A Study of Clinico-Pathological Parameters of Squamous Cell Carcinoma Cervix and their Correlation with Treatment Outcome in A Tertiary Care Hospital of Punjab

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Abstract

In India, cervical cancer is the second most common cancer in women accounting for almost 14% of all female cancer. Carcinoma cervix has known risk factors, has a long pre-clinical period when it can be effectively detected and treated. However, preventive measures are rarely practiced in India, and women often present to hospitals only when they are symptomatic. The higher mortality rate can be attributed largely to the lack of appropriate healthcare infrastructure in India. In this prospective study total 60 patients with proven squamous cell ca cervix of age 18-70yrs, stage IIB to IIIB with ECOG PS≤2were treated conventionally by Cobalt-60 with EBRT dose of 50Gy in 25 fractions in 5 weeks with concomitant Injection Cisplatin 50 mg weekly followed by 2 sessions of intra cavitory brachytherapy of 9.5 Grey per fraction by Iridium 192-HDR brachytherapy. Various risk prameters related to the patient tumor and treatment related parameters were studied. Response was evaluated as per RECIST's criteria and individual parameter was correlated with response. using the SPSS version 20. In our study carcinoma cervix was more common in elderly women (>40yrs), majority of them were from rural background (81.7%) with low literacy rate, low socioeconomic class. Early marriage(<17years), multiple child birth (>)3, there was association with HPV 16 followed by 18 but there was no significant correlation with treatment outcome. Parameter like hemoglobin (<10gm/dl), tumour size (>67cm^3), poor grade of differentiation, advance stage (≥IIIB), treatment time >48 days was associated with poor outcome (satistically significant). The RTOG grade 3,4 hematological & gastrointestinal toxicities was not significant. Twe conclude that carcinoma cervix remains to be a health problem in developing country. Implementation of adequate screening might aid in detection at early stage & adequate outcome as the disease has long pre-clinical course. HPV vaccination might aid in the prevention of development of disease but it would require large sample size & longer follow up. The chemoradiotherapy remains to be the standard of care.

Keywords: carcinoma cervix, Human Papilloma Virus, Chemoradiotherapy.

Introduction

Over the last few decades, cervical cancer incidence and mortality rates reportedly have been declining in many populations worldwide. The beneficial effects of population based cytological screening programs hastened declines in cervical cancer rates upon their implementation in many European countries.

In the absence of effective screening, as in Eastern Europe and Central Asia there have been rapid increases in premature cervical cancer mortality. Cervical cancer ranks second in incidence and mortality behind breast cancer in lower HDI settings and the leading cause of cancer death. the vast majority of which are in Sub-Saharan Africa and South- Eastern Asia. In such high-risk regions, the challenge is to ensure that resource-dependent programs of screening and vaccination are implemented to transform the situation.1

In India, cervical cancer is the second most common cancer in women (aged 15–44 years) after breast cancer accounting for almost 14% of all female cancer. The age-adjusted incidence rate is 27.0 per 100,000 female population and age-adjusted mortality rate per 10,000 population is reported to be 12.4. Cervical cancer in its advanced stage has a dismal outcome in terms of both prognosis and quality of life, registering approximately 67,477 deaths (23.3% of all cancer-related deaths) each year in Indian women..The higher mortality rate can be attributed largely to the lack of appropriate healthcare infrastructure in India.[2]

In Punjab, Malwa region is cancer prone area and in Faridkot area cervical cancer accounts for about 20% of all female cancers.[3]

Carcinoma cervix has known risk factors, has a long pre-clinical period when it can be effectively detected and treated. However, preventive measures are rarely practiced in India, and women often present to hospitals only when they are symptomatic. Risk factors in the etiology of cervical cancer include increasing age, longer duration of sexual activity, increasing parity and viral infections with human papilloma virus and human immunodeficiency virus 2. Low socioeconomic status and poor genital hygiene also contribute to the risk. There have been few studies on the association of HPV 16 and 18 from India in relation to cervical lesions.[4]

The accumulated evidence suggests that cervical cancer is preventable and is highly suitable for primary prevention.5

The usual 10-20 years of natural history of progression from mild dysplasia to carcinoma cervix makes this cancer as relatively early preventable disease and provides the rationale for screening. Despite existence of national guidelines, the screening coverage in India is low. As a result, the diagnosis of carcinoma cervix is based on opportunistic screening or after the onset of the symptoms.6

Materials and method

This is a prospective study conducted from March 2018 to August 2019 at tertiary care center of Faridkot, Punjab. A total 60 consecutive patients biopsy proven squamous cell carcinoma cervix of age between 18 -70 years, of stage IIB to IIIB with ECOG PS≤2 were enrolled with their informed consent and were treated conventionally by Cobalt-60 with EBRT dose of 50Gy in 25 fractions in 5 weeks with concomitant Injection Cisplatin 50 mg weekly followed by 2 sessions of intra cavitory brachytherapy of 9.5 Grey per fraction by Iridium 192-HDR brachytherapy. Various factors related to patient Socio economic status age of the patient, age of first intercourse, parity, number of partners, HPV, pre-treatment hemoglobin, stage at presentation), tumor related factors (histological grade of differentiation,

tumor volume) and treatment related parameters (overall treatment time) were studied. Response was evaluated as per RECIST's criteria and individual parameter was correlated with response. Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 20. Descriptive statistics like Frequency, percentages, mean, standard deviation, range were used to describe treatment characteristics. Inferential statistics were applied to draw inferences. For continuous variables mean values were compared between the groups using the ANOVA. A p-value of < 0.05 was considered statistically significant.

Results:

Table1

Variables	Distribution	Response			Chi-square/ F-value	p-value
		CR	PR	PRG		
Age group (years) < 40 >40	9 (15%) 51 (85%)	7 (16.3%) 36(83.7%)	1(7.7%) 12(92.3%)	1 (25%) 3 (75%)	0.913	0.633
Social background Rural Urban	49 (81.7%) 11 (18.3%)	34(79.1%) 9 (20.9%)	12(92.3%) 1 (7.7%)	3(75%) 1 (25%)	1.29	0.523
Age at first intercourse <18 years >18 years	17 (28.3%) 42 (71.7%)	19.23 (±2.29) Mean(±SD)	19.23 (±2.29) Mean(±SD)	17.50 (±1.29) Mean(±SD)		
Number of partners 1 >1	60 (100%) 0	43(100%) 0	13(100%) 0	4 (100%)	0.93	0.62
Parity Uniparous Multiparous 2	8 (13.3%) 19 (31.7%)	8 (18.6%) 17(39.5%)	0 1 (7.7%)	0 1 (25%)	14.769	0.62

3	23 (38.3%)	11(25.6%)	10(76.9%)	2 (50%)		
4	8 (13.3%)	5 (11.6%)	2 (15.4%)	1 (25%)		
5	2 (3.3%)	2 (4.7%)	0	0		
Stage at presentation						
IIB	27 (45%)	25(58.1%)	2 (15.4%)	0		
IIIA	4 (6.7%)	4 (9.3%)	0	0		
IIIB	29 48.3%)	14(32.6%)	11(84.6%)	4(100%)		
HPV					7.348	0.500
Not detected	10 (16.6%)	9(20.9%)	1 (7.7%)	0		
Type 16	39 (65%)	9(20.9%)	9 (69.2%)	4 (100%)		
Type 18	9 (15%)	7(16.3%)	2 (15.4%)	0		
Type 31	1 (1.7%)	1 (2.3%)	0	0		
Type 52	1 (1.7%)	0	1 (7.7%)	0		
Pre-treatment Hemoglobin (g/dl)	12 (20%)	10.20 ($\pm$1.24)	7.75 ($\pm$0.74)	8.85 ($\pm$1.88)	21.58	0.00
<8	29 (48.3%)					
8-10	19 (38.7%)					
>10		Mean($\pm$SD)	Mean($\pm$SD)	Mean($\pm$SD)		
Mean + SD (9.6$\pm$1.6)						
Range (6.5-12.5)						
Histological grades of differentiation					18.561	0.001
Well differentiated	6(10%)	6(14%)	0	0		
Moderately differentiated	50 (83.3%)	37(86%)	11(84.6%)	2 (50%)		
Poorly differentiated	4 (6.7%)	0	2 (15.4%)	2 (50%)		
Volume of tumour in cubic centimeters (cc)					67.814	0.000
<50cc	27 (45%)	42.44($\pm$ 24.71)	135.6($\pm$ 33.87)	136($\pm$ 41.6)		
51-100cc	17 (28.3%)					
>100cc						

