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RESEARCH ARTICLE

PATTERNS OF FAILURE AND FACTORS AFFECTING IT IN CARCINOMA CERVIX STAGE (IIB – IVA) TREATED WITH CHEMORADIOTHERAPY OR RADIOTHERAPY ALONE.

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Abstract

Introduction: Several factors i.e. age, anthropometric parameters, socio-economic profile, Histopathology, lymph node status not considered in staging & treatment outcome have definitely a conclusive role in treatment response & recurrence. Also there are acute & late toxicities occur at different stages of treatment i.e cervical os stenosis, vaginal atrophy, bowel & bladder toxicities. Recently different studies are being conducted evaluating overall survival (OS), disease free survival, progression of disease, recurrence, patterns of recurrence (local or distant) & factors affecting it. Multiple patient related & treatment related factors have impact on disease outcome. So it is very important to assess the patterns of failure & the factors affecting it in a cohort of patients treated in a single institution.

In this retrospective study, we have tried to evaluate recurrence & its patterns, time to recurrence & factors affecting it.

Material & Methods: A retrospective single institutional study including patients of CA cervix from stage IIB – IV A, from December 2014 – May 2016. Various parameters were studied with their relation with 3yr DFS & 3yr overall survival. Statistical Analysis was done by SPSS V.23, using standard statistical tests.

Results: Factors i.e age at presentation, age at marriage, age of 1st child birth, parity, tobacco addiction, other co-morbid medical conditions, Pre-treatment Hb% < 11gm/dl, treatment type (RT alone), overall treatment time (>56D), Tumour volume (>4cm), Both parametrium involvement, Delay in diagnosis, Gap between EBRT & ICRT, Gross residual tumour after EBRT have significant association with recurrence, recurrence pattern & 3 year survival. Among them age at presentation, L.N involvement, overall treatment time are found as significant prognostic factor in multivariate analysis.

Conclusions: The findings of this study are not conclusive as a result of the small sample size & single institutional, Retrospective study. Further multicenter, controlled, randomized phase III trials will be needed to prove the factors affecting the treatment failure.

Introduction:-

According to the Population Based Cancer Registries (PBCR) 2004-2005, in India, cancer uterine cervix is second leading cause of cancer in females after breast cancer in all regional registries (except in Barshi), indicating its relatively higher prevalence in rural populations(2). It is the leading cause of mortality due to malignancy in females in India (Age adjusted standardized Mortality rate: 15.2/100000 in 2008(2)).

In developing countries like India significant no of the patients presents with late stages(stages IIB-IVA) due to less access to health care & screening facility, poor nutritional & immune status, presence of other infections.

Several factors i.e. age, anthropometric parameters, socio-economic profile, Histopathology, lymph node status not considered in staging & treatment outcome have definitely a conclusive role in treatment response & recurrence. Also there are acute & late toxicities occur at different stages of treatment i.e cervical os stenosis, vaginal atrophy, bowel & bladder toxicities. Recently different studies are being conducted evaluating overall survival (OS), disease free survival, progression of disease, recurrence, patterns of recurrence (local or distant) & factors affecting it. Multiple patient related & