Clinicopathological, but not socio-demographic factors affect the prognosis in cervical carcinoma

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Abstract. The purpose of this study was to investigate the prognostic factors, such as clinical, histological and socio-demographic features affecting the event-free and overall survival of the patients with stage I-III carcinoma of the cervix. Eighty-nine patients with International FIGO stage I-III cervical cancer were treated radiation therapy and follow-up of 5-7 years were analyzed for various clinical, histopathological and socio-demographic factors influencing prognosis. Survival estimations were performed using the Kaplan-Meier method, and were compared using the un-weighted log-rank test and multivariable analysis using the Cox proportional hazards model. The median age was 46 years (range, 28-65 years). The 5-year event-free survival (EFS) and overall survival (OAS), along with standard error (SE), were 65.2% (7.0%) and 81.4% (6.1%), respectively. Significant prognostic factors for EFS include, stage (P=0.019), pelvic lymph node metastasis (P=0.013), parametrial (PMT) involvement (P=0.025), number of parametria involved (P=0.000) and tumor size (P=0.034). However, number of parametrial invasion was only significant prognostic factors for overall survival (P=0.015); 5-year survival rate was significantly lower in patients with both PMT involved (58%) than with one PMT involved (>85%). Using a multivariable analysis, we found that number of PMT involved being the only independent significant factor for the development of recurrent disease. None of the socio-demographic factors analyzed were of prognostic importance on event-free and overall survival in cervical cancer patients. Several clinicopathological factors were of prognostic significance but none of the socio-demographic factors analyzed had any role in determining patient outcome. Hence, in cervical cancer, prognosis is more likely dependent on clinical than socio-demographic factors unlike several other cancers where their significant role is well documented. Study of clinical and demographic characteristics for their influence on patient survival could help design better patient management strategies.

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Introduction

Cervical cancer is the second most common cancer among women after breast cancer and is a major cause of mortality worldwide (1). It occupies the top rank among cancers in women in most developing countries, constituting 34% of all women's cancers and is the most common cancer among women in Southern India. To an estimated annual global incidence of approximately 500,000 cervical cancers, India contributes nearly 1/5 of the world burden (2). The magnitude of the problem is thus more than evident. The world pattern of cervical cancer, together with the age-adjusted rate and ranking, clearly indicate that cervical cancer is predominantly a problem of poorer socio-economic societies (1).

Radiation therapy has been widely used in the treatment of patients with carcinoma of the uterine cervix for the last 80 years (3). The treatment involves a combination of external beam radiation therapy (EBRT) followed by intracavitary radiation treatment (ICRT). High dose-rate intracavitary brachytherapy (HDRICB) has been widely used in Asia and Europe, despite its questionable radiobiological efficacy (4). Definitive radiation therapy alone or irradiation combined with surgery has been established as effective treatment for locally-advanced cervical cancer (5). Several studies have also shown advantages of cisplatin-based chemotherapy given concurrently with RT (6-9).

Many investigators have emphasized the importance of patient characteristics (age, and anemia), tumor (stage, size, lymph node, and grade) and treatment factors (treatment modality, irradiation technique, dose, and duration) and indicated influence on outcome (10-14).

Socio-demographic factors have been found to be of significance in prognosis of many advanced cancers such as head

and neck (15), oral (16) and breast cancer (17,18). However, not many studies have concentrated on the socio-demographic factors for their potential prognostic importance. Hence, analyses of clinical, histopathologic and socio-demographic factors that could influence the survival would be of great importance and could be taken into consideration when selecting treatment options.

The current study analyzes the relative importance of clinical and histopathologic factors such as stage, nodal status, parametrial invasion, number of involved parametria, histology, grade, tumor size and treatment modalities; and several socio-demographic parameters such as age, education, marital status, consanguinity, age at 1st intercourse, age at first pregnancy, number of pregnancies, abortions, addictions and family history of cancer with regard to treatment outcome in patients with cervical carcinoma treated.

Materials and methods

Patient characteristics. In this study 89 patients diagnosed with invasive carcinoma of the cervix and treated at the Cancer Institute, Chennai, India between 2000 and 2005 were enrolled. All patients belonged to below poverty line of the economic strata and were admitted in the in-patient general ward of the hospital during the course of the treatment. Patients were evaluated by medical history and physical examination. Routine blood counts and chemistry profiles were performed. All patients had a chest X-ray. Some patients underwent a lymphangiogram, intravenous urogram, computed tomographic scan of the abdomen and pelvis, and barium enema. All patients underwent a pelvic examination by gynecological and radiation oncologist. Their pathological reports had any one of the following findings: pelvic lymph node metastasis, parametrial invasion, positive surgical margins, lymphovascular invasion or stromal invasion of more than two thirds of the cervical thickness. The patient's disease was classified according to FIGO (International Federation of Gynecology and Obstetrics).

