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Prognostic Factors in Cervical Cancer: A Hospital-based Retrospective Study from Visakhapatnam City, Andhra Pradesh

K. Geetha Kumari, G. Sudhakar, M. Ramesh, V. L. Kalpana and G. Paddaiah

Department of Human Genetics, Andhra University, Visakhapatnam 530 003, Andhra Pradesh, India
Email: dgeetakumari@yahoo.com, profgsudhakar@gmail.com

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ABSTRACT Cancer of uterine cervix is the second most common cause of cancer related deaths among women. The purpose of this retrospective study was to determine the survival rates of cervical cancer patients, to evaluate the prognostic significance of clinicopathological factors by univariate and multivariate analysis, and to compare the incidence and survival rates of cervical cancer patients. The mean length of the follow-up period was 29.5 months from the date of surgery or radiotherapy, with a follow up period of 60 months. The overall survival is 83.3% and disease free survival is 76.8%. It was found by Cox Regression Analysis (CRA) that only clinical stage ($p<0.001$) is the independent prognostic factor. In multivariate analysis, patients with cervical adenocarcinoma had a worse prognosis than patients with squamous cell carcinoma after correction for confounders such as age, stage and histological types. In univariate analysis the patients with age group of above 50 years, advanced stage and treatment with radiotherapy alone emerged as independent prognostic factors with a significant p value ($p < 0.05$).

INTRODUCTION

Cancer of the uterine cervix is the second most common cause of cancer related deaths among women, especially in the developing countries. According to WHO projections in 2005, over 500,000 new cases were diagnosed of which >90% were in developing countries. In India, nearly 50,000 women were suffering with cervical cancer every year. Cervical cancer is rare in women under 30 years of age and most common in women over 40 years, with the greatest number of deaths usually occurring in women in their 50s and 60s. Cervical cancer occurs worldwide, but the highest incidence rates are found in Central and South America, Eastern Africa, South and South-East Asia, and Melanesia (WHO 2006).

The most important factor responsible for cervical cancer is Human Papilloma Virus (HPV). This virus infects mucosa and skin. To date, more than 100 HPV types have been identified. With regard to cervical cancer development, low-risk HPVs include types 6,11,42 and 43, intermediate risk HPVs include types 35, 44, 45, 51, 52 and 58, and high-risk HPVs include types 16, 18, 31 and 33. Types 16 and 18 are mostly found in cervical cancer and are transmitted by sexual contact (Rughooputh et al. 2007).

While HPV vaccines have been launched recently to prevent infection by the two major types of HPV causing cervical cancer, prevention will still need to rely on early detection of cervical cancer precursors by screening for several years before the full impact from affordable and efficient immunization programmes can be felt. Cervical cancer deaths need to be prevented urgently in the developing world to reduce disparities and improve women's health.

In our study the clinicopathological factors age, stage, grade, pathology, histology and treatment were considered for prognosis. The effect of young age on survival in cervical cancer is not fully known, although evidence has suggested that it is a poor prognostic factor and that young patients should therefore be treated differently from older patients (Clive et al. 1988). The incidence and mortality levels differ significantly within every stage (Ruta Grigiene et al. 2007). The clinical stage was very important in relation to prognosis. The prognosis depends on the stage of the disease at the time of diagnosis. The 5-year survival rate for all stages of cervical cancer combined is approximately 70%. As to survival, there was no difference between

Address for correspondence:
K. Geetha Kumari
Department of Human Genetics, Andhra University
Visakhapatnam 530 003, Andhra Pradesh, India
E-mail: dgeetakumari@yahoo.com

adenocarcinoma and squamous cell carcinoma when compared in all patients, but adenocarcinoma had a worse prognosis than squamous cell carcinoma when surgery was employed (Nippon 1989). The treatment of choice for invasive cervical cancer in the initial stages is radiotherapy or radical hysterectomy with pelvic bilateral lymphadenectomy. Surgery is preferable among young patients because of the possibilities of ovary preservation, hormonal function maintenance and better sexual performance (Sao Paulo 2009).

MATERIALS AND METHODS

This is a retrospective analytic study of 552 cervical cancer patients treated in Lions Cancer Hospital, Visakhapatnam between January 2001 to December 2003. These cases were evaluated over a period of five years from January 2001 to December 2008. Treatment records of patients under active follow up were abstracted. Regular follow–up investigations were performed at department of Gynecology, Lion's Cancer Hospital at 3 months intervals during the first 3 years following treatment and twice yearly thereafter.

The following variables were analyzed: age group (21-80 years), pathological grade (I-III) and stage (IA, IB, IIA, IIB, IIIB, IVA, IVB), pathology (squamous or adenocarcinoma) histological type (LCK-Large cell keratinizing OR LCNK-Large cell non-keratinizing) date of primary diagnosis, the type of primary treatment (radiotherapy, chemotherapy, both or none) and date of treatment completion, date and sites of recurrences, treatment for recurrence, the follow-up data , death date and date of last follow-up visit were recorded.

The surgical pathological staging standard issued by the International Federation of Gynecology and Obstetrics (FIGO) in 1994 was used. Statistical analysis of the data was carried out by the SPSS (version 13.0). Descriptive statistics were used for demographic data and summarized as mean with standard deviation or frequency with percentage. The survival rate was analyzed with the Kaplan-Meier method. Survival data between groups were compared with the Log-rank test for univariate analysis and Cox regression analysis for multivariate analysis. The 95% confidence interval (CI) was calculated for the risk ratios for each of the significant prognosticators. A p-value <0.05 was considered to indicate statistical significance.

RESULTS

The women with cervical carcinoma were registered by the Lions Cancer Registration System, from 2001-2003. Patients were excluded for the following reasons: clinical doubt concerning the primary site, pathological doubt concerning primary site and inadequate or unavailable clinical follow-up. We analysed the clinical and pathological data of 416 patients with an invasive squamous and adenosquamous carcinoma of the cervix. The mean length of the follow-up period was 29.5 months from the date of surgery or radiotherapy, with a median of 30 months, with a follow up period of 60 months. The 5 year survival rate for the all patients is overall survival is 83.3% and disease free survival 76.8%.

Table 1 shows the data from 2001 to 2003. Out of 1823 cancer cases, 552 were cervical cancer patients. There was a complete response from 304 cases and partial response from 112 cases (residue – 53, recurrence – 59) and no follow – up for 136 cases. These 416 cases were evaluated over a period of five years from January 2001 to December 2008.

Table 1: Incidence of cervical cancer from 2001-2003

Cervical cancer	*2001*	*2002*	*2003*	*2001-2003*
Total no. of cancer cases	687	554	582	1823
No. of cervix cases	224	163	165	552
Complete response cases	126	100	78	304
Partial response cases	48	26	38	112
No follow-up cases	50	37	49	136

Figure 1 shows the age of patients for three different years. Age at presentation ranged from 21-80, mean 35.6 years. The age of onset of cervical cancer is higher in the age group of 41-60 with 271/416 patients accounting for 65% of the study population. The Figure also shows that the younger women below 30 years 8(1.92%) and older age group women of above 70 years 9 (2.16%) the occurrence of cervical cancer is less. In 2001 the age of onset was higher in age group 41-60 years and then there was gradual decrease observed in the subsequent two years, the same was found for the age group of 31-40 years. Though there was increment observed in the age group of above 60 years in the year 2002 but in

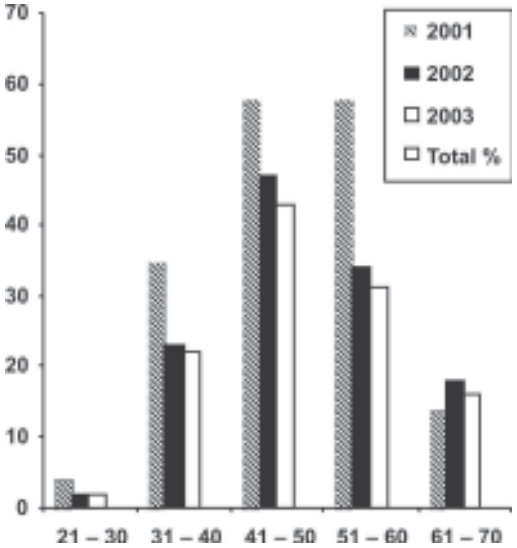

Fig. 1. Distribution of women in relation to age at presentation

2003 this scenario has changed and the decrement was seen. This indicates that the rate of incidence of cervical cancer patients in the age group of 40-60 years is decreasing and as well there is decrease in the incidence of cervical cancer.

The stages of patients for three different years are shown in Figure 2. The frequency of locally advanced stages IIB and IIIB are more with 87% than the early stage and metastatic stage IV. The Figure also shows the distribution of IIIB and IIB that is the locally advanced stages to be higher in all the three years. When we observe the

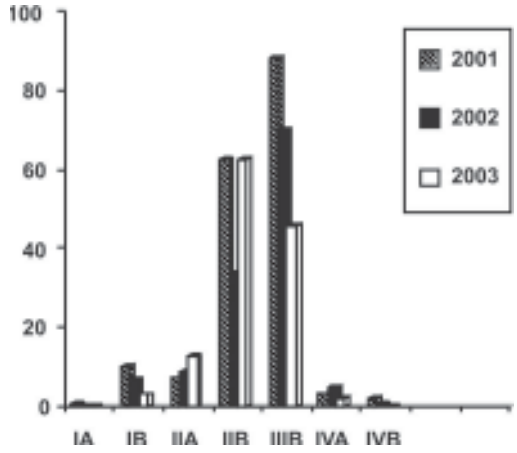

Fig. 2. Distribution of women in relation to stage at presentation.

occurrence, again the locally advanced are higher in 2001 in comparison to the other two years i.e., 2002 and 2003.

Survival time was computed from the date of first diagnosis to the end-point, defined as death from any cause. Closing date was defined as the date 5 years after the first diagnosis. Relative 5-year survival was calculated adjusting for differences in the probability of dying of causes other than cancer among subjects. Patients who died of intercurrent disease or who were lost to follow-up were censored at the time of last known follow-up. Relative survival was calculated as the ratio of observed survival to expected survival, with respect to stage, age and calendar year at diagnosis. Differences between survival probabilities were analyzed with the log-rank test. Variables influencing survival probabilities were evaluated with the Cox proportional hazard regression model (Mantel 1966). A p-value <0.05 was considered to indicate statistical significance.

Table 2 shows the survival analysis for three years**.** The overall survival of patients were 100%, 85%, 89, 80%, 75%, and 100% and disease free survival were 100%, 64%, 61%, 63%, 44% and 100% for the patients with the age group of less than 30 years, 40 years,50 years, 60 years, 70 and 80 years. For Stage IA, IB, IIA, IIB, IIIB and IVA overall survival were 100%,94%, 94%,81%,42% and 33% and disease free survival were 100%, 87%, 70%,61%,55% and 33%. The overall survival (OS) of patients for grade I is 89%, grade II is 88%, and grade III is 89% and the disease free survival (DFS) of patients with grade I is 75% , grade II is 67% , grade III is 54%. OS and DFS for pathology were 89% and 85% for SCC, and 65% and 70% for ASC. For histology types LCNK and LCK the OS are 82% and 87%, 66% and 70% are disease free survival. For the patients in 2002 who got only RT treatment alone the OS is 84% and DFS is 63%, for RT and CT is 75% and 50%.

As shown in table 3, the cervical cancer patients with age above 50 years showed a 1.6 fold higher risk of failure than patients with below 50 years of age with a statistical significance of $p=0.022$. Patients with advanced stage also showed similar risk of 1.6 times higher risk of failure with a significant p value of 0.023 than with early stage. Combination treatment of Radiotherapy and Chemotherapy showed the treatment failure risk of 2.3 times than Radiotherapy alone with a statistical significance of $p=0.003$. Adenocarcinoma had 87% higher risk of

Table 2: Survival analysis for the three years (2001-2003)

		Total Samples N = 416			
Group	*Variable*	*N*	*OS %*	*DFS%*	*P - Value*
Age in years	21 – 30	8	100	100	0.435
	31 – 40	80	85	64	
	41 – 50	148	89	61	
	51 – 60	123	80	63	
	61 – 70	48	75	44	
	71 – 80	8	100	100	
Stage	IA	1	100	100	<0.001
	IB	20	94	87	
	IIA	19	94	70	
	IIB	159	81	61	
	IIIB	203	80	55	
	IVA	10	42	33	
	IVB	3	33	0	
Tumourgrade	I	30	89	75	0.737
	II	176	88	67	
	III	209	89	54	
Pathology	SSC	393	89	65	0.223
	ADC	23	85	70	
Histology	LCNK	375	82	66	0.897
	LCK	41	87	70	
RT/CT	RT	379	84	63	0.094
	RT+CT	37	75	50	

