

CLINICO-PATHOLOGICAL AND RADIOLOGICAL PROGNOSTIC FACTORS IN CANCER CERVIX TREATED WITH CONCURRENT CHEMORADIATION

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Abstract

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Introduction: Cervical cancer is most common cancer in the rural and second most common in urban areas of our country. It accounts for 16% of all cancers. There are various clinical, pathological and radiological factors which dictate the prognosis of these cancer cervix patients. The present study evaluates clinical, pathological and radiological prognostic factors in cancer cervix treated with concurrent chemoradiation.

Material and Methods: A total of 32 patients seen between 2012 and 2014 patients planned concurrent chemoradiation were evaluated in terms of clinical (age, stage, Hb% and HPV infection), pathological (histopathology type and subtype, grade, mitotic index, lymphovascular invasion and necrosis) and radiological (parametrial extension, disease dimension, lymph node, hydronephrosis and vascularity of tumour) prognostic factors. After pre-treatment evaluation patient was planned for 3 Dimensional - Conformal Radiotherapy (50Gy/25#/5 weeks) with concurrent chemotherapy (Cisplatin 35mg/m²) followed by 3 applications of Intracavitary radiotherapy (6Gy/fraction) with 6 months follow up. Response was assessed according to WHO response criteria and univariate analysis was done using chi-square test.

Results: Clinical factors: Age – better disease free survival in older patients (p value=0.003), stage - Lower stage had better survival (for stage Ib-IIa vs stage IIb p value = 0.003 and for stage Ib vs. IIIb p value = 0.0005), Hb% - 57% patients with Hb <10g/dl had recurrence at end of 6 months (p value=0.00001), HPV – High recurrence with HPV presence. Pathological factors like high Mitotic Index had more residual disease (p=0.0009), grade - No statistical significance. Radiological factors- volume of disease - 35 % patients with volume of disease > 6 cm had disease at end of 6 months, hydronephrosis - 40 % patient with hydronephrosis had recurrence (p value = 0.0005) at end of 6 months follow up and vascularity of tumour showed statistically no difference.

Conclusion: Hb <10%, HPV infection, Mitotic index (3-5/HPF), stage IIIB, pelvic nodes were concluded as the independent poor prognostic factors.

Keywords: Cervical cancer, concurrent chemoradiation, prognostic Factors.

INTRODUCTION

More than 85% of the global burden occurs in the developing countries where it accounts for 13% of all the female cancers¹ while in India it is 16% of all cancers (ICMR).² Cervical cancer is the second most common cancer in developing countries after carcinoma breast, but only the tenth most common in developed countries. Major risk factors identified in epidemiologic studies are sex at a young age, multiple sexual partners, and promiscuous male partners, history of sexually transmitted diseases, poor genital hygiene and smoking. Cervical cancer results from

genital infection with HPV (Human Papilloma Virus), which is a known human carcinogen.^{3,4}

Many prognostic factors have been recognized in the outcome of disease in patients with cancer cervix. These have been divided into patient related, tumour related and treatment related factors. The present study evaluates clinical, pathological and radiological prognostic factors in cancer cervix treated with concurrent chemoradiation.

MATERIAL AND METHODS

A total of 32 patients seen between 2012 and 2014 patients planned concurrent chemoradiation were evaluated in

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terms of clinical (age, stage, Hb% and HPV infection), pathological (histopathology type and subtype, grade, mitotic index, lymph-vascular invasion and necrosis) and radiological (parametrial extension, disease dimension, lymph node, hydronephrosis and vascularity of tumour) prognostic factors.

The inclusion criteria was biopsy proven cancer cervix, age >18 years, Karnofsky Performance Scale above 70, stage IA to IV, no history of previous malignancy, hepatic, renal, and cardiopulmonary functions adequate. The only exclusion criteria was metastatic disease.

Pre-treatment evaluation included a complete clinical history and physical examination including bimanual pelvic and rectal examination, cervical biopsy, baseline haematological tests (Haemogram, renal function tests, liver function tests) and chest radiography, ultrasound abdomen or CECT abdomen and pelvis (whichever is feasible), cystoscopy and proctosigmoidoscopy (only if clinically indicated). Treatment planned was 3 Dimensional Conformal Radiotherapy (50Gy/25#/5weeks) with concurrent chemotherapy (Cisplatin 35mg/m²) followed by 3 applications of Intracavitary radiotherapy (6Gy/fraction) with 6 months follow up.

RESULTS

Clinical factors (Table-1)

Age : Out of total of 32 cases studied patients in age group <50 years, 34% (8/23) had residual or recurrence \geq 6 months, 66 % had no evidence of disease while 11 % (1/9) of cases had residual or recurrence \geq 6 months and 89 % were disease free above the age of 50 yrs. This difference in both the age groups for recurrence was statistically significant (p value=0.003). Patients older than 50 years fared better in terms of disease free survival than compared to younger patients.

Stage : Patients in stages group IB-IIA, IIB & IIIA-B had residual/recurrence at \geq 6 months 0% (0/6), 35% (6/17) & 42% (3/7) respectively. Two patients in stage IV were given neoadjuvant chemotherapy followed by concurrent chemoradiation as disease showed regression and these patients were restaged as II B. Lower is the stage better is the survival. (For stage IB-IIA vs stage IIB p value = 0.003 and for stage IB vs. IIIB, p value = 0.0005) These differences in various stages were statistically significant.

In 57 % of the patients residual/recurrence was observed at end of 6 months when patient initially had low hemoglobin

Table - 1 : Clinical factors

Factor	Total number of patients (n)	Number of patients NED 6 after months n (%)	Number of patients with residual after 6 months n (%)	P value
Age				
<50 yrs	23	15 (66)	8 (34)	0.003
>50 yrs	9	8 (89)	1 (11)	
Stage				
IB	1	1	-	0.003
IIA	5	5	-	
IIB	17	11 (65)	6 (35)	
IIIA	2	1 (50)	1 (50)	
IIIB	5	3 (60)	2 (40)	
IVA	2	2	-	
Haemoglobin				
Below 10g/dl	14	6 (43)	8 (57)	0.00001
Above 10g/dl	18	17 (95)	1 (5)	
Human Papilloma Virus				
Positive	16	10 (63)	6 (37)	0.0001
Negative	8	8	0	

NED - No evidence of disease

(below 10 g/dl), 5% residual when patients had hemoglobin above this level.

Hemoglobin : Ninety-five percent of patients with hemoglobin above 10 g/dl had no evidence of disease as compared to only 43 % hemoglobin below this level. Patients with low hemoglobin were given repeated transfusions. The difference was very significant both with recurrence (p value=0.00001).

Human papilloma virus : In this study sixty six percent (16/24) patients studied had HPV positive disease. Thirty seven percent of positive cases had residual/recurrence (p value=0.00001).

Pathological factors (Table-2)

Histopathological type and subtype : All the patients were graded as squamous cell carcinomas, 29% in keratinizing squamous cell carcinoma & 20% in non-keratinizing squamous cell carcinoma were having recurrence at end of 6 months. Though the p value is insignificant (p value=0.17), the trend of better survival is toward non-keratinized squamous cell carcinomas.

Grade : Out of total of 32 patients who had residual/recurrence at 6 months, 27 % belonged to moderately differentiated and 25 % were well differentiated

Table - 2 : Pathological factors

Factor	Total number of patients (n)	Number of patients NED 6 after months n (%)	Number of patients with residual after 6 months n (%)	P value
Histological subtype				
Non-keratinizing	10	8 (80)	2 (20)	0.17
Keratinizing	22	16 (71)	7 (29)	
Grades of differentiation				
Well differentiated	8	6 (75)	2 (25)	NS
Moderately differentiated	22	16 (73)	6 (27)	
Poorly differentiated	2	1 (50)	1 (50)	
Mitotic index				
Category I (1-2/HPF)	8	7 (88)	1 (12)	0.0009
Category II (3-5/HPF)	24	16 (77)	8 (23)	

NED - No evidence of disease, NS - Not Significant

(75% NED). No difference was observed in recurrence in well differentiated vs moderately differentiated. One patient of the 2 poorly differentiated carcinoma in patient there was disease recurrence.

Mitotic Index : In the present study patients who presented with recurrence at end of 6 months, 23 % had mitotic index (3-5/HPF) and that means 77 % had no evidence of disease. Twelve percent of the patients had mitotic index (1-2/HPF) and that means 88 % had no evidence of disease. There was statistically difference between the two groups for recurrences (p value=0.0009).

