

## An epidemiological analysis of cervical cancer in women age less than 30 years and their prognosis, a regional cancer center experience

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### Abstract

**Objective:** Cervical cancer though common among the developing world, still very few data is available for young patients with cervical cancer. This paper attempts to evaluate the epidemiology with special focus on disease free survival and the prognostic significance of the young age in cervical cancer.

**Material & Methods:** For this retrospective study young patient with age less than 30 years & cervical cancer, over duration of 2009 to 2014 were included. Pertinent data were collected retrogradely from the case records & whenever required patients were contacted over phone.

**Results:** Between 2009 to 2014, a total of 8363 cervical cancer patients were referred to us, out of which 169 patients with carcinoma cervix in the age group of < 30 years were treated at our hospital. From the 169 patients, 52 patients were lost to follow up. Among 117 patients who were treated, 65(55.55%) had Disease Free survival of less than 6 months. According to the histopathology squamous cell carcinoma had a disease free survival (DFS) of 8.5 months, followed by adenocarcinoma 10.62 months.

**Conclusion:** We have found the poor prognosis of cervical cancer in young patients compared to older patients. More studies are required to study the pathophysiology and factors implicating the prognosis in young patients with cervical cancer to know this basic difference in survival among old and young patients with cervical cancer.

**Keywords:** Cervical cancer, Radiotherapy, Young age

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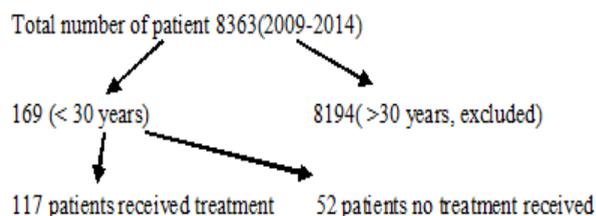
### Introduction

Cervical cancer is on the declining trend in India according to the population-based registries; yet it continues to be a major public health problem for women in India.<sup>(1)</sup> Cervical cancer is rare in women under 30 years of age, worldwide median age is 50 years. The effect of young age on survival in cervical cancer is not fully known, very few studies are there. This paper attempts to evaluate the epidemiology with special focus on disease free survival and the prognostic significance of the young age.

### Material & Methodology

For this retrospective study, all patients in the age group of less than equal to 30 years with cervical malignancy were identified from the hospital computer database for the last six years (2009-2014). Pertinent data was collected retrogradely from the case records & patients were contacted over phone. Patients with cervical cancer in the age group of  $\leq 30$  years, those who underwent treatment (surgery, radiotherapy or both) at GCRI (Gujarat Cancer Research & Institute) were included in the study. Those who were operated elsewhere but received radiotherapy were also included. Patients with cervical cancer with age more than 30 years were excluded. All the histopathological slides were reported or reviewed by gynecologic oncopathologists at GCRI. Following variables were analyzed- mean age at disease, age of marriage, age at

first child, use of tobacco, tumor size, stage of disease, pathological type, tumor grade, Presence or absence of uremia, type of primary treatment received & disease free survival. The study is approved by the ethical committee of the institution.



### Results

Between 2009 to 2014 a total of 8363 cervical cancer patients were referred to us. Out of which 169 patients with carcinoma cervix in the age group of < 30 years were treated at GCRI. The mean age of the patient was 28.6 years. The mean age of marriage was 18.4 years, out of which 130(76.92%) of patient had marriage before 20 years of age. More than 58% of patients had first child birth before 20 years of age with a mean age of 19.55 years. All patients of the study group belong to Hindu religion except one who is a Muslim woman. Most of the woman 138(81.65%) were from low socioeconomic status with a rural background. Mean parity of > 2 was found in 145 (85.79%) of patients. Forty two patients (42.86%) use

some form tobacco. The demographic profiles of patients are summarized in Table 1.

**Table 1: Epidemiological variables**

Demographic profile	Number
Age, years	28.6
Less than 25 years	21(12.42%)
Age of marriage	18.40
< 20 years	130(76.92%)
> 20 years	34(20.11%)
Unmarried	05(2.95%)
Age at first child birth	19.55
< 20 years	99(58.57%)
> 20 years	57(33.72%)
Nulliparous	13(7.6%)
Religion	
Hindu	168(99.4%)
Muslims	1(0.6%)
Socioeconomic status	
Low	138(81.65%)
Middle	30(17.75%)
upper	1(0.59%)
Rural	154(91.12%)
Urban	15(8.87%)
No tobacco	127(75.14%)
Using tobacco	42(24.86%)
Parity	2.68 (0-6)
> 2 child	145 (85.79%)
< 2 child	24 (14.20%)

More than 70% of the patients presented with some form of menstrual disorder for a mean duration of 2.64 months. One hundred and thirty eight (78.11%) patients presented to the hospital in an advanced stage (stage II B –IV B). The grade of the carcinoma was known for all patients, with grade 2 differentiation seen in majority of patients 108(63.90%) followed by grade 3 45(26.62%) and grade 1 16(9.4%) as shown in table 2. Squamous cell carcinoma was the most common histological type seen among 153(90.53%) of the patients followed by adenocarcinoma in 10(5.9%). Other histological types were rare 6(3.5%). Mean tumor size was 4.6×5.3 cm. In the study population 132(83%) had tumor size of ≥4cm & in 27(17%) mean tumor size was ≤4cm. Out of 169 patients, 34(20.1%) of patients presented with either unilateral or bilateral hydronephrosis and 16 (9.46%) had presented with uremia. Ten patients had coexistent HIV infection along with carcinoma cervix. The clinical details of patients are summarized in Table 2.