OS – overall survival; DFS – Disease free survival; significant p Value p<0.05; SSC-Squamous cell carcinoma; ADC-Adenocarcinoma; LCNK-Large cell non keratinizing; LCK-Large cell keratinizing; RT-Radiotherapy; CT-Chemotherapy

Table 3: Univariate analysis for clinicopathological parameters as prognostic factors

Parameters	*N*	*DFS(%)*	*Relative Risk*	*95% CI*	*p-value*
Age (in years)					
Below 50	236	79	1		
Above 50	180	71	1.6	0.384 – 0.928	0.022
Stage					
Early	200	78	1		
Advanced	216	71	1.624	1.064-2.477	0.023
Tumour Grade					
I	30	83	1		
II	176	77	0.889	0.372 - 2.121	0.79
III	209	73	1.232	0.529 - 2.868	0.628
Pathology					
SCC	393	75	1		
ADC	23	58	1.876	0.908 - 3.877	0.089
Histology					
LCNK	375	74	1		
LCK	41	82	0.748	0.346 - 1.616	0.46
RT/CT					
RT	379	77	1		
+CT	37	54	2.285	1.313 -3.976	0.003

DFS – Disease free survival; significant p Value - p<0.05; 95% ; 95% confidence Interval; SSC-Squamous cell carcinoma; ADC- Adenocarcinoma; LCNK-Large cell non keratinizing; LCK-Large cell keratinizing; RT-Radiotherapy; CT- Chemotherapy

failure than squamous cell carcinoma though no statistical significance has been obtained.

In Figure 3, the graph shows the overall survival (involving all the patients in the study) with a follow-up of 60 months which was 88.3%. The log rank test was used to compare the overall survival with the survival of the patients with squamous cell carcinoma and adenocarcinoma.

Figure 4 shows the overall survival of all 416 patients in the study compared to the survival in the group with Radiotherapy alone or radiotherapy along with chemotherapy.

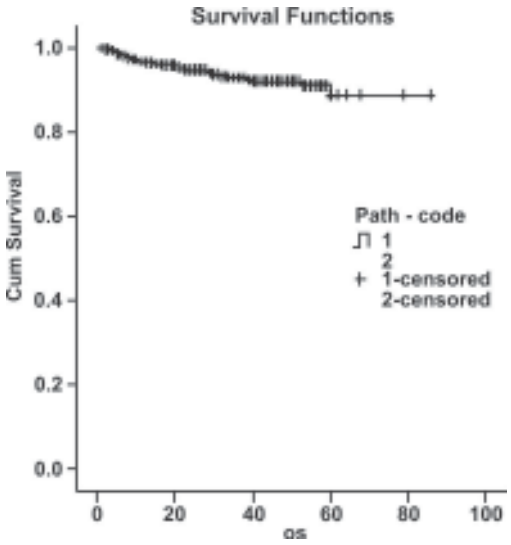

Fig. 3. Distribution of women in relation to survival and pathology at presentation.

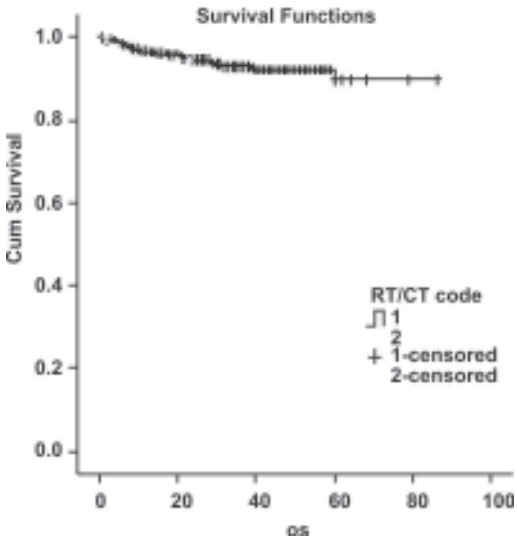

Fig. 4. Distribution of women in relationsurvival and treatment at presentation.

DISCUSSION

Cervical cancer Carcinomas of the anogenital tract — particularly cancer of the cervix, account for almost 12% of all cancers in women, and so represent the second most Frequent gynaecological malignancy in the world (Harald zur Hausen 2002). The incidence of cervical cancer from 2001 to 2003 is 32.6% to 28.3% indicating a decrease in the incidence of cervical cancer. It is still the second most common cause of mortality in women though there is decrease in incidence of cervical cancer, which was similar to the results of previous reports. (Ciatto et al. 1995).

Our result shows that the occurrence of cervical cancer is less in younger women (below 30 years) and older women (above 70 years), is in agreement with previous published results of Surveillance Epidemiology and End Results (SEER 2009). Relative 5-year survival for cervical cancer has been reported to be lower in older women in Japan. Lower survival among older women was caused mainly by the presence of more advanced disease at diagnosis (Akiko Loka et al. 2005). The same was observed in our study, patients with age group of above 50 years had a lower survival rate and higher failure rate and old age resulted as one of the prognostic factors.

The incidence of squamous cell carcinoma of the cervix has been failing for some time, although that of adenocarcinoma of the cervix is now rising (Wang et al. 2004; Bray et al. 2005). Small cell carcinoma and adenocarcinoma were associated with poorer survival (Vinh-hung et al. 2007). Women with adenocarcinoma of the uterine cervix have an intrinsically increased risk of death compared with women with squamous cell carcinoma (Burger et al. 1996). Patients with cervical adenocarcinoma were slightly younger at diagnosis than patients with squamous cell carcinoma, 48 and 50 years, respectively.

Viladiu et al. (1977) identified clinical stage as the only independent prognostic factor. Advanced stage was identified as a prognostic factor in our study. The survival rate of advanced stage patients is also less. The prognostic models of age and stage are powerful in predicting death and relapse. Longest survival was for patients with early stage disease, younger patients and after primary surgery. We found International Federation of Gynecology and Obstetrics (FIGO) stage, grade and lymph node metastases of significant prognostic value for survival in cervical adenocarcinoma (Baalbergen et al. 2004).

Radiation therapy along with surgery is the most effective mode of treatment for cervical cancer. However, treatment failures have been encountered even after radiotherapy, and postirradion adjuvant hysterectomy or chemotherapy may be recommended for such cases (Nagai et al.

2004). Cervical cancer treatment by radiotherapy is often encountered with local recurrence (3-8% for stage I to 45% for stage III) (Hunter et al. 1986) .Conflicting reports have been found in the timing of recurrence, most recurrence in cervical carcinoma occurs within 5 years after the initial radiation therapy as we got the results in our study, more than 5 years have been reported in few cases (Sakurai et al. 2001).

CONCLUSION

After analyzing the age, tumor size, staging, histological grades and pathological classifications such as squamous and adenosquamous carcinoma of the patients using Cox regression model, we found that only clinical stage ($p<0.001$) was the independent prognostic factor. It meant that the higher the clinical stage was, the poorer the prognosis would be. Thus, longest survival was for patients with early stage disease, younger patients and after primary surgery.

Deaths due to cervical cancer are projected to rise by almost 25% over the next ten years. Prevention of these deaths by adequate screening and treatment will contribute to the achievement of the Millennium Developmental Goals. The biggest impacts of cervical cancer are on poverty, education, and gender equity – the first three Millennium Developmental Goals (MDGs). It should be noted that lower levels of female education are linked to decreased maternal and infant health, and the differential economic and social impact on women and girls makes it more difficult to achieve gender equity. There are many barriers to realize this potential, such as the current high cost of HPV vaccine, weakness of existing cervical cancer screening and adolescent health systems, and low levels of knowledge about HPV, which are now being challenged. With sufficient political will and resources, these barriers surely can be overcome in the interest of the family and the Millennium Developmental Goals (Willet and Tsu 2008).

Cervical cancer is one of the most preventable and treatable forms of cancer, as long as it is detected early and managed effectively. A great deal of experience and evidence-based knowledge is available for the prevention (and treatment) of cervical cancer and related mortality and morbidity. In particular, this guide seeks to ensure that there is lot of decrement in the mortality rate of the cervical cancer patients.

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