

CERVICAL CANCER STAGING DISPARITIES BY AGE AND MORPHOLOGY. A 10- YEAR RETROSPECTIVE ANALYSIS. STUDY AT TERTIARY CARE HOSPITAL NAWABSHAH, SINDH

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Abstract

Background and objective: cervical cancer remains an over burden on health system in low to middle income countries worldwide. The early accurate staging and Histopathological morphology are vital to guide therapeutic decisions and predict better outcome. Methodology: This Retrospective Cohort study was conducted in the department of Oncology, AECH Norin Cancer Hospital Nawabshah combined with Department of Pathology, Peoples University of Medical and Health Sciences, from June 2015 to June 2025. All the medical record of histopathologically proven followed by immunohistochemistry and staged clinically according to the 2009 and 2018 revised International Federation of Gynecology and Obstetrics (FIGO) guideline for Cervical cancer, were collected on pre-designed proforma and carefully analyzed by using SPSS Version 25. Results: The registered number of patients with carcinoma cervix was 589, the mean age of patient was 55.5 years found in this study. The most common stage presented here were stage III (49.24%). The most common age group involved was 51 to 60 years age (28.86%). The most prevalent histological morphology is squamous cell carcinoma 82.3%, with 67% moderately differentiated grade. Conclusions: The disease is more prevalent in middle age and advance stage, Squamous cell carcinoma with grade II, moderately differentiated disease was found in this study.



INTRODUCTION

Cancer since beginning a global challenge till now, holding a major impacting illnesses for millions of people registered and a large population unregistered globally.¹ The GLOBOCON data exhibit variability in incidence and mortality globally, and the malignancy of cervix imposes a tectonic threat on female population with high mortality rates in lower to middle income countries.² Cervical cancer holds as the fourth most prevailing cancer among female population, with around 604,000 newer cases with 342,000 deaths documented in year 2020. Asia, home to over half of the global population, bears a significant burden of mortality and suffering due to socio-economic, cultural, and health system disparities that contribute to high rates of incidence and death. In this region, cervical cancer is a major cause of cancer-related fatalities among women, especially in South-Central Asian nations like India, Bangladesh, and Nepal, and Pakistan where health systems are under-resourced and preventive measures such as HPV vaccination and cervical screening programs are not consistently implemented.^{3,4} The FIGO (International Federation of Gynecology and Obstetrics) updated the staging system for cervical cancer in year 2018 to include imaging and pathological results, in addition to clinical assessments. This enhancement increases precision, especially concerning tumor dimensions and lymph node involvement.^{5,6,7,8,9,10} Predominant Histological Subtypes of carcinoma cervix are Squamous Cell Carcinoma (SCC), which arises from the squamous epithelium of the ecto-cervix or the squamo-columnar junction.^{11,12} Adenocarcinoma is the second most common type, glandular lesions located higher in the endo-cervical canal,¹³ Adenosquamous Carcinoma, and

Neuroendocrine Tumors are less common varieties.¹³ Other Rare Variant, histological types, such as small cell carcinoma, clear cell carcinoma, and adenoid cystic carcinoma, are occasionally reported.¹⁴ Globally, SCC accounts for the over 80% of cervical cancer cases, with AC making up a smaller portion around 12%. Sub-Saharan Africa has the highest SCC incidence, while South-Eastern Asia leads in AC incidence. SCC incidence peaks around age 55, whereas AC incidence stabilizes after age 45.¹¹ The main focus is that Squamous Cell Carcinoma or SCC is the overwhelmingly dominant cervical cancer sub-type globally, making up more than 80% of cases. It's the primary type in all 15 regions studied, ranging from 70% in Oceania to more than 90% in the Sub-Saharan Africa. Adenocarcinoma or AC accounts for a smaller portion 12% of global cases, with its regional share varying from 6.35% in the Sub-Saharan Africa to 23.72% in Oceania.¹¹ Studies from various Asian countries, including Pakistan, Vietnam, India, and China, consistently report that SCC accounts for approximately 70% to over 80% of all invasive cervical carcinomas.^{12, 13,14} Despite all these figures The prevalence of glandular tumors is reported to be increasing in some regions in Europe¹⁵ and some high income countries,¹⁶ particularly among younger women, across all Asian regions.¹² SCC is typically graded on the basis of degree of differentiation into three grades; Grade I is well differentiated, the Grade II is named as moderately differentiated and Grade III called as poorly differentiated.^{14,17,18} Early detection to morphology, accurate staging and grading are vital to guide therapeutic decisions and predict outcomes. The Summarized FIGO staging^{19,20}

