

A retrospective study of prognostic factors in locally advanced cancer of uterine cervix in a Rural based Medical College of West Bengal –updated version

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Abstract- India alone accounts for one-fourth of global burden of cervical cancers. It is the commonest malignancy in female population in rural India. Usually it present in a locally advanced stage [1]. Chemoradiotherapy usually the treatment of choice for locally advanced stage [1,2]. The main aim of this study is to find out the prognostic factors which are most important for treatment outcome & survival. It is a retrospective study done in the department of Radiotherapy in a rural based medical college of west Bengal (Bankura sammilani medical college & Hospital Bankura) from september 2008 to august 2013. A total of three hundred fifty six patients were included in this retrospective study. Patients were treated with Radical radiotherapy with concomitant cisplatin chemotherapy. Patients were followed up every three months for the first two years, every four months for the third year, every six months for the fourth and fifth year. The most important prognostic factor for survival is stage of disease at presentation. The 4 year survival rate in stage IIB is 72.11%, in stage III it is 57.14% whereas in IV it is 11.90%.

Key words- cancer cervix, radiotherapy, chemotherapy, prognostic factor, survival.

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I. Introduction

Cervical cancer is the most common gynaecological malignancy in rural Bengal. [1]. usually it presents in advanced stage particularly due to lack of screening. & awareness. The standard protocol for treatment in advanced stage is chemoradiotherapy. There is significant improvement in pelvic disease control and survival when concurrent chemotherapy is added to radiotherapy in stage IB2 –IVA cervical cancer [1-4]. Although concurrent chemo-radiotherapy followed by intracavitary brachytherapy is standard treatment paradigm for locally advanced cervical cancer., in our study mainly the nonbulky stage II disease were treated with Radiotherapy. The factors which are usually responsible for predicting prognosis & survival are histology, grade, stage of disease, tumor size, pelvic nodal status, addition of chemotherapy [1-4]. In our study it is the stage of disease which is the most important prognostic factor for predicting survival.

II. Materials & Methods:

Total three hundred fifty six (n=356) patients of carcinoma cervix, of stage IB2 to IV were included in this study from january 2008 to august 2013 in the department of Radiotherapy Bankura sammilani medical college. It is a retrospective study, inclusion criteria-

- a) all biopsy proven patients of cervical cancer.
- b) age eligible for study: 18 - 70 years.
- c) ecog performance status (ps): 0- 2
- d) figo stage IIB to IV
- e) creatinine clearance \geq 60 ml/min so that no contraindication or dose modification for cisplatin used during concurrent chemo-radiation.
- f) baseline bilirubin \leq 1.5 x uln (upper limit of normal value), liver enzymes \leq 2.5 x uln
- g) those who signed the informed consent for participating in the study.
- h) had not received radiation to pelvis previously.
- i) patient is not pregnant.
- j) not suffering from severe pulmonary, cardiac or metabolic disorder which is likely to

interfere with treatment protocol
exclusion criteria

- a) ECOG Performance status ≥ 3
- b) Age < 18 years or > 70 years.
- c) FIGO Stage IA1 TO IIA & IVB
- d) Creatinine clearance < 60 ml/min
- e) Baseline Bilirubin > 1.5 xuln
- f) Had not received radiation to pelvis previously
- g) Patient is pregnant
- h) Suffering from severe pulmonary, cardiac or metabolic disorder which is likely to interfere with treatment protocol.

The median age of patients was 57 year (range 25-70 years). The patients were evaluated with physical examination and pelvic examination for staging of cervical cancer, Routine blood count, blood biochemistry profile, MRI Pelvis with contrast, . CECT Thorax & Abdomen . Pelvic and para- aortic lymph node more than 10 mm in greatest dimension considered to be metastatic lymphnode by CT scan .The treatment schedule: External beam radiotherapy to pelvis delivered with AP/ PA portal or Four field box technique to a total dose of 50 Gy in 25 fractions in five weeks followed by three HDR intracavitary brachytherapy of weekly 7 Gy insertion for three consecutive weeks. . Weekly platinum based concurrent chemotherapy was administered with weekly dose of cisplatin 40 mg/M2.Total thirty patients (n-30) presented with paraaortic lymphnode metastasis. Paraaortic radiation was given in these patients with a dose of 45 Gy in 25 fractions. Follow up: Both radiation oncologist and gynaecologist examine the patients every three months for the first two years, every four months for the third year, every six months for the fourth and fifth year and yearly afterward. . Follow up procedure includes general and systemic examination and routine pelvic examination