Lymph-vascular invasion and necrosis : As most cases were in advanced stages of disease therefore not much inference could be drawn as lymph vascular and necrosis was present in majority of cases.

Radiological factors (Table-3)

Parametrial Extension : Fifty percent (n=32) having parametrial extension up to pelvic wall had recurrence/residual disease at end of 6 months after treatment while 32% patients having unilateral or bilateral extension not up to pelvic wall had recurrence/ residual disease after 6 months (p value = 0.001).

Disease dimension : In present study 28% having greatest dimension of disease >6 cm had disease recurrence after 6 months of treatment. Patients having volume of disease less than 4 cm or more belonged to stage I-IIA and 100% showed no evidence of disease (p value=0.016).

Table - 3 : Radiological factors

Factor	Total number of patients (n)	Number of patients NED 6 after months n (%)	Number of patients with residual after 6 months n (%)	P value
Parametrial extension				
Present less than lateral pelvic wall	22	15 (68)	7 (32)	0.001
Present upto lateral pelvic wall	4	2 (50)	2 (50)	
No involvement	6	6	-	
Disease dimension				
< 4cm	2	2	-	0.016
4-6 cm	4	4	-	
>6 cm	26	17 (72)	9 (28)	
Lymph node status				
Node positive	8	4 (50)	4 (50)	0.0002
Node negative	24	19 (79.1)	5 (20.8)	
Hydronephrosis				
Present	3	1	2	0.0005
Grades of Vascularity				
Grade I	1	1	-	NS
Grade II	9	6 (67)	3 (33)	
Grade III	22	16 (72)	6 (28)	

NED - No evidence of disease, NS - Not Significant

Lymph node status : Lymph node positivity was observed in 25% (8/32). Out of 8 pelvic node positive patients, one patient also had para-aortic node and one had inguinal lymph node and in both these cases recurrence was observed. Out of node positive patients i.e. in 50% (4/8) there was disease recurrence. Patient with para-aortic lymph node had bilateral iliac lymph node involvement (p value=0.0002).

Hydronephrosis : In 3 patients of stage IIIB, two presented with recurrence/residual at the end of 6 months after treatment which though very small in number indicate a significant poor prognostic factor (p value = 0.0005).

Vascularity : There is no difference between grades II and grade III vascularity noticed in our study groups.

DISCUSSION

In cervical carcinoma in spite of best possible treatment a large number of cases present with local pelvic failure. Various attempts have been done to find out the prognostic factors in order to improve the survival by surgery alone, surgery combined with radiotherapy, radiotherapy alone, chemo radiotherapy, chemo radiotherapy plus targeted

therapy. Present study evaluates prognostic factors in squamous cell carcinoma of cervix.

Clinical factors

Age : Age as a prognostic factor is controversial while Datolli et al. (1989)⁷ showed a decreased survival in younger ages in contrast Meanwell et.al. (1998)⁸ showed improved outcome for younger patients. In elderly patients (above 70 yrs) poor survival is linked with incomplete treatment and presence of co-morbid conditions. The reason for poor survival in younger ages is correlated with more aggressive tumours such as adenocarcinoma and adenosquamous carcinomas. The exact etiology however is uncertain. In our series we noticed a similar pattern, more recurrences (8/23) 34% were observed in women under the age of 50 yrs when compared to (1/9) 11% in women older than 50 yrs. The mitotic index in both the age groups with residual/recurrence was higher (6/9 patients had mitotic index in the range of 3-5/HPF). Thus suggesting an aggressive behaviour of disease.

Stage: The FIGO system has many shortcomings, still FIGO stage is considered to correlate well with treatment outcome. According to FIGO staging 5 yr survival rates according to AJCC (2014) for stage IA- 93 %, IB- 80 %, IIA- 63%, IIB- 58%, IIIA- 35 %, IIIB- 32 %, IVA- 16 % and IVB- 15 % respectively have been reported. In Indian series published from Tata Memorial Hospital FIGO stage also has emerged as strong prognostic indicator (Shrivastava et al. 2014).⁶ In the current years concurrent chemo radiation has increased the survival has become the standard care. Cochrane meta-analysis collaboration (CCMAC 2010)⁹ has shown 6% benefit in OS using concurrent chemo-radiation. In the present of 32 patients, 0% (0/6), 35% (6/17) & 42% (3/7) patients in stages group IB-IIA, IIB & IIIA-B had residual/recurrence at ≥ 6 months which is well accordance with literature. (For stage IB-IIA vs stage IIB p value = 0.003 and for stage IB vs. IIIB p value = 0.0005) all were statistically significant. Two patients in stage IV were given neo adjuvant chemotherapy followed by concurrent chemo radiation as disease showed regression and these patients were restaged as FIGO IIB). Lower is the stage better is the survival.

