DOI: https://doi.org/10.53350/pjmhs20221612375

ORIGINAL ARTICLE

Prognostic Value of Histopathology and Trends in Cervical Cancer

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ABSTRACT

Background: Cervical cancer has an increased rate of morbidity and mortality among women most commonly in terms of cervical adenocarcinoma. Histopathology has been considered as the foundation for diagnosing the tissue changes associated with cervical cancer. However, there are controversies in identifying their prognostic value.

Methods: It is a retrospective study in which 100 participants suffering from cervical adenocarcinoma and 200 participants of squamous cell carcinoma between the time period of 2017-2020 at the cancer center Pakistan were analyzed. The study was conducted between the time period of Dec, 2021 to Nov, 2022. All the patients were diagnosed histologically and were treated through radiotherapy or surgery. Demographic history along with area of registry, grade, size, stage and histology of tumor, diagnosis year, examination and involvement of lymph nodes, radiotherapy and type of surgery were assessed with the help of Akaike information criteria (AIC).

Results: Total cancer records available for evaluation were 40,000 which were observed to be decreased from year after year from 2017-2020 but cases of squamous cell carcinoma and adenocarcinoma were observed to be increased with a rate of 100 patients per year. Their median age was recorded to be 52 years. Mortality associated with cause and without cause were dependent upon few variables including race, gender, diagnosis year, stage and grade of disease, ratio of nodes, size of tumor, radiotherapy and hysterectomy. Significance has been observed in the histological types ($p = 0.003$).

Practical Implication: This study will be helpful for the oncologists, physicians and researchers in order to decide the best approach in terms of histopathology studies in the diagnosis of cervical cancer patients. It will help the community by carrying out a proper screening protocol for all the patients in order to prevent the patient from serious conditions.

Conclusion: Study concluded that the chances of developing adenocarcinoma and squamous cell carcinoma are dependent upon the rate of poor survival. A large number of adenocarcinoma cases suggests that there is poor screening of the people reporting any signs and symptoms. Therefore, it is suggested to properly screen the women on a regular basis and specially those who report any of the symptoms associated with cervical cancer.

Keywords: Cervical cancer, carcinoma, adenocarcinoma, squamous cell carcinoma, histopathology, histological types.

INTRODUCTION

Cervical cancer has been considered as the fourth leading cause of morbidity and mortality throughout the world and second leading cause of death across Pakistan[1]. It directly affects the cells in the cervix region causing mutations in their DNA which causes the cells to grow at a rapid pace without being died [2]. This cancer falls into different categories but the most common of them are squamous cell carcinoma and adenocarcinoma [3]. Squamous cell carcinoma is dominant of all types estimating for ¾th of all cancer types [4]. A study has been carried in year 2019 which suggests that Adeno-squamous carcinoma and adenocarcinoma account for 10-15 % whereas other non-specified cancer types account for the remaining 20 % of cancers. Several controversies exist regarding the prognosis of different histological types [1]. A study carried in 2015 suggests that cervical cancer has affected a large number of females suffering from any symptom of severe pain, abnormal menstruation, vaginal bleeding and abnormal discharge therefore, proper screening is required for all females who had displayed any of the underlying symptoms [4]. Literature suggests that adenocarcinoma has a low prognosis rate as compared to other types of cancer and can be diagnosed only through histopathologic studies [5]. Considering histopathology as an important diagnostic factor therefore, it is essential to detect the value of prognosis according to pathological type which has a direct influence on management, planning and treatment of newly investigated cases of cervical cancer [2]. This study has highlighted the records of cancer center population of Pakistan for determining the role of prognosis in histopathological types on patients suffering from cervical carcinoma. It will play an important role in targeting the accurate screening of histopathological studies that are sensitive in the diagnosis of cervical carcinoma. Previous studies carried on this topic had not accurately addressed the issue owing to limitation of the time and cancer population in their study area.

METHODS

It is a retrospective study in which Data of the cancer patients were obtained from the records of cancer center Pakistan most commonly of cervical adenocarcinoma and squamous cell carcinoma patients [7]. All 300 patients were women aged between 35-44 years, as this has been recorded as the most common age for getting cancer [3]. Patients having their diagnosis confirmed through histopathological studies were selected.

Histopathology of tumors was carried out according to the criteria of international classification of diseases for oncology (ICDO). Kaplan Meier method was used for the purpose of univariate (death due to any cause) as well as cause specific (death due to cervical cancer) analysis [8]. In addition, some models like models of professional hazards were used to carry multivariate analysis. Akaike information criteria (AIC) led to the selection of the variables associated with multivariate analysis [9]. AIC has retained the variables on the basis of balance improvement and selection of parameters. Selected variables for this purpose include; cancer center registry area, demographics (age, gender, race, marital status), histopathology of tumor, stage and grade of tumor (benign or malignant), radiotherapy and surgical approach.

Report was condensed by dividing the histopathological types into different groups such as unspecified carcinoma, microinvasive squamous cell carcinoma, non-microinvasive squamous cell carcinoma, adeno, mucinous and adeno-squamous carcinoma, and small cell carcinoma.

RESULTS

Characteristics and trends of histopathological types: Total cases that were confirmed histologically of invasive cervical cancer were 45,000, out of them 40,000 cases met the inclusion criteria of the study having 18 histological types. The total follow-up period for this was recorded as 10 years. Characteristics of tumor in patients according to histological types are tabulated below (see table no 1). It has been observed that radiotherapy (62 %) and

hysterectomy (55 %) has been performed in more than half of the population [10].

Table 1: Characteristics of tumors in patients according to histological type.

Characteristics	Microinvasive SCC	Unspecified carcinoma	Squamous cell carcinoma.	Adeno-squamous	Mucinous adeno-carcinoma.	Small cell carcinoma
Age	32 (30 ~ 50)	35 (31 ~ 44)	45 (40 ~ 50)	42 (40 ~ 49)	38 (35 ~ 50).	50 (45 ~ 60)
Marital status						
Single	20 %	30 %	10 %	17 %	20 %	22 %
Married	40 %	50 %	47 %	50 %	53 %	54 %
Ethnicity	70 %	69 %	75 %	71 %	63 %	59 %
Size of tumor (mm)	2 mm (1 ~ 2)	3mm (1 ~ 50)	39 mm (10 ~ 50)	24 mm (8 ~ 40)	25 mm (10 ~ 50)	40 mm (5 ~ 60)
Grade of histological type.	25 %	80 %	20 %	50 %	40 %	25 %
AJCC grades						
I	85 %	72 %	81 %	64 %	75 %	80 %
II	12 %	28 %	10 %	24 %	15 %	10 %
III	2 %	0 %	8 %	12 %	10 %	9 %
IV	1 %	0 %	1 %	0 %	0 %	1 %
Radiotherapy	10 %	38 %	58 %	47 %	29 %	57 %
Hysterectomy.	72 %	55 %	39 %	47 %	69 %	39 %

Analysis of survival: The overall rate of 10-year survival is 55 % whereas rate of cause specific 10-year survival is 72 %. Statistically significant ($p < 0.001$) differences have been observed between the overall rate of histopathological groups [5]. Histopathological groups were ranked according to the cause specific rates of survival comparable to the best cause specific survival rates in microinvasive SCC (95 %) to the poor rates of survival seen in small cell carcinoma (40 %) [9].

Table 2: Kaplan Meier estimation of case specific and overall survival rates according to histopathology.