| Stage | Criteria |
|-------------|---|
| I | Tumor confined to cervix; subdivided by size and depth |
| IA1 | Invasion ≤3mm in depth |
| A2 | Invasion >3mm and ≤5mm in depth |
| IB1 | Lesion >5mm depth, ≤2cm size |
| IB2 | Lesion >2cm and ≤4cm |
| IB3 | Lesion >4cm |
| II | Tumor extends beyond uterus, not to pelvic wall/lower 1/3 vagina |
| IIA1 / IIA2 | Involvement limited to upper 2/3 vagina, ≤4cm or >4cm |
| IIB | Parametrial involvement |
| III | Invades pelvic wall, lower 1/3 vagina, hydronephrosis, or lymph nodes |
| IIIA/IIIB | Vaginal/pelvic wall/hydronephrosis involvement |
| IIIC1/IIIC2 | Pelvic/para-aortic lymph node metastasis |
| IV | Tumor invades bladder/rectum or distant spread |

Stage IIIC (new in 2018) recognizes metastatic pelvic (IIIC1) or para-aortic (IIIC2) lymph nodes, detected by imaging (r) or pathology (p), to reflect prognostic significance.

The lateral extension is no longer considered for staging; vascular/lymphatic space invasion does not alter stage. Imaging (MRI, CT, PET) is recommended where available to refine stage and treatment decisions.²¹

METHODOLOGY:

Study design The study is retrospective, Cohort type, utilizing the existing medical records and pathology reports from a defined study period (June 1, 2015, to June 31, 2025) at PUMHS and AECH Norin Cancer Hospital

Inclusion Criteria & Exclusion Criteria

Inclusion Criteria: All patients with a confirmed diagnosis of primary invasive cervical carcinoma during the study period, regardless of treatment modality will be included.

Exclusion Criteria: Patients with *in situ* carcinoma (Stage 0), recurrent disease, or incomplete or missing data required for staging, morphology, or grading will be excluded.

Data Sources: Data will be extracted from the institution's Cancer Registry, Pathology Department records, and Electronic Health Records (EHR).

Data variables and definitions

The important variables of study:

Patient Demographic Details

Age at Diagnosis: Recorded in years and categorized into predefined age groups for analysis (e.g., up to 30 years, 31-40, 41-50, 51-60, 61-70,71-80, above 80 years).

Cervical Cancer Staging

The Staging of cancer will determined by the FIGO system for cervical cancer which is based on clinical examination, imaging available, and pathological findings. The specific FIGO stage (I, II, III, IV, with all relevant substages, e.g., IB2, IIIC1) will be recorded.

Tumor Morphology (Histological Type)

The histological type will be recorded based on the final pathology report, using the World Health Organization (WHO) classification.

Table No 01: CARCINOMA CERVIX STAGES AT PRESENTATION

| S: NO | STAGE | NUMBER OF CASES | PERCENTAGE |
|-------|-------|-----------------|------------|
| 1. | 0-1 | 72 | 12.22% |
| 2. | II | 160 | 27.16% |
| 3. | III | 290 | 49.24% |

Common Types:

Squamous Cell Carcinoma (SCC): Keratinizing, Non-keratinizing, Verrucous, etc.

Adenocarcinoma: Endocervical, Endometrioid, Clear cell, Serous, etc.

Adenosquamous Carcinoma.

Rare Types: Small cell neuroendocrine carcinoma, sarcoma, etc.

Tumor Grading (Differentiation)

The histological grade (G), reflecting the degree of cellular differentiation and nuclear pleomorphism, will be recorded. Grade 1 is Well-differentiated, Low grade. Grade 2 is Moderately-differentiated, Intermediate grade. Grade 3 is Poorly-differentiated and Grade 4 is Undifferentiated, or High grade.

Immunohistochemistry (IHC) and Biomarker Analysis

Immunohistochemistry reports to confirm the histological subtype (morphology), assess proliferation (grading), and differentiate primary cervical cancer from metastases or other entities where necessary.

Ki-67- Proliferation Marker used for grading the tumor.

DATA ANALYSIS

The SPSS 25 Version will be used for statistical analysis.