	16 (26.7%)					
Treatment duration (days)						
<50	40 (66.7%)	40(93%)	0	0	47.4	0.000
>50	20 (33.3%)	3 (7%)	13(100%)	4 (100%)	42	

Discussion

Cervical cancer is the second most commonly diagnosed cancer and the third leading cause of cancer death among females in less developed countries.

The large geographic variation in cervical cancer rates reflects differences in the availability of screening. For many years, the Papanicolaou (Pap) test has been the standard method for cervical cancer screening, However, the limitations of this cytology-based test are the sensitivity (∼ 50%) and significant proportion of inadequate specimens. HPV is detected in 99% of cervical tumors, particularly the oncogenic subtypes such as HPV 16 and 18 More recently, an HPV test has been introduced as a screening tool as HPV deoxyribonucleic acid (DNA) is present in almost all cervical cancers and it has demonstrated higher sensitivity for high grade cervical intraepithelial neoplasia.

Radiotherapy has been the standard of care for patients with bulky IB2–IVA disease.7

Recently, five randomized trials performed by the Gynecologic Oncology Group (GOG), Radiation Therapy Oncology Group (RTOG) and the South West Oncology Group (SWOG) studying cisplatin-based chemoradiation have demonstrated a significant survival advantage. Based on the results of these five randomized trials, the National Cancer Institute released a Clinical Announcement stating that Cisplatin based chemotherapy, as used in these trials (i.e. concurrently with radiation therapy), as the standard of therapy for cervical cancer.8

The age of the patients ranged from 30-66 years with a mean age ± S.D was (49.8± 8.5). Majority of the patients in our study were in the range of 41 to 65 years of age. Data from cancer registries in developing countries, suggest that about 80% to 90% of confirmed cervical cancer cases occur among women age 35 or older. The incidence of cancer in most countries is very low in women under age 25 while incidence increases at about ages 35 to 40 and reaches a maximum in their 50s and 60s mainly because of slow progression of cervical cancers from pre-cancerous lesions to advanced cancer.9

Similar results were obtained in a study in 2009 that had also shown that most cervical cancers in India occurred in 45-60 years of age.10

In our study, majority of patients (81.7%) were from rural background. In a study the highest age specific incidence rate of 98.2 per 100,000 for cancer cervix was seen in the 60 to 64year age group. over 70 per cent of the Indian population resides in the rural areas.11

Awareness is significantly associated with age, education, and income. Poor awareness lowers the possibility of early diagnosis in spite of availability of screening test. Thus education may be having important role in awareness.12

In a study of sociodemographic and behavioral risk factors of cervical cancer the author concluded that a large number of risk factors were present in both areas, the prevalence being higher in the rural areas.13

Smoking is an important risk factor for high grade CIN in young females who become sexually active by impairing antibody response to HPV. In this study none of the females were smoker. Similar result was obtained in a study where smoking not found to have increased risk of acquiring or prolonging duration of HPV. And concluded that other mechanisms have to be invoked to explain its association with cervical neoplasia.14

Alongside active cigarette smoking, passive smoking is an independent risk factor for cervix cancer. Smoking maintains cervical HPV infection longer and decreases potential of clearing an oncogenic infection. It is quite possible that polymorphism at detoxifying enzyme coding loci such as GSTM1, GSTT1, and GSTP1 may determine susceptibility to cervix cancer. Passive smokers having genotypes GSTM1, GSTT1 and GSTP1 have an increased risk of developing cervix cancer.15

In this study majority of the patients had HPV 16 positivity in all three response groups followed by HPV 18, 31 and 52. This leads to conclusion that HPV as an important risk factor in the development of carcinoma cervix. But there was no correlation was found in the treatment outcome Similar result was obtained in a study where it concluded that squamous cell carcinoma is associated more with HPV infection in carcinogenesis than adenocarcinoma. HPV did not have an apparent influence on any recurrence. Furthermore, no obvious differences with regard to HPV infection in any survival curves, including cause specific survival, recurrence free survival, and local recurrence free survival, were detected .16