Histology	ICDO	No of population	Over all 10-year survival (95 % CI)	Cause-specific 10-year survival (95 % CI).
All		40,000	55 % (54.8 – 56.4)	72 % (71.2 – 72.9)
Unspecified carcinoma.	8011	1588	70 (69.5 – 71.2)	80.9 (79.9 – 81.2)
Microinvasive SCC.	8075	5343	65.9 (64.9 – 65.3)	95.2 (94.9 – 96.1)
Squamous cell carcinoma (SCC).				
SCC non-keratinizing.	8071	2456	56.8 (56.3 – 56.9)	76.3 (75.9 – 76.8)
SCC keratinizing large cells.	8070	12015	67.9 (67.0 - 68.1)	71.1 (70.8 – 72.3)
NOS SCC.	8559	2500	64.2 (63.9 – 64.9)	75.4 (74.1 – 76.2)
Adeno-squamous carcinoma.	8381	1500	67.9 (67.1 – 68.2)	76.6 (75.7 – 77.2)
Adeno-carcinoma without mucous.				
Endometrioid carcinoma.	8141	4169	67.5 (66.0 – 67.9)	73.3 (72.8 – 74.1)
Adenocarcinoma NOS.	8160	8714	59.4 (58.9 – 59.1)	80.2 (79.7 – 81.2)
Papillary adenocarcinoma NOS.	8210	8587	86.9 (86.0 – 87.2)	78.4 (77.8 – 79.1)
Clear cell adenocarcinoma, NOS.	8380	413	71.2 (70.9 – 72.3)	65.7 (64.9 – 66.2)
Adenocarcinoma with mucous.				
Mucous adeno-carcinoma.	8381	1286	54.3 (53.3 – 55.5)	70.1 (69.2 – 71.2)
Mucin excreting adenocarcinoma.	8221	813	55.2 (54.0 – 56.2)	54.3 (53.2 – 55.3)
Small cell carcinoma.	8040	1398	53.3 (52.9 – 54.1)	60.1 (59.1 – 61.0)

Analysis involving multivariate variables: Analysis conducted for checking the overall rate of mortality were dependent upon the variables of age, gender, ethnicity, registry of cancer center Pakistan, marital status, grade and stage of cervical tumor, type of associated histopathology, use of radiography and surgical approach in its management. For throwing light on the cause specific rate of mortality, it is not essential to add the variables such as marital status and area of registry [7]. However, the type of histopathology is an important and significant factor to be included in the analysis in order to differentiate among the characteristic features of different types. Few cases were reported that highlighted the size of tumor along with the involvement of nodes and staging of AJCC stages (shown in table 1) [10].

Table 3: Multivariate analysis of mortality origin fully based on 2,458 cases along with complete data of pathology

	A		B	
Variable	Model including tumor size and nodal variables Hazard ratio (95% confidence interval)	P	Model ignoring tumor size and nodal variables Hazard ratio (95% confidence interval)	P
Pathology				
Histology		<0.001		<0.001
SCC microinvasive	1.25 (0.30-4.02)	0.692	0.62	0.406
Carcinoma NOS	0.95 (0.30-2.15)	0.870	1.33	0.473
Adenocarcinoma excl. mucinous	1.41 (1.05-1.80)	0.015	1.28	0.076
Adeno-squamous carcinoma	1.59 (1.13-2.20)	0.006	1.56	0.006
Mucinous	1.93 (1.05-3.45)	0.026	2.06	0.014
Small cell	7.01 (3.92-12.6)	<0.001	7.58	<0.001
Histological grade 3-4	1.55 (1.25-1.92)	<0.002	1.82	<0.002
Log tumor size (mm)	1.88 (1.53-2.30)	<0.001		
Log odds of nodal involvement	1.25 (1.10-1.35)	<0.002		
Stage				
Historical stage localized			0.23 (0.18-0.30)	<0.001
Stage II	0.96 (0.60-1.56)	0.955		
Stage III	2.30 (1.64-3.10)	<0.002		
Stage IV	2.50 (1.60-4.00)	<0.002		
Other				
Year of diagnosis	0.96 (0.92-0.98)	0.014	0.98 (0.92-0.98)	0.008
African-American ethnicity	1.47 (1.05-1.99)	0.009	1.50 (1.10-2.06)	0.002
Hysterectomy	0.60 (0.45-0.70)	<0.002	0.39 (0.31-0.55)	<0.002