ETHICAL CONSIDERATIONS

This research study plan was approved by the Ethical Review Committee and Ethics Committee of the AECH Norin Cancer Hospital before any data collection commences. Due to the retrospective nature of the study and the use of anonymized archival patient data and pathology reports, a waiver of informed consent will be requested from the ERC.

RESULTS

The number of patients presented here were 589 among them 72 (12.22%) patient presented with stage 0- I, 160 (27.16%) patient were diagnosed as stage II diseases, the highest number of patient present with stage III were 290 (49.24%), patient present at stage IV were 67(11.38%).



| | | | |
|--------------|----|------------|-------------|
| 4. | IV | 67 | 11.38% |
| TOTAL | | 589 | 100% |

The age were divided into four groups in which 10(1.7%) patients were present with in up to 30 years age group, 36 (6.11%) patients were registered in 31 to 40 years age group, 160(27.16%) patients presented in 41 to 50 years age group,170 (28.86%) patients came into 51 to 60 years group, 130 (22.07%) were registered in group of 61-70 years, 62 (10.53%), and 21 (3.57%) patients included in 71-80years and above 80 years age group respectively.

Table No 02: DISTRIBUTION OF VARIOUS AGE GROUP INVOLVED BY CARCINOMA CERVIX

| S.NO | AGE GROUP | NO: OF PATIENTS | PERCENTAGE |
|--------------|----------------|-----------------|-------------|
| 1 | Up to 30 years | 10 | 1.70% |
| 2 | 31-40years | 36 | 6.11% |
| 3 | 41-50 years | 160 | 27.16% |
| 4 | 51-60 years | 170 | 28.86% |
| 5 | 61-70years | 130 | 22.07% |
| 6 | 71-80years | 62 | 10.53% |
| 7 | Above 80 years | 21 | 3.57% |
| Total | | 589 | 100% |

According to the microscopic features 485(82.3%) were diagnosed as Squamous cell carcinoma, 73(12.4%) were Adenocarcinoma, 10(1.7%) were diagnosed as metastatic diseases came from tumor elsewhere in the body, 9(1.5%) were Adenosquamous type, 8(1.4%) were cases of malignant mixed Mullarian tumors,4(0.7%) were Neuroendocrine tumors.

TABLE NO 03: MORPHOLOGICAL SUBTYPES OF CARCINOMA CERVIX

| | | |
|----------------|------------|-------------|
| SCC | 485 | 82.3% |
| AC | 73 | 12.4 |
| METASTATIC | 10 | 1.7 |
| ADENOSQUAMOUS | 9 | 1.5 |
| MMT | 8 | 1.4 |
| NEUROENDOCRINE | 4 | 0.7 |
| TOTAL | 589 | 100% |

The most common grade identified here were moderately differentiated grade 395(67%), 129 (22%) and 65(11%) were poorly and well differentiated respectively.

TABLE 04: CARCINOMA CERVIX: TUMOR GRADING

| GRADING OF TUMOR | | |
|--------------------------|------------|-------------|
| TYPE OF TUMOR | Number | Percentage |
| WELL DIFFERENTIATED | 65 | 11% |
| MODERATELYDIFFERENTIATED | 395 | 67% |
| POORLY DIFFERENTIATED | 129 | 22% |
| TOTAL | 589 | 100% |

DISCUSSIONS

Precise staging of carcinoma cervix at the time of diagnosis, which incorporates clinical examination, imaging studies, and pathological evaluation following the 2018 FIGO criteria, is essential for guiding optimal treatment. The lymph node status assessment has an important predictor for prognosis and therapeutic decisions.

The age of patients in this study ranges from 25 to 90 years, while the mean age was 55.5 years. This is consistent with findings from other research. For

example, Kaku²² documented the mean age 56 years, range: from 33to 82 years, while the mean age in Orakzai's²³ study was 54.46 years. Similarly, Aziz²⁴ reported 51 years as mean age, the range: is 29-73 years.

