacanthoma with 3 cases, adenosquamous and verrucous SCC had 2 cases each while 1 case of acantholytic variant was recorded.

The commonest site for SCC on the body was the scrotum which constituted 29.4 % (5 cases). Other areas included the vulva 23.5% (4 cases), the abdomen 11.8% (2 cases), the groin 17.6% (3 cases) and back 17.6% (3 cases). The extremities recorded 11 cases for SCC NOS while adenosquamous, acanatholytic and verrucous SCC recorded 3 cases each. The least common tumour in the extremities was keratoacanthoma with a frequency of 2. In the upper and lower limbs, SCC was found mostly on the forearm accounting for 45.5% (10 cases). Other affected sites included the foot, thigh, knee, leg and hand which accounted for 22.7% (5 of 22 cases), 13.6% (3 cases), 9.1% (2 cases) 4.5% (1 case) and 4.5% (1 case) respectively (Table 3). There was no significant relationship between the prevalence of histological subtypes of squamous cell carcinoma and anatomical sites of the body ($p>0.05$) (Table 3).

Table 2: Site distribution of histologic variants of cutaneoussquamous cell carcinoma

Site	**Variants of cutaneous squamous cell carcinoma**				
	Adenosquamous	Acantholytic	SCC Nos	Verrucous	Kerathoacanthoma
Head & Neck	4	2	9	-	1
Body	2	1	9	2	3
Extremities	3	3	11	3	2
Total	**9(16%)**	**6(11%)**	**29(53%)**	**5(9%)**	**6(11%)**

Table 3: Site distribution of cutaneous squamous cell carcinoma

Anatomical sites	**Number of cases (%)**	**Chi-square**	**P-value**
Head and Neck			
Scalp	6(37.5)	8.0	0.238
Chin	1(6.3)		
Face	8(50)		
Ear	1(6.3)		
Body			
Groin	3(17.6)	15.0	0.241
Scrotum	5(29.4)		
Back	3(17.6)		
Abdomen	2(11.8)		
Vulva	4(23.5)		
Extremities			
Thigh	3(13.6)	24.0	0.242
Leg	1(4.5)		
Forearm	10(45.5)		
Hand	1(4.5)		
Foot	5(22.7)		
Knee	2(9.1)		

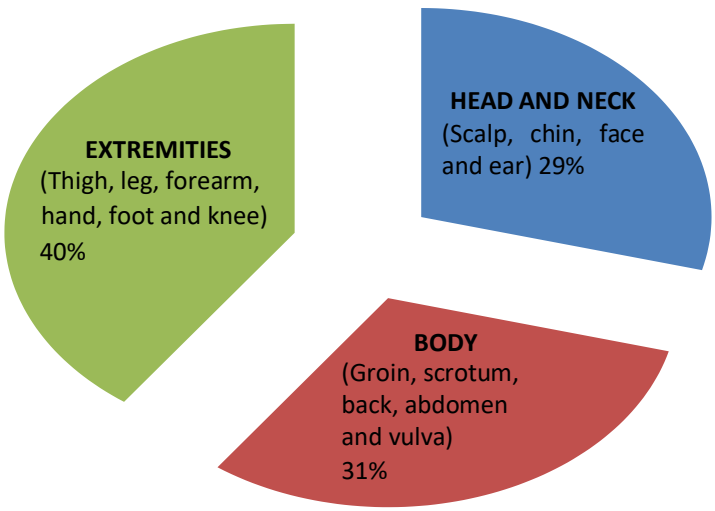

Figure 3: Site distribution of cutaneous squamous cell carcinoma

DISCUSSION

This study provides baseline data on the histologic variants of cutaneous squamous cell carcinoma at the Federal Medical Centre, Umuahia, Nigeria. The findings indicated that cutaneous squamous cell carcinoma predominantly affects the elderly, with a prevalence of 36.6%. This prevalence is higher compared to 15% in Egypt [16], 28% in South Africa [17], 8.4% in Tanzania [18], 19% in Nnewi, Nigeria [19], and 13.6% in Benin City, Nigeria [20]. However, similar studies conducted in Jos and Benin City reported higher prevalences of 51% and 82.61%, respectively, which exceed the prevalence observed in this study [21, 22]. The differences between these reports and the findings of this study may be attributed to variations in study duration and/or sample sizes [19].