The patient characteristics are presented in Tables II and III as predictive factors of event-free (EFS) and overall survival (OAS). The median age was 46 years (range, 28-65 years; interquartile range, 15). Eleven patients had stage I, 48 patients had stage II and 30 patients had stage III disease. Tumor size was <4 cm in 25 patients and ≥4 cm in 64 patients. Seventy-eight patients had histology of squamous cell carcinoma and 11 patients had adenocarcinoma. Thirty-nine patients had lymph node metastasis and 50 patients had no pelvic lymph node metastasis. Sixty-seven patients had PMT (Parametrial) invasion whereas 22 patients had no PMT invasion. Among patients with PMT involvement 36 had unilateral and 31 had bilateral PMT involvement. The primary mode of therapy was radiation alone for the bulk of the study period (2000-2005). It was only in the year 2005-2006 that chemoradiation was introduced for all patients, prior to this only patients with very advanced disease/poor grade received chemotherapy. Seventy-seven patients received radiation therapy alone, 5 patients underwent radiation therapy and surgery, and 7 patients were treated with radiation and chemotherapy of 3-5 cycles weekly of cisplatin (CDDP). All patients were followed for a minimum of 5 and maximum of 7 years.

Radiation therapy

External beam therapy. Patients were treated with 4 or 6 MV X-rays from a linear accelerator. Commonly employed field arrangement was 4 fields box technique: 1 anterior, 1 posterior and 2 lateral fields. The superior border of the pelvic portal was at the L4-L5 interspace to include all the external iliac and hypogastric lymph nodes. This margin was extended to L3-L4 interspace if common iliac nodal coverage was indicated. If there was no vaginal extension, the lower margin of the portal was at the inferior border of the obturator foramen. If there was vaginal involvement, the entire length of the vagina up to introitus was treated. The lateral margins were outside the pelvic brim by about 1 cm. The anterior margin of the lateral portal was at the public symphysis. Posterior margin was usually designed to cover the sacral hollow in more advanced tumors. The field width is commonly 14-15 cm and the field length 15-17 cm. Dose delivered was 200 cGy/day.

Intracavitary application. Intracavitary application was by using LDR-Cs-137 or HDR-Lr-192. When initial whole pelvic irradiation was given as a dose of 40 Gy delivered in 20 fractions over 4 weeks, the LDR intracavitary application which followed delivered, a further dose of 30 Gy at point A or 3 HDR applications of 800 cGy each, to a total dose of 24 Gy. When initial whole pelvic irradiation was given as a dose of 50 Gy delivered in 25 fractions over 5 weeks, the LDR intracavitary application which followed delivered, a further dose of 23 Gy at point A or 2 HDR applications of 800 cGy each, to a total dose of 16 Gy. Dose to point A, point B, bladder and rectum were reported as per ICRU-38 (International Commission on Radiation Units and Measurements) recommendations.

Response evaluation. After completion of treatment, each patient underwent regular follow-up every month for 3 months; then every 3 months during the first year; every 4 months during the second year; every 6 months in years 3, 4 and 5; and yearly thereafter. A pelvic examination was performed during each follow-up. Pap smear was performed every 6 months. Radiographic examinations [chest X-ray, abdomino-pelvic Magnetic Resonance Imaging (MRI)] were conducted every year. Treatment failure was defined either by pathological proof of recurrence or by image study showing recurrence of tumor or enlargement of lymph nodes. Acute and late toxicities derived from treatments were scored according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) grading scale (19).

Statistical analysis. Descriptive statistics derived from the study population included patient characteristics, treatment and prognostic factors. The event-free survival (EFS) was defined as the time from the end of treatment to local failure, systemic failure or death resulting from any cause, whichever occurred first. Patients who were alive without local failure or systemic failure were classified as censored observations at the time of the last follow-up for EFS. The overall survival (OAS) was defined as the time from the end of treatment to death resulting from any cause. Patients who were alive were classified as censored observations at the time of the last

Table I. Patients with disease progression or recurrence.