In developed countries because of routine cervical screening it is being detected in an early stage but in developing country like India most of the patients seek treatment in an advanced stage. In our institute, out of 169 patients, 132 (78.10%) were presented in an advanced stage and only 37(21.90%) were in an early stage. Patients who were referred to GCRI with the

primary diagnosis of carcinoma cervix only 70% of patients received some form of treatment & about 52(30%) lost to follow up & didn't receive any treatment. As most patients were in advanced stage, 69(58.97%) received radiotherapy with the curative intent and 28(23.93%) received palliative radiotherapy. Surgery followed by radiotherapy was required in 15(12.82%) patients. Surgery without radiotherapy was received by 5 patients. Mean disease free survival according to stage for 1B1, 1B2, IIB, IIIB & IV B were 13.5, 12.7, 11.4, 10.2 & 2 months respectively. Patients who have received any treatment (surgery, radiotherapy or both), 65(55%) had a DFS (Disease Free survival) of <6 months. According to the histopathology squamous cell carcinoma had a DFS of 8.5 months & adenocarcinoma 10.62 months. Correlation of disease free survival with histopathology, stage of the disease and treatment received is summarized in Table 3.

**Table 2: Clinico-pathological distribution**

Symptoms	N (%)
Inter menstrual bleeding	48(28.40%)
Post coital bleeding	38(22.48%)
Menorrhagia	38(22.48%)
Abdominal pain	26(15.38%)
Vaginal discharge	19(11.24%)
Mean duration of symptoms in months	2.64 (1-12)
Mean tumor size, cms	4.6×5.3
Type of cervical malignancy	N (%)
Squamous cell carcinoma	153(90.53%)
Adeno carcinoma	10(5.9%)
Others	6 (3.5%)
Stage of tumor	N (%)
Early stage(stage I A- Stage II A)	37 (21.89%)
Advanced stage(Stage II B – Stage IV B)	132(78.11%)
Grade of tumor	N (%)
Grade 1	16(9.4%)
Grade 2	108(63.90%)
Grade 3	45(26.62%)
Renal involvement (as hydronephrosis)	N (%)
No	135(79.88%)
yes	34(20.10%)
Uremia	N (%)
No	153(90.53%)
yes	16(9.46%)
Fistula	2(1.1%)
Patients with HIV	10(5.9%)
Patients without HIV	159(93.1%)

**Table 3: Correlation with disease free survival with histopathology, treatment received and stage of disease**

Curative Radiotherapy	69(58.97%)
Palliative radiotherapy	28(23.93%)
Surgery with radiotherapy	15(12.82%)
Surgery	5(4.27%)
No treatment	52(30.76%)
Disease free survival (DFS)	Month
Mean DFS	10.5
Stage 1b1	13.5
Stage 1b2	12.7
Stage II B	11.4
Stage III B	10.2
Stage IV B	2
Disease free survival (DFS) < 6 month	65(55.55%)
Disease free survival (DFS)	N (month)
Squamous cell carcinoma	105(8.5)
Adeno carcinoma	08(10.62)
Others	4(11)

### Discussions

In the developing world carcinoma cervix is the most common genital tract malignancy and overall second commonest cause of death in women due to malignancy. Due to poor health care facility and cervical cancer screening the mortality rate is high in developing country. The median age of cervical cancer is 50 years worldwide and its incidence rises after the age of 25 years.<sup>(2)</sup> The pattern and characteristics of cervical malignancy in the age group of less than 30 years has not been extensively documented. According to IARC data 2007, incidence of cervical cancer in general population of less than 29 years was 0.23 per 1, 00,000 in India.<sup>(3)</sup> In our study we have an incidence of cervical cancer of 2% in women less than 30 years of age. The low incidence of cervical cancer among women with less than 30 years is partly because of the spontaneous clearance of human papilloma virus (HPV) infection. In recent days HPV DNA testing has emerged as a new modality for the screening of cervical cancer in the age group of above 30 years.<sup>(4-8)</sup> As persistence of HPV infection are more likely to be associated with cervical cancer.<sup>(9,10)</sup>

The most important factor related to cervical cancer is HPV infection. HPV is a highly infectious disease & transmitted mainly through sexual contact. It is confirmed from many epidemiological studies, as described by Plummer et al, early age at sexual initiation serves as a proxy marker for HPV infection and increases the risk of cervical cancer.<sup>(11)</sup> Besides this multiple male sexual partner increases the risk of acquiring high risk HPV infection which is the most important factor for the development of cervical cancer.<sup>(12-14)</sup> In our study, we were not able to document the exact age of initiation of sexual activity because of many social factors. In the present study 76% of patient

had marriage before 20 years which implies early initiation of sexual act and inoculation of HPV infection.