SCC was more common in males than females, with a ratio of 1.8:1. This higher male-to-female ratio aligns with the 1.4:1 ratio reported in Tanzania and the 1.03:1 ratio in Benin City, Nigeria [22], but contrasts with the 1:1.3 ratio reported in Nnewi, Nigeria [19]. The higher prevalence in males in this study could be due to men being more involved in outdoor work, which increases their risk of UV exposure [23]. Additionally, the weakening of the immune system due to disease or medication may contribute to the higher incidence in late adulthood [15]. Elderly individuals might also have difficulties recognizing changes in their skin lesions, leading to delayed diagnoses [15].

Abia State, a major commercial hub in southeastern Nigeria, has many men who are exposed to the sun for extended periods while working. It is important to note that this study was conducted at a referral center for skin diseases in Abia State, though the findings may not fully reflect the prevalence of cutaneous SCC across South-East Nigeria.

The mean age of SCC in this study was 51.8 ± 17.1 years, ranging from 22 to 95 years, with bimodal peaks in the 5th and 7th decades. Similar peak age incidences were noted in studies from the South-South region of Nigeria, which reported peaks in the 5th and 6th decades [11-14]. Mahmoud in Egypt observed a peak in the 7th decade, while Lear et al. and David et al. in Australia and Northern Europe found similar peak age incidences to this study [16, 27, 29]. In contrast, Madubuike *et al*. in Nnewi reported a peak age incidence in the 3rd decade [19]. A study in Tanzania also found that the majority of SCC patients were in the 5th and 6th decades of life [18].

Although cutaneous SCC can occur on any part of the skin, the most common sites in this study were the trunk and extremities, especially the forearm and foot. These locations are also frequently reported in studies from various parts of Nigeria, Africa, and among Caucasians [17, 24, 25]. For example, a study in Nnewi, Nigeria, found that the most commonly affected anatomical site was the head and neck region (78%), followed by the lower limbs (66%) [19]. Similarly, Dele and Adesuwa in Benin City, Edo State, Nigeria, reported that the head and neck region was the most common site for SCC. This study's findings align with those of Adinarayan and Krishnamurthy [26], who noted that SCC often affects sun-exposed areas such as the face, scalp, and upper arm. However, there was no significant association found between the prevalence of cSCC and specific anatomical sites on the body.

The most common variant of SCC in the present study was squamous cell carcinoma NOS, which accounted for more than half of the variants of SCC. This finding is comparable with those of Valerie *et al* in USA and WHO 2018 [27, 28]. This was closely followed in order of frequency by adenosquamous, keratoacanthoma, acantholytic and verrucous variants of squamous cell carcinoma. Acantholytic variant accounted for 11% and was ranked as the third most common variant of SCC in the current study. This proportion however, did not differ with observed frequency from other parts of the world [27]. Verrucous squamous cell carcinoma, the least common variant in this present study had a prevalence of 9%. Verrucous carcinoma can be found in any part of the body to a range of 5-25% in the perineum and 2-12 % in the oral cavity[28].

Conclusion

This study unraveled the prevailing subtypes of cutaneous squamous cell carcinoma histologically diagnosed in the Centre between 2012-2018 with the squamous cell carcinoma NOS being the most prevalent variant. Knowledge of the prevailing subtypes of squamous cell carcinoma would guide interventions in the management of the disease.

Authors' contribution

FEE: Concept, design, literature search, experimental studies, data acquisition. **SEO**: Literature search, experimental studies. **MAN**: Concept, design, manuscript editing. **OOJ**: Design, literature search, manuscript editing **CCC:** Concept, design, literature search, **GOE**: Statistical analysis, manuscript preparation, manuscript editing. **MOS:** Design, literature search, manuscript editing **LAO:** Experimental studies, data acquisition, manuscript editing.

Conflicts of interest

The authors declare that they have no conflict of interest.

Acknowledgement

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