Patient no.	Age	Stage	Histology	Grade	Initial response	Time to failure (months)	Site of failure	Outcome[a] (months)
1	49	I B	ADC	II	SR	2	Nodes	NED, 67
2	60	I B	ADC	II	SR	14	Nodes	SM, 64
3	55	I B	ADC	III	PR	41	Nodes	NED, 41
4	60	II B	ADC	II	SR	22	Thyroid	SM, 66
5	28	II B	SCC	II	PR	24	Nodes	NED, 31
6	60	II B	SCC	III	PR	16	Nodes	DOD, 16
7	43	II B	SCC	III	PR	2	Local	PD, 9
8	55	II B	SCC	III	PR	2	Local	DOD, 8
9	40	II B	SCC	III	PR	2	Local	DOD, 8
10	34	II B	ADC	III	PR	2	Local	PD, 20
11	42	II B	SCC	III	PR	16	Local	PD, 16
12	59	II B	SCC	III	PR	12	Local	DOD, 34
13	47	II B	ADC	III	PR	5	Local	DOD, 5
14	62	II B	ADC	III	PR	3	Local	NED, 72
15	60	II B	SCC	III	PR	6	Nodes	SM, 6
16	29	III B	SCC	III	PR	2	Local	DOD, 13
17	45	III B	SCC	III	PR	2	Local	PD, 7
18	52	III B	SCC	III	PR	6	Local	PD, 7
19	50	III B	SCC	III	PR	18	Local	PD, 18
20	46	III B	SCC	III	PR	14	Nodes + Local	PD, 14
21	55	III B	SCC	III	PR	4	Local	DOD, 4
22	35	III B	ADC	II	PR	2	Local	DOD, 28
23	46	III B	SCC	III	PR	3	Local + Nodes	SM, 74
24	52	III B	SCC	III	PR	12	Local	PD, 23
25	45	III B	SCC	III	PR	42	Bone	SM, 42
26	32	III B	SCC	III	PR	4	Local	PD, 32
27	52	III B	SCC	III	PR	14	Nodes	NED, 80
28	30	III B	SCC	III	PR	2	Local	DOD, 40
29	52	III B	SCC	III	PR	4	Local	NED, 5
30	35	III B	SCC	III	PR	2	Local	DOD, 34
31	45	III B	SCC	III	PR	2	Local	DOD, 6

SCC, squamous cell carcinoma; ADC, adenocarcinoma; PR, partial response; SR, satisfactory response; PD, progressive disease; SM, second malignancy; DOD, died of disease; NED, no evidence of disease. [a]Outcome, status of the patient till the available last follow-up.

follow-up for OAS. Survival estimations were performed using the Kaplan-Meier method, and were compared using the unweighted log-rank test and multivariable analysis using the Cox proportional hazards model (20). All calculations were performed with SAS statistical software (version 9.2; SAS Institute Inc., Cary, NC).

Results

Actuarial failure rate and pattern of failure. The 5- and 7-year EFS was 65.2 and 60.0% respectively, whereas 5- and 7-year OAS was 81.4 and 78.4%, respectively. Thirty-one of 89 (34.8%) patients developed recurrent disease at the following sites: 20 in pelvis only, 2 in pelvis with distant metastasis and 9 with distant metastasis. Recurrent disease occurred from 2 months to 42 months (mean 9.7 months) (Table I). Three of 11 stage I (27.2%), 12 of 48 stage II (25%) and 17 of 30 stage III (53.3%) developed recurrent disease.

Risk factors predicting survival

Univariable analysis. Univariable analysis of prognostic factors of 5- and 7-year EFS and OAS are shown in Tables II and III. As evident in Tables II and III, 5- and 7-year EFS and OAS rates were similar for several prognostic factors;

Table II. Patient characteristics and predictive factors of EFS.