Co-morbid conditions have been correlated with poor outcome in elderly because of incomplete treatment. In our series the oldest patient was 67 years old. No patient was such that who could not tolerate the treatment.

Hemoglobin : There are conflicting reports of initial low hemoglobin level or nadir hemoglobin correlates with

survival. Most reports are having strong correlation with later. Relapses are more if hemoglobin is less during treatment. Dunst. et.al¹⁰ 2003 noted 67% relapse vs. only 7% if hemoglobin was <11 g/dl vs 13 g/dl. Haengsen et al. 2001¹¹ and Grinski¹² noted similar results. Lima et al. 2012 found that pre-treatment <120 g/dl was a negative factor for disease recurrence (HR 4.20, p value=0.031) and death (HR 8.19, p value= 0.020). The low hemoglobin had a marked impact on survival in our series (8/14) 57% of recurrence was observed when patients had haemoglobin less than 10 g/dl while only (1/18) 5 % of patients had recurrence above the level of 10 g/dl. We have taken this 10 g/dl value of hemoglobin as most women have hemoglobin in this range. Patients with low hemoglobin were given repeated transfusions. The difference was very significant for recurrence (p value=0.00001). This appeared to be one of the strongest factors to impact on disease free survival in the present series.

HPV (Human Papilloma Virus Infection) : The results of outcome in HPV infected patients of cervix are controversial. Among patients with the rare cases of cervical cancer that do not have detectable HPV, prognosis is poor. Ann et al. reported that the risk of recurrence among patients with squamous cell carcinoma of the cervix was twice as high for patients with HPV-18 as it was for patients with non-HPV-18 subtypes.¹³ In this study sixty six percent (16/24) patients studied had HPV positive disease. Thirty seven percent of positive cases had residual/recurrence (p value=0.00001). No recurrence was observed in 8 cases with negative HPV infection. In this study the results suggest a high recurrence rate in HPV positive cases.

Pathological factors

Histopathology type and subtypes : Various studies have indicated lower response to therapy and poor overall prognosis for adenocarcinoma, especially for non-early stages, i.e. locally advanced carcinoma. According to Geetha et al.¹⁴ adenocarcinoma had 87 % higher risk of failure than squamous cell carcinoma though no statistical significance was obtained. Increased incidence of lymph node involvement (31.6% vs 14.8%) and distant metastasis (37% vs 21%) in adenocarcinoma as compared to squamous cell carcinoma of similar stage and tumour diameter has also been reported.¹⁵

But a very large recent study by Geethakumari et al.¹⁴ demonstrated that keratinizing SCC may be less radiosensitive and associated with poorer survival in comparison to non-keratinizing SCC. Data showed that

tumour histological grade ($P < 0.001$) and clinical stage ($P < 0.001$) were well correlated with cervical cancer recurrence after surgery. Patients with moderately and highly differentiated cancer of IB stage cancer were subject to lower recurrence rates when compared to patients with poorly differentiated cancer of IB stage cancer, respectively.¹⁶

In the present series of 32 patients studied all the patients were squamous cell carcinomas. Twenty nine percent & 20% in keratinizing squamous cell carcinoma & non-keratinizing squamous cell carcinoma were having recurrence at end of 6 months. Though the p value was insignificant (p value = 0.17), the trend of better survival is towards non-keratinized squamous cell carcinomas.

Grade : No statistical difference p value=0.35 was observed in recurrence in well differentiated vs moderately differentiated. One patient of the 2 poorly differentiated carcinoma in patient there was disease recurrence.

Mitotic Index : Not enough literature was available to show that mitotic index is an established prognostic factor in cancer cervix. In present study who presented with recurrence at end of 6 months, 23 % had mitotic index (3-5/HPF) and 12 % had mitotic index (1-2/HPF). There was statistically difference between the two groups for recurrences (p value=0.0009).

Lymph-vascular invasion and necrosis : Lymph-vascular has not been correlated with pelvic recurrences but has been correlated with distant metastasis. In the present series as the majority of cases presented in advanced stage therefore lymph vascular and necrosis was present in the most of the cases. Therefore not much inference could be drawn.

Radiological factors

Parametrial Extension : Coia et al. reported a better 4-year survival rate (67% and 54%) and in-field tumour control rate (78% and 68%) in patients with unilateral versus bilateral parametrial involvement, respectively.¹⁷ This study also compared the significance of unilateral/ bilateral parametrial involvement less or upto lateral pelvic wall. If the involvement was less than lateral wall recurrence was in 35% vs 50% in patients with lateral pelvic wall involvement. Similarly, in a review of 1,178 patients with stage IIB disease treated at Washington University, the 5-year survival rates were 70% with medial parametrial and 58% with lateral parametrial involvement (p = 0.004).¹⁸ In the present study studied 50% having parametrial extension up to pelvic wall had recurrence/residual disease at end of 6

months after treatment. The results of our study are comparable where recurrence was greater in patients having unilateral or bilateral extension up to pelvic wall (50% vs 32%, p value = 0.001).

Lymph nodes : In multivariate survival analysis, only lymph nodes (p=0.01; p<0.05) and FIGO stage (p=0.002; p=0.002) were associated with disease free and overall survival, respectively. Patients with lymph nodes >10% showed impaired disease free and overall survival compared with patients with lymph nodes <10%.¹⁹ Common iliac node involvement is the significant factor that influences the prognosis of patients with cervical carcinoma and pelvic node metastasis.²⁰ Among stages IIB-IVA, 5-year OS was observed to be 57%, 34% and 12% among patients with node-negative, pelvic-node positive and para-aortic node positive status respectively. Impact of Lymph Node involvement on 3 years disease free survival node negative - Stage IB-IIA 100 % and node positive were 67 % and for Stage IIB-IVA -56 % for node negative and 24 % for node positive.^{21,22} Most notably, the FIGO system is oblivious to the lymph nodal status. In the present study lymph node positivity was observed in 25 % (8/32). Out of 8 pelvic node positive patients, one also had para-aortic node and one had inguinal lymph node and in both these cases recurrence was observed. Out of node positive patients 50% (4/8) had disease recurrence. Patient with para-aortic lymph node had bilateral iliac lymph node involvement (p value=0.0002).

Greatest dimension : The results of tumour size and its impact on survival have been shown in above table. Toita et al.1995²⁶, in a review of 70 patients with stage IIB and IIIB carcinoma of the uterine cervix treated with RT alone, reported no significant correlation of 5-year disease free survival with size of the cervical tumour <40 mm (70% to 85%) : however, in patients with tumour >40 mm, the 5 year disease free survival was 28.6%. Delgado et al²³, in study of 732 patients, found the 3 year disease free survival (DFS) to be 95% for occult tumours, 86 % for those less than 3 cm and 68% for those greater than 3 cm (p < 0.0001). Eifel et al.^{24,25} also found similar results. In the present series 28 % having greatest dimension of disease >6 cm had disease recurrence after 6 months of treatment. Patients having greatest dimension of disease less than 4 cm belonged to stage I-IIA and 100 % showed no evidence of disease (p value=0.016). This value was statistically quite significant.

Hydronephrosis : There have been many studies conducted to determine hydronephrosis as an independent prognostic indicator of survival among patients with advanced

cervical carcinoma. Pradhan et al. conducted a study of 143 patients, 73 patients had no hydronephrosis (HN). Twenty nine patients (40%) with no hydronephrosis died compared to 61.5 % with unilateral hydronephrosis and 67 % with bilateral hydronephrosis.⁵ Out of 2/3 patients studied having hydronephrosis presented with disease/ recurrence at end of 6 months after treatment (p value = 0.0005).

Vascularity : At present, micro vessel density does not appear to be a useful biomarker. There was no difference between grades II and grade III vascularity noticed in our study groups.¹³

CONCLUSION

Patients under less than 50 years, higher stage (IB-IIA vs stage IIB and stage IB vs. IIIB), haemoglobin less than 10 g/dl, positive human papilloma virus, mitotic figures 3-5/HPF, parametrial extension up to pelvic wall, lymph nodes on imaging, hydronephrosis, greatest dimension >6cm were associated with pelvic failure of the disease at follow-up of 6 months or more.

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