Multiple studies have confirmed that increase in parity is a risk factor for the development of cervical cancer though the explanatory mechanism behind this is not so clear.<sup>(15)</sup> We have more than 85% of patient had at least two or more children. The probable mechanism behind this is due to more traumas during child birth leading more reparative process in cervix, change of hormonal profile due to pregnancy, immunosuppression and last but not the least alteration of the transformation zone of cervix. All leads to persistence of HPV infection and genesis of cervical cancer. Parikh et al have done a meta-analysis where they have found that women belonging to low socioeconomic strata were twice the more risk to acquire cervical cancer in comparison to upper class women.<sup>(16)</sup> We have results consistent with the above meta-analysis, where more than 80% of women belong to low socioeconomic class with cervical cancer. The main reason behind increase incidence of cervical cancer is due to poor access to health care system leading to delay in diagnosis and treatment. This is also true for developed country where the areas with poor access to health care system and poverty risking the women for the development of cervical cancer.<sup>(17)</sup> Smoking is an independent risk factor for the development of cervical cancer. It's mainly because of immunosuppressive effect or due to the generation of oxygen free radical causing persistence of HPV infection.<sup>(18)</sup> We have found around 25% of patients use some form of tobacco which have made them more prone to develop cervical cancer. It is a well-known fact that the patients with HIV/AIDS have defective clearance of HPV infection, making them more prone to develop cervical cancer. Beside this an alternative hypothesis for the genesis of cervical cancer is that HIV-speci-c Tat protein up regulates expression of HPV E6 and E7 oncogenes and enhances their oncogenetic transformation efficacy.<sup>(19)</sup> We have 10 patients who had coexisting HIV with cervical cancer. Cervical cancer has an indolent course from preinvasive to invasive cancer. Around 70% patients present with some form of menstrual problem. Though most of the patient in our study, had symptoms for a short duration before seeking to any medical care. This could be due to low access to medical care and lack of health education among general people. Histologically cervical cancer can be divided into commonest squamous cell carcinoma followed by adenocarcinoma & others rare variety of cancer. Because of improved screening and HPV vaccination the incidence of squamous cell carcinoma is decreasing and adenocarcinoma is on rise.<sup>(20)</sup> In our study the incidence of adenocarcinoma is around 6%, this may be because of lack of HPV & PAP smear screening among these group of people, where squamous cell carcinoma is still the leading form of cancer. Squamous cell carcinoma is

histopathologically categorized into well differentiated, moderately differentiated and poorly differentiated carcinoma, though treatment protocols as well as prognosis do not depend on the grade of the tumor. Kristensen GB et al studied the correlation between the grading of squamous cell carcinoma with the prognosis of the tumor and found grading may not correlate prognostically with the DFS or overall survival.<sup>(21)</sup> The management of cervical cancer can either be categorized into surgery, chemoradiation or both depending on the stage of the patients and other associated comorbidities. Prognosis of the patient is almost comparable with either surgery or chemoradiation. The disease free survival for the patient with adenocarcinoma and squamous carcinoma is almost comparable after the advancement of concurrent chemoradiation. We too have comparable result in terms of disease free survival rate between squamous and adenocarcinoma. In our study almost 65(55.55%) of patients had a DFS of less than 6 months. Most of the studies available in literature studied overall stage wise prognosis of cervical cancer, but we didn't come across any study regarding the prognosis and DFS in cervical cancer in young patient of less than 30 years. Our study is an initiative in this regard. We have found the overall DFS was 10.5 months, but more than 65(55.55%) of patients had DFS of less than 6 months which is contrasting with the DFS in older patients. Patient with locally advanced disease those who received concurrent chemoradiation the progression free survival is between 40 to 60 month according to different trials conducted by Gynecology oncology groups.<sup>(22-24)</sup> In the present study during treatment, out of 117 women who have received some form of treatment 11(10.67%) patients died during treatment, which is not acceptable. Out of 11, ten patients were in stage IIIB and one belongs to stage IV B. our study showed comparatively high mortality rate of patient during treatment and also poor DFS among young women. More studies are required to confirm our findings. Besides this studies are required to carry out in young population to know the pathophysiology and factors implicating the prognosis in young patients with cervical cancer.

### Conclusion

Cervical cancer is a major health issue in the developing country. The survival among all stage of patients has improved over the years due to the advancement in chemoradiotherapy as well as surgery. But On contrary to the belief we have found the poor prognosis of cervical cancer in young patients compared to older patients. This could be due to higher virulence of HPV in young patients which needs to be studied. More research is required to study the pathophysiology and factors implicating the prognosis in young patients.

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### Conflict of interest

None

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