			Event-free survival				
			5-year		7-year		Univariate analysis
Characteristics	No.	(%)	(%) EFS	(%) SE	(%) EFS	(%) SE	P-value
All	89	100	65.2	7	60	37.9	
Age (years)							0.106
≤50	32	36.0	82.2	8.9	75.4	37.4	
>50	57	64.0	54.3	9.5	50.1	35.4	
Education[a]							0.642
No	79	88.8	64.8	7.7	61.6	38.2	
Yes	10	11.2	71.4	15.6	57.1	26.5	
Marital status							0.776
Currently married	77	86.5	64.0	7.5	61.1	38.1	
Previously married	12	13.5	73.3	16.9	48.9	35.0	
Consanguinity							0.471
No	42	47.2	70.2	8.8	65.5	11.6	
Yes	47	52.8	58.6	10.9	52.8	36.3	
Age at 1st intercourse							0.528
≤17	52	58.4	70.7	9.3	65.2	38.5	
>17	37	41.6	59.8	10.1	54.8	36.8	
Age at puberty							0.514
≤14	35	39.3	57.1	11.3	49.0	35.0	
>14	54	60.7	70.1	8.6	66.3	38.5	
1st pregnancy							0.098
≤18	51	57.3	58.1	9.7	52.9	36.3	
>18	38	42.7	74.3	9.4	68.9	38.4	
No. of pregnancies							0.742
≤3	57	64.0	69.4	8.4	60.7	11.5	
>3	32	36.0	57.1	11.8	57.1	37.4	
Abortions							0.909
Yes	16	18.0	63.2	13.6	65.8	8.0	
No	73	82.0	65.8	8.0	58.5	37.7	
Menopause attained							0.511
Yes	53	59.6	74.6	8.9	63.9	38.4	
No	36	40.4	55.1	10.7	55.1	36.9	
Addictions[b]							0.800
No	73	82.0	65.5	14.5	65.6	38.5	
Yes	16	18.0	64.5	8.0	58.7	37.7	
Family history of cancer							0.172
Yes	12	13.5	21.4	13.4	21.4	19.0	
No	77	86.5	70.6	7.1	64.7	0.4	
Locality							0.569
Rural	76	85.4	64.9	7.3	59.3	37.8	
Urban	13	14.6	61.5	22.0	61.5	21.0	
Stage							0.019
I	11	12.4	68.2	15.7	68.2	27.2	
II	48	53.9	85.1	7.5	80.3	35.6	
III	30	33.7	36.6	11.9	29.3	14.2	

Table II. Continued.

Characteristics	No.	(%)	Event-free survival 5-year (%) EFS	5-year (%) SE	7-year (%) EFS	7-year (%) SE	Univariate analysis P-value
Nodal status							0.013
Negative	39	43.8	74.1	7.7	74.1	37.7	
Positive	50	56.2	52.2	13.6	26.1	22.4	
PMT invasion							0.025
Negative	22	24.7	81.8	11.6	81.8	15.6	
Positive	67	75.3	59.6	8.3	53.0	36.3	
PMT involvement							0.000
None	22	24.7	80.0	12.6	80.0	17.9	
One	36	40.4	78.6	9.1	72.6	3.8	
Both	31	34.8	39.7	11.7	33.1	13.5	
Histotype							0.313
SCC	78	87.6	66.7	7.7	63.8	38.4	
ADC	11	12.4	58.4	15.4	29.2	24.6	
Grade							0.643
Grade I	4	4.5	N/A	N/A	N/A	N/A	
Grade II	5	5.6	50.0	25.0	50.0	35.4	
Grade III	80	89.9	64.9	7.1	59.5	37.9	
Tumor size (cm)							0.034
<4	25	28.1	82.9	9.9	82.9	34.3	
≥4	64	71.9	57.1	8.8	48.9	35.0	
Type of treatment							0.425
Radiation alone	77	86.5	66.6	7.7	63.3	38.3	
Radiation + surgery	5	5.6	66.7	22.2	66.7	38.5	
Radiation + chemotherapy	7	7.9	51.4	17.9	34.3	27.8	

EFS, event-free survival; SE, standard error; SCC, squamous cell carcinoma; ADC, adenocarcinoma. [a]Education: Yes, attended school (know to read and write); No, never attended school (illiterate). [b]Addictions: Yes, addiction to tobacco, tobacco-products or betel nut; No, no addiction to tobacco, tobacco-products or betel nut.