Loco regional recurrence was suspected by pelvic examination and or papanicolaou smear and biopsy was taken for confirmation . Radiological examination of abdomen or chest ware performed as clinically indicated .Adverse events were graded according CTCAEv4.1 NCI Common Terminology Criteria for Adverse Events&RTOG criteria. Statistical analysis was done using SPSS version 17 . Survival(overall survival) was calculated using Kaplan-Meier survival analysis .

Ethical clearance-As it is a Retrospective study no ethical clearance needed as per institutional protocol.

III. Observation & Results:

Total three hundred fifty six patients were included in the study.From Table 1 it shows that most common stage of disease at presentation was stage III (n-210 -58.98%) of which IIC1 is 21.91% & IIC2 is 8.43%.. Bulky disease at presentation (size of Tumor 4 cm or more.) is 50.28%.Median age is fifty six year.Chemoradiotherapy usually was the treatment of choice though stage II nonbulky diseases & some patients who are not suitable for chemotherapy treated by Radiotherapy alone. The median follow up was fourty six month.Four year survival (overall survival) was 59.55% in chemoradiotherapy arm which is greater than Radiotherapy only arm(52.80%) though it was not significant.It may be due to inclusion of nonbulky diseases only in radiotherapy arm .Stage of the disease at diagnosis followed by nodal involvement remains the two most important & significant prognostic factor for survival in our study.

Table 1

Charateristics	Number	Percentage	Statistics(p value)
Age in year	<56	174	48.87
	>56	182	51.13
Tumor size in cm	<4cm	177	49.71
	>4 cm	179	50.28
Stage of disease(FIGO stage)	IIB	104	29.21
	III	210	58.98
	IV	42	11.79
Lymphnode involvement	Present	78	21.91

	pelvic				
		absent	278	78.08	
		present	30	8.43	
	paraaortic				0.043
		absent	326	91.57	
Treatment		Radiotherapy	178	50.0	0.045
		chemoradiotherapy	178	50.0	

Table2-estimation of survival			survival	P value	RR
Age in year	<56	174	98(56.32%)	0.63	0.93(0.70-1.24)
	>56	182	102(56.04%)		
Tumor size in centimeter	<4cm	177	102(57.67%)	0.29	1.17(0.87-1.56)
	>4 cm	179	98(54.79%)		
Stage of disease(FIGO)	IIB	104	75(72.11%)	.0019	4.38(1.18-16.25)
	III	210	120(57.14%)		
	IV	42	5(11.90%)		
LN	Pelvic	yes	78	0.0008	4.02(1.79-9.04)
		no	278		
	Paraaortic	yes	30	0.010	5.35(0.84-34.11)
		no	326		
Treatment		Radiotherapy	178	0.40	0.88(0.66-1.18)
		chemoradiotherapy	178		

IV. Discussion:

Locally advanced carcinoma cervix usually treated by chemoradiotherapy.[1] Radiotherapy alone may be an alternative particularly in nonbulky stage II diseases who refused surgery or where surgery contraindicated or not feasible[1-4] due to nonavailability of oncosurgery department particularly in rural based medical college. In our setup we have treated all nonbulky cases (Tumor size <4 cm) with Radiotherapy alone. One patient with bulky disease refused to take chemotherapy, so total one hundred seventy eight patients were treated with Radiotherapy alone[1-4]. According to Perez et al The factors which are usually responsible for predicting prognosis & survival are histology, grade, stage of disease, tumor size, pelvic nodal status, addition of chemotherapy. There are five landmark trials which studied the role of chemoradiotherapy in carcinoma cervix..they are GOG 123(Keys et al) GOG 85(Whitney et al) GOG 120(Rose et al) RTOG90-01(Eifel et al) GOG109(Peters et al). In RTOG 90-01 & GOG123 it had been shown that addition of chemotherapy to Radiation improved overall survival which is statistically significant. but another two studies SWOG8797(Peters et al) & NCIC(Pearcey et al) showed that addition of chemotherapy has a survival advantage but that was not statistically significant[7,8]. This difference between us trials & Canadian trials were analyzed by Lehman & Thomas. Some theoretical explanation was that more early stage patients were accrued so that that is a less difference in survival as well as high baseline survival rate in both arms[8'9]. In our study it has been shown that chemoradiotherapy has survival advantage over Radiotherapy alone arm(60.42% vs 52.80%) though it was not significant. It may be due to accrual of more early stages & nonbulky tumor in Radiotherapy