Staging at presentation

In this study, the presentation of disease stages was as follows: Stage 0-I accounted for 12.22% of cases. This is comparable to consistent findings in other studies: Aziz²⁴ reported a similar trend at 14.28%, Mukhtar²⁵ observed 19%, Nasreen's²⁶ study in Kashmir showed



24%, while Jawad Ali²⁷ noted 8.5%, and Orakzai²³ reported 51% which is inconsistent with our finding. In this study, Stage II disease was present in 27.16% of cases. This is compared to findings in other studies: 35.68% in Aziz²⁴, 32% in Orakzai²³, and 46% in Mukhtar study²⁵, 46.2% in Jawad Ali²⁷ study. The highest number of patients in this study presented with Stage III disease, accounting for 49.24% of cases. This is a higher percentage compared to other studies: Aziz²⁴ reported 39.28%, Nasreen²⁶ had 30.35%, Mukhtar²⁵ observed 22%, Jawad Ali²⁷ noted 18.5%, and Orakzai²³ found. Patients presenting with Stage IV disease comprised 11.38% of the study population. This is comparable to other research findings, with Aziz²⁴ reporting 10.71%, Mukhtar²⁵ at 10.8%, and Jawad Ali²⁷ at 6.4%.

AGE DISTRIBUTION

There is wide variation in the number of patients in 30 year age group in multiple studies at various places: 1.7% in this study, 1.3% at Saurabh's²⁸ while 5.35% at Aziz.²⁴ The group aged 31-40 years, were showed a similar results in several studies, 6.11% in our study, 9.2% at Jawad Ali's study²⁷, 10.2% at Saurabh's study²⁸, 10.71 at Aziz's study²⁴ while 13.3 at Ellian's study.²⁹ The 41-50 years group represent 27.16% of our study and this is consistent with the results of other studies with little variations, including Saurabh²⁸ with 26.32%, Sharma³² 24.1%, Nasreen²⁶ 22.46%, and Aziz²⁴ with 35.71%. The further analysis showed that 28.86% were belongs to the 51-60 year age. This aligns with data from other comparable studies, reported 25% in Aziz study.²⁴ The next group 61-70 years were 22.07% in our study. This figure is consistent with the 19.64% reported by Aziz²⁴, and 22.49% by Saurabh²⁸. These finding somewhat differs from the 69.2% reported by Jawad Ali²⁷, showing a remarkable variation in age demographics among all studies. In this study, 71-80 age groups comprised 10.53% of the study population, which is higher than the 3.57% reported in Aziz²⁴ study, but is lower than the 22.26% reported in the Saurabh²⁸ study. The 3.57% of participants were above 80 years, this proportion aligns with the 2.4% observed by Jawad Ali²⁷, indicating a consistent, even though a small, proportion of this age group across both studies.

MORPHOLOGY OF TUMORS

The morphology of carcinoma cervix in our study is consistent with rest of world, the most common type is Squamous cell carcinoma 82.3% consistent with 70-

85% of all cervical cancer cases by Maniar,³² Jalil³³ and 87% by Sana.³⁴ The second most prevalent type is adenocarcinoma 12.4% in this study, consistent with Maniar³² which is 10-20%, and 12% found in study by Sana³⁴ while Adenosquamous is 1.7% in our study, consistent with 3-10% study by Jalil.³³ Based on histological grading the moderately differentiated type is most prevalent in this study and concordant with the study results by Khan¹² and Wang,¹⁴ Rare variants found in our study were Malignant Mixed Mullarian Tumor, Neuroendocrine tumors. Clear cell carcinoma, Small cell neuroendocrine carcinoma, and Basaloid SCC seen in Asia,^{34,11} but rare in African countries.¹⁴ The study also identified several rare variants, including Malignant Mixed Mullerian Tumor, Neuroendocrine tumors, at our place but the Clear cell carcinoma, Small cell neuroendocrine carcinoma, and Basaloid SCC, which have been noted in studies in Asian countries^{11,34,35} but are less common in African¹⁴ countries.

CONCLUSION

While global data confirm that more prevalent morphological type is Squamous Cell Carcinoma, the relative proportion of subtypes especially the rising incidence of Adenocarcinoma can vary significantly by geography, age group, and the time period, even within Europe. This current study establishes the local prevalence of all the subtypes of cervical malignancy in the region, which is crucial for accurately planning regional oncology services and resource distribution.

The scenario of cancer presentation trends is variable across many places/populations around the globe, reflecting a need for awareness spread to improve screening at our place. To understand the local range of multiple carcinoma types, whether are rare or aggressive are identified, public health efforts can be better targeted to improve awareness, optimizing screening efficacies, ultimately lead to earlier detection and diagnosis.

RECOMMENDATIONS: More deeper research required for further analysis other pathological parameters along with a strong focus on screening /preventive measure implementation at health care centers.

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