hence, 5-year survival is discussed in detail. EFS in the log-rank test, stage (P=0.019), pelvic lymph node metastasis (P=0.013), parametrial (PMT) invasion (P=0.025), number of parametria involved (P=0.000) and tumor size (P=0.034) were significant prognostic factors for 5-year EFS, favoring early stage of the disease, tumor size <4 cm, and absence of pelvic lymph node metastasis, no parametrial invasion and unilateral parametrial involvement, respectively. Stage II patients had 85.1% rate of 5-year EFS compared with that of stage III patients who had only 36.6% rate. Stage I patients had rate of EFS of 68.2%, this could be due to the fact that 3 (27.2%) of 11 stage I patients had positive lymph nodes (Fig. 1). The patients without pelvic lymph node metastasis had a 5-year EFS rate of 74.1 versus 52.2% for the patients with pelvic lymph node metastasis (Fig. 2). No parametrial invasion had higher rate of 5-year EFS (81.8%) compared to that of patients with parametrial invasion (59.6%) (Fig. 3). Number of parametria involved was also a significant prognostic factor in patients with no parametrial invasion had somewhat higher rate of 5-year EFS (80.0%) compared to patients with one or both parametrial invasion (78.6 and 39.7%, respectively) (Fig. 4). Patients whose tumor size was <4 cm had a higher 5-year EFS (82.9%) versus those whose tumor size was ≥4 cm (57.1%) (Fig. 5). There was no evidence of a relation between EFS and grade of tumor, histology and treatment modalities. None of the socio-demographic factors were found to be associated with EFS.

In case of OAS, PMT involvement was the only significant prognostic factor favoring no or unilateral PMT involvement over bilateral PMT invasion of tumor (Fig. 6). Patients with none or unilateral invasion had 80.0% and 97.1% rate of 5-year OAS compared to patients with bilateral PMT invasion

Table III. Patient characteristics and predictive factors of OAS.

			Overall survival				
			5-year		7-year		Univariate analysis
Characteristics	No.	(%)	(%) OAS	(%) SE	(%) OAS	(%) SE	P-value
All	89	100	81.4	6.2	78.4	36.4	
Age (years)							0.361
≤50	32	36.0	90.4	7.2	82.9	34.3	
>50	57	64.0	75.3	9.1	75.3	37.4	
Education[a]							0.134
No	79	88.8	77.8	7.2	74.1	0.4	
Yes	10	11.2	100.0	0.0	100.0	0.0	
Marital status							0.179
Currently married	77	86.5	78.8	7.0	75.2	37.4	
Previously married	12	13.5	100.0	0.0	100.0	0.0	
Consanguinity							0.725
No	42	47.2	87.1	7.2	81.3	10.6	
Yes	47	52.8	74.3	10.1	74.3	37.7	
Age at 1st intercourse							0.439
≤17	52	58.4	78.8	8.8	72.8	38.0	
>17	37	41.6	84.3	8.4	84.3	33.4	
Age at puberty							0.581
≤14	35	39.3	75	10.4	75	37.5	
>14	54	60.7	85.7	7.2	80.9	35.3	
1st pregnancy							0.124
≤18	51	57.3	74.1	9.4	74.1	37.7	
>18	38	42.7	90.0	6.9	84.0	33.6	
No. of pregnancies							0.351
≤3	57	64.0	88.6	6.2	83.7	10.2	
>3	32	36.0	66.7	12.2	66.7	38.5	
Abortions							0.328
Yes	16	18.0	88.9	9.9	88.9	29.6	
No	73	82.0	79.7	7.3	75.5	37.4	
Menopause attained							0.167
Yes	53	59.6	90.9	6.3	84.9	33.0	
No	36	40.4	70.5	10.6	70.5	38.3	
Addictions[b]							0.995
No	73	82.0	87.1	11.8	87.1	31.3	
Yes	16	18.0	80.0	7.2	76.7	3.7	
Family history of cancer							0.372
Yes	12	13.5	53.3	2.1	53.3	36.4	
No	77	86.5	84.5	6.1	81.1	35.2	
Locality							0.807
Rural	76	85.4	80.7	6.7	77.5	36.8	
Urban	13	14.6	90.9	15.8	90.9	19.4	
Stage							0.115
I	11	12.4	100.0	0.0	100.0	0.0	
II	48	53.9	88.7	6.9	83.7	33.8	
III	30	33.7	61.1	14.4	61.1	22.0	

Table III. Continued.

Characteristics	No.	(%)	Overall survival 5-year (%) EFS	5-year (%) SE	7-year (%) EFS	7-year (%) SE	Univariate analysis P-value
Nodal status							0.567
Negative	39	43.8	82.3	6.9	82.3	34.6	
Positive	50	56.2	74.1	13.3	59.2	0.4	
PMT invasion							0.471
Negative	22	24.7	81.8	11.6	81.8	15.6	
Positive	67	75.3	81.1	7.4	77.0	36.9	
PMT involvement							0.015
None	22	24.7	80.0	12.6	80.0	17.9	
One	36	40.4	97.1	3.9	90.7	27.7	
Both	31	34.8	57.9	14.2	57.9	18.8	
Histotype							0.252
SCC	78	87.6	82	6.8	82	34.8	
ADC	11	12.4	77.1	13.9	51.4	35.8	
Grade							0.705
Grade I	4	4.5	N/A	N/A	N/A	N/A	
Grade II	5	5.6	50.0	25.0	50.0	35.4	
Grade III	80	89.9	82.5	6.1	79.3	36.1	
Tumor size (cm)							0.664
<4	64	71.9	79.3	8.1	74.3	37.7	
≥4	25	28.1	84.6	0.1	84.6	0.3	
Type of treatment							0.334
Radiation alone	77	86.5	77.9	7.2	74.2	37.7	
Radiation + surgery	5	5.6	100.0	0.0	100.0	0.0	
Radiation + chemotherapy	7	7.9	100.0	0.0	100.0	0.0	