In this study 28.3% of the cases had early age (<18years) at first sexual contact due to early marriage and the response group with progression had mean age of 17years. Around 28.35% of the patients had history of STD. Around 54.9% of the patients had parity ≥ 3 (with 38.3% patients had parity 3). There was no significant p-value for the treatment outcome for each of these factors but due to their significant percentage it can be said that early age of first intercourse, sexually transmitted diseases and high parity are important risk factor for carcinoma cervix. Similar observation was made in a study where early age of first intercourse, high parity is important risk factors or invasive cervical carcinoma.17

The risk of cervical cancer to be three folds higher among women who gave history of age at first intercourse to be <17 years as compared to women who had their first sexual debut at >20 years of age. The possible explanation for the significance of this factor is the fact that early sexual debut results in more frequent and prolonged sexual activity and prolonged hormonal stimulation, and the young cervical tissue is more susceptible to oncogenic change. In addition, those marrying at younger age are exposed to sexually transmitted diseases including HPV which is the prime factor in this disease. High parity with >3 children was found to be a significant risk factor. Trauma to cervix during delivery as well as increased susceptibility to infection can be given as the possible explanations. 18

Early age at first child birth was found to increase the risk of cervical cancer. A hospital-based case-control study in India showed that early age at first marriage was a single independent risk factor for cervical cancer. This study also suggested that the rapidity of multiple pregnancies was a more important factor than the parity itself in increasing the cervical cancer risk.19

In this study mean pretreatment hemoglobin in complete response group was 10.20 g/dl and patients having hemoglobin <10g/dl had poor treatment outcome (p value <0.001). In a study it was observed that the patients having hemoglobin <10g/dl were correlated with lower disease specific survival. 20

In this study loco-regionally advanced disease (stage IIIB) with tumor size >67 cm3 and poor histopathological grade of differentiation were associated with poor treatment outcome significant p value

these results are corroborative with a study in which it was concluded that advanced stage along with poor histopathological differentiation influences the aggressiveness of the tumor responsible for distant relapse. However, histopathological differentiation has no correlation with local treatment response and overall survival.

The main factor influencing the treatment outcome is the intrinsic radio sensitivity of the tumor and volume of the disease.21

In a study it was suggested that higher tumor grade was associated with poorer survival.22

In a study role of tumor volume as prognostic factor in carcinoma cervix patients post radiotherapy and conclusion was made that tumor volume >60cc were associated with poor outcome.23

Length of overall treatment time has significant impact on treatment outcome of carcinoma cervix. In our study mean duration of overall treatment was 46 days (<8 weeks) in the patients having complete response. The partial response and the progression groups had overall treatment time >8 weeks. In a study it was concluded that loss of local control and overall survival occurs, when treatment exceeded 52 days.24

Similar results were obtained by song et al where he observed that in the setting of CCRT, treatment time >56 days is detrimental to pelvic control to maximize pelvic control.25

Conclusion

The observation made in our study has helped us to arrive at the conclusion that carcinoma cervix is second most common malignancy in females in our outpatient department after carcinoma breast. It is common in rural population of Punjab and in low socioeconomic class. It is commonly seen in females after 40years of age who had early sexual contact due to early marriages. HPV 16 and 18 was detectable in majority of the patients. Due to poor awareness late presentation was common when disease was loco-regionally advanced. Due to longer duration of blood loss most of them were anemic and had to admitted frequently for blood transfusions during treatment. Majority of the patients completed their treatment on day care basis within fifty days. Reason for hospital admission was mainly for blood transfusion, neutropenia, loose stool and for hydration. Injection cisplatin has proved to be standard chemotherapeutic agent with acceptable toxicities and overall good treatment results in most of the patients.

Stage of the disease, histological grade, pretreatment hemoglobin, volume of the tumor, duration of treatment significant correlation with treatment outcome. Thus we have reached to a conclusion that cervical cancer screening should be optimized in resource limited socioeconomically backward areas for early detection. HPV vaccination in young sexually active female should be emphasized as it highly prevalent and important etiological agent in the pathogenesis of the disease.

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