DISCUSSION

The rate of incidence and mortality of disease is dependent upon the geographical region or the country with highest rates observed among the population of Pakistan[12]. These rates have been seen to decline in the last 30 decades which reflected the improvement in clinical supervision and screening. However, despite all this, there are many risks and hazards associated with the development of cervical cancer among the females aged after 40 years [13]. In Pakistan, the incidence of these cases had been observed among Pakistani groups with 5.3 % cases per 100,000 population. The risk for the development of invasive cervix cancer among females has become higher among the age group of 40-59 years which has suggested this disease to be a major health issue among Pakistan and other countries [14].

Current findings suggest that the incident rates of cancer have declined, however, many cases of adeno-carcinoma and squamous cell carcinoma have increased from the last few years. Those histopathologic types of carcinomas that were not specified in the previous years, got characterized in the recent years to their specifications and increased research in that area resulting in the decline of unspecified cases (62 cases / year) within Pakistan. The average incidence of adenocarcinoma was observed to be 130 cases per year showing their rate to be twice that of unspecified cases of carcinoma. To further understand the cause, it is important to correlate the clinical symptoms with the cause of the disease. It has been observed from literature that human papillomavirus (HPV) has a direct role in producing cancer related carcinogens within the cervical cells. This association has been observed to be similar with that of the development of adeno-carcinoma however, differences lie within different cofactors that cause the disease. If HPV has a role in development of adeno-carcinoma then it would be predicted that the population suffering from cervical cancer would have HPV in their cells. A survey was carried out in this aspect in 2003-2004 which depicted that about 25 % of the women suffering from carcinoma had HPV stains in their blood which has created a gap for the future researchers in order to get a more in- depth knowledge about it [9].

In view of the records collected from cancer center Pakistan, carcinomic lesions have been found in the patients depending upon the histological type of pathology. The current findings suggest that histopathological studies are very significant for throwing light on the type of cancer. Further, they also differentiate between different stages of cancer on the basis of the stains present in it. Owing to the increasing trend of adenocarcinoma cases within the population, the rate of patient's association to HPV, poor rate of prognosis, and age of diagnosis, it has been observed that there is need to improve the screening of tumors and increasing the chances of vaccination of HPV [16]. Some studies suggest that the types of histopathological studies have a limited value of prognosis or had their significance in only limited amounts of subsets. However, in another study conducted by Alfsen et al, it has been observed that among all the sub types, only squamous cell carcinoma is the only type whose importance is independent in terms of prognosis [17].

Some limitations of this study acknowledged by us are that there were lack of details targeting the type of screening, nature of screening, whether the tumor has been screened or not, marginal status of patients in case of surgery, procedures utilized in radiotherapy, and comorbid conditions of the patients. This study also lacked the extent of histopathology that has an effect on the decision of treatment. Further, only 10 % of the patients had full examination in terms of pathology which should be extended to all the patients. These limitations should be addressed in future research in order to close the gap of the study.

CONCLUSION

This study suggests that the histological type was an important prognostic factor that is independent in case of cervical carcinomas. Poor rates of survival had been observed in patients suffering from small squamous cell carcinoma, some subtypes of mucin related adeno-carcinoma, and most commonly among adeno-squamous carcinoma and adeno-carcinoma. The rate of diagnosis was common among the women aged between 45 – 53 years. However, an increase in the incidence of adenocarcinoma and squamous cell carcinoma suggests that proper screening should be required in all females after the age of 40 years in order to properly deal with the cases.

Conflicts of interest: There are no conflicts of interest in this study.

Abbreviations:

AIC = Akaike information center.
DNA = Deoxyribonucleic acid.
SCC = Squamous cell carcinoma.
ICDO = International classification of diseases for oncology.
HPV = Human papillomavirus.
CI = Confidence interval.

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