OAS, overall survival; SE, standard error; SCC, squamous cell carcinoma; ADC, adenocarcinoma. [a]Education: Yes, attended school (know to read and write); No, never attended school (illiterate). [b]Addictions: Yes, addiction to tobacco, tobacco-products or betel nut; No, no addiction to tobacco, tobacco-products or betel nut.

who had only 57.9% rate of OAS. No other clinical, histopathological and socio-demographic factors had any prognostic importance on OAS.

Multivariate analysis. The risk of pelvic failure depends on tumor stage, tumor size, nodal status, parametrial invasion and number of parametria involved. Cox multivariate analysis was performed to evaluate the role of these prognostic factors in the development of recurrent disease in the pelvis. Only number of parametria involved was of significance for development of recurrent disease (Table IV).

Analyses for association of stage of the disease with selected demographic and clinical factors such as age at 1st pregnancy, family history of cancer, nodal status, PMT invasion, number of PMT involved and tumor size was performed (Table V). Only PMT invasion and number of PMT involved were found to have association with the stage of the disease. Factors such as age at 1st pregnancy, family history of cancer and tumor size show a trend of association but failed to achieve statistical significance.

Discussion

Radiotherapy is an effective treatment modality for all stages of cervical cancer and is widely used in developing countries (21). The conventional treatment of local tumors is radiation therapy, surgery or a combination of both modalities. Chemotherapy on other hand is used for treatment of systemic disease. Chemotherapy is also known to increase the sensitivity of the tumor to radiation (22,23). Several prognostic factors influencing survival in cervical cancer patients have been established so far. These include host related, clinical

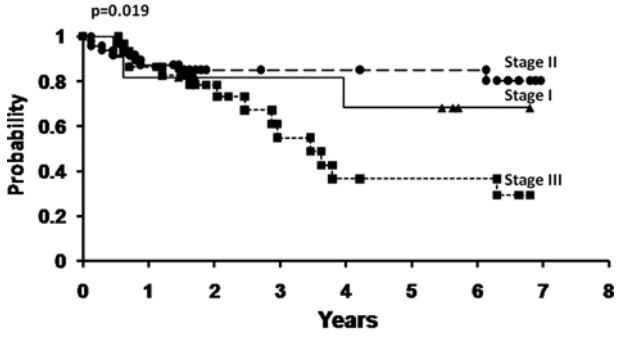

Figure 1. Event-free survival in cervical cancer patients by stage (n=89).

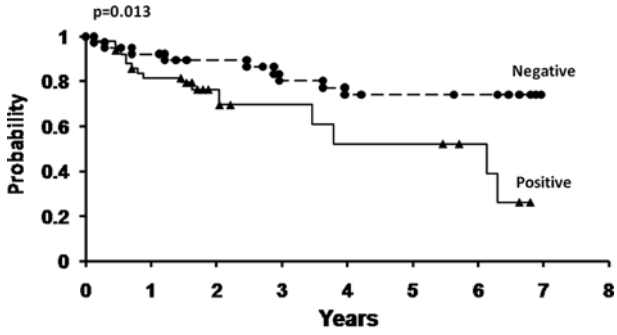

Figure 2. Event-free survival in cervical cancer patients by nodal status (n=89).

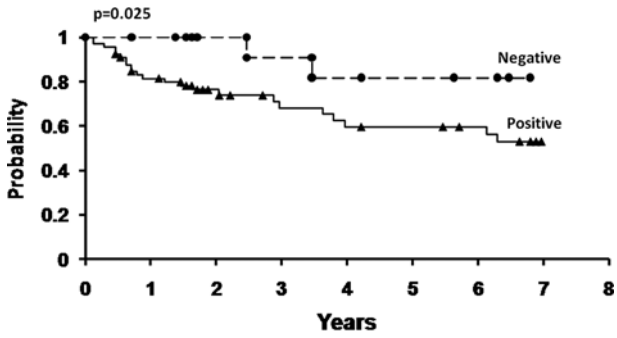

Figure 3. Event-free survival in cervical cancer patients by PMT invasion (n=89).