arm. Toita et al in a review of seventy patients with stage IIB to IIIB carcinoma cervix reported that no significant correlation between size of tumor (<60 mm vs >60 mm) & 5 year OS, though the 5 year OS was only 28.6% in large tumor. Piver & chung showed that larger tumor has a lower survival rate in stage IB & IIA tumor treated with Radical hysterectomy. It has been shown by Fletcher, Eifel et al, Perez et al that Larger tumor treated with Radiotherapy has a higher incidence of pelvic recurrence, distant metastases, & decreased survival. In contrast Grigsby et al observed no correlation between tumor volume & outcome like local recurrence. In our study it has been shown that size of tumor is important prognostic factor. Smaller size of Tumor (<4cm) has an impact on survival (57.67% vs 54.79%) though it is not statistically significant. According to Leveque et al it is the FIGO stage of the disease, & pelvic lymph node involvement which are the most important prognostic factor for survival. In our study it has been shown that FIGO stage of the disease at presentation is the most important prognostic factor for survival which is statistically significant, (vide chart 2). Survival according to stage as follows, stage II -72.11% stage III-57.11% stage IV-11.90%. Next important factor for survival is Lymph node involvement. There is significant survival advantage in patients without lymph node involvement. (Vide chart 2). Considering the age as a prognostic factor it has been shown that in our study younger female (<56 year) has a better survival than older female (56.32%) vs (56.04%) though it is not statistically significant. 4 year OS is 56.17% in our study. Although the addition of concurrent chemotherapy to radiation undoubtedly has benefited many patients, there is still considerable room for improvement. Some patients, particularly those with bulky tumors or regionally advanced disease, continue to experience local recurrences, suggesting the need for even more effective chemo radiotherapy regimens. However, investigators face major challenges in trying to design future chemo radiotherapy trials as because: 1) The fact that Cisplatin was included in the most successful arms of so many trials has caused investigators to question whether it is ethical to omit cisplatin or even to compromise the cisplatin dose in new chemo radiotherapy regimens [9]. 2) The hematologic toxicity of weekly cisplatin and of the combination of Cisplatin and 5FU limits the dose that can be safely delivered in combination with radiation. For this reason, one attractive approach for future studies will be the incorporation of relatively non-myelo suppressive biologic response modifiers into current regimens. Recent interest has focused on epidermal growth [8,9]

factor modulators and vascular endothelial growth factor modulators, cyclooxygenase-2 inhibitors, and agents that specifically target hypoxic cells [10]. Despite the challenges, we must also continue to evaluate potentially radiosensitizing drugs that could prove to be more effective than cisplatin or equally effective but less toxic or less costly. In doing so, we should consider concurrent chemo radiotherapy regimens that have proved to be successful against tumors at other sites—particularly carcinomas of the head and neck, which have response characteristics that are in many ways similar to those of cervical cancers. Conversely, although preradiation chemotherapy has been used with some success in other sites, randomized trials have repeatedly failed to show a benefit from neoadjuvant chemotherapy in patients with cervical cancer. [9,10] Although some investigators have suggested sequencing neoadjuvant chemotherapy and chemo radiotherapy, the possibility that preradiation induction chemotherapy could compromise the intensity of subsequent chemo radiotherapy, diminishes the attractiveness of this approach.

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V. Conclusion

Carcinoma cervix is the commonest gynaecological malignancy in our rural based medical college. It usually presents in FIGO stage II & III. As there is no oncosurgery setup, we usually treat non bulky stage II diseases by Radiotherapy alone & others by chemoradiotherapy. The most important prognostic factor predicting survival are stage of disease, size of tumor, presence of pelvic and paraaortic lymphadenopathy, addition of chemotherapy, age. But in our study stage of disease is the most significant prognostic factor predicting survival followed by presence of pelvic & paraaortic lymphadenopathy..

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