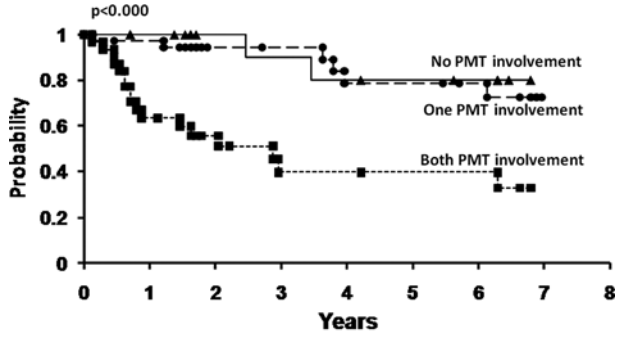

Figure 4. Event-free survival in cervical cancer patients by PMT count (n=89).

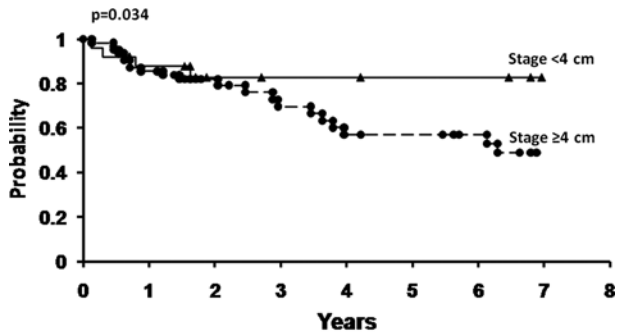

Figure 5. Event-free survival in cervical cancer patients by tumor size (n=89).

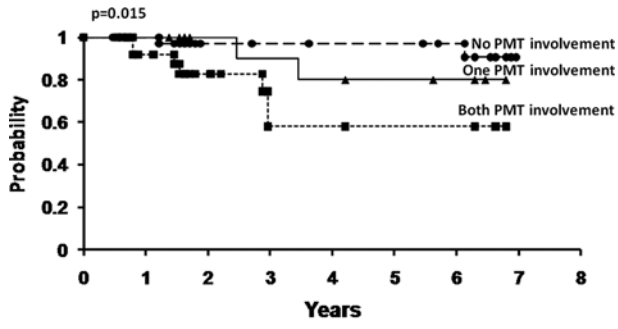

Figure 6. Over-all survival in cervical cancer patients by PMT count (n=89).

and treatment related factors (5,10-12). In this study clinical, histopathologic and socio-demographic factor were analyzed to assess their prognostic significance.

Of the 31 patients with recurrent disease 20 (64.5%) developed in the pelvis only, 2 (6.5%) developed in the pelvis with distant metastasis and 9 (29.0%) had distant metastasis alone. Recurrent disease occurred as early as 2 months to as delayed as 3.5 years. Early stage of disease had lower recurrent rates (27.2% and 25% for stage I and II disease, respectively) compared with advanced stage III tumors (53.3%).

Clinical stage of cervical tumor is the most important and consistent predictor for survival in patients with carcinoma of the cervix. The 5-year event-free survival was significantly lower in stage III patients compared to early stage patients. Stage I patients had slightly higher recurrent rates compared to stage II, this could be because stage I had only 11 patients and also that 3 (27.2%) of them had positive lymph node status. Stehman *et al* reported similar trend with stage I

Table IV. Multivariable analysis for recurrence.

Prognostic factor	Hazard ratio	95% CI	P-value
Stage	1.0	0.473-1.969	0.922
Nodal status	0.5	0.208-1.207	0.123
Positive PMT	1.7	0.238-12.835	0.582
No. of PMT	3.9	1.443-10.396	0.007

Table V. Association of stage of the disease with selected clinical and demographic factors.

Patient characteristics	Stage I (n=11)	Stage II (n=48)	Stage III (n=30)	P-value
Age (years)				0.95
≤50	7	31	19	
>50	4	17	11	
1st pregnancy				0.089
≤18	5	25	21	
>18	6	23	9	
Family history of cancer				0.096
Yes	1	4	7	
No	10	44	23	
Nodal status				0.648
Negative	7	24	19	
Positive	4	24	11	
PMT invasion				0.027
Negative	6	34	26	
Positive	5	14	4	
PMT involvement				<0.001
None	5	13	4	
One	4	24	8	
Both	2	11	18	
Tumor size (cm)				0.105
<4	2	20	3	
≥4	9	28	27	

patients who had positive PA lymph nodes (24). Many investigators found FIGO stage to be an independent prognostic factor for disease-free survival as well as overall survival (5,25,26).

In addition to clinical stage, nodal involvement has an obvious impact on prognosis. FIGO system of staging does not include evaluation of lymph nodes. Surgical staging is the definitive method of assessing nodal status, patients with positive lymph nodes were significantly prone to recurrence with lower 5-year EFS rates compared to patients with negative lymph nodes (26,27). A similar observation was made in this study where positive nodal status was associated with poorer EFS rates. However, it did not affect the OAS rates. Stehman *et al* (24) performed a multivariate analysis of prognostic variables in 626 patients and demonstrated that pelvic lymph node metastasis was a predictor for a poorer progression-free survival compared to patients with negative pelvic lymph nodes. This study, however, did not find lymph node involvement to be a prognostic factor for survival in multivariate analysis.

Parametrial invasion is an important criterion in FIGO staging, however, no distinction is made between one versus two involved parametria. In this study, the presence and absence of parametrial invasion as well as the extent of parametrial involvement (none versus one versus both) was analyzed. The results showed a significant reduction in 5-year EFS in patient with positive parametrial invasion (59.6%) compared with patients with negative parametrial invasion (81.8%). We also observed that the number of parametria involved had prognostic significance in both EFS and OAS and was an independent significant factor for poor prognosis in multivariate analysis. It should be noted that treatment plan might not change in view of bilateral involvement over unilateral involvement of PMT, as radiation treatment is given bilateral even for unilateral disease. However, Werner-Wasik *et al* (11) reported that the probability of recurrence increased with the number of involved parametria as did the probability of initial distant failure rather than a local failure. In another study Winter *et al* (28) reported the association of PMT involvement with several clinical factors and concluded that size of PMT metastasis was significantly associated with metastasis.

This study also suggested that the tumor size of ≥4 cm versus <4 cm was significantly (P=0.034) associated with decreased EFS and but not with OAS. Tumor size was shown to be a strong predictor of poor prognosis or early recurrence (10,12). Eifel *et al* (29), in a series of 1494 patients, found that disease-specific survival was 88% at 5-years for <5 cm, 69% for tumors 5-7.9 cm and 47% for tumors >8 cm. This illustrates that tumor size affects the outcome in a continuous fashion rather than in a step-wise fashion. Among other clinical factors analyzed grade, histology of tumor and treatment modalities were not associated with the outcome.

We observed association of stage of the disease with PMT invasion, and number of PMT involved. Factors such as age at 1st pregnancy, family history of cancer and tumor size show the trend of association but failed to achieve statistical significance. Small sample size precluded a definitive conclusion on association of stage of the disease with other clinical and demographic factors.

Socio-demographic factors have been identified as independent prognostic indicators or along with clinical factors (15,18). Recently, much emphasis has been laid on analyzing these factors and is assumed to be of much value in determining the overall well-being and survival of cancer patients. These demographic factors have been studied as potential risk factors for cervical cancer (30-32). However, studies with cervical cancer have not been analyzed for their potential role in prognosis of cervical cancer. Factors such as age, education, reproduction related factors such as marital status, consanguinity and age at 1st intercourse, age at first pregnancy, number of pregnancies and abortions; addictions and family history of cancer were analyzed for influence on EFS and OAS. Though age has been controversial prognostic factor, in this study age had no impact on the survival of cervical cancer patients. Our results suggested no significant correlation of the above mentioned demographic factors as prognostic indicators. In cervical cancer, unlike other cancers, clinical factors have more pronounced impact on the outcome than the demographic factors. However, the small sample size of this study should be taken into account before conclusions are drawn on their lack of prognostic importance.

In conclusion, clinical and pathological factors such as stage, nodal status, PMT invasion, number of parametria involved and tumor size were critical in dictating 5-year EFS in cervical cancer patients. Our study indicated that none of socio-demographic factors were of prognostic importance. These factors however, need to be further studied and validated in larger sample size, as influence of clinical and demographic characteristics on the patient outcome and survival could help in designing better patient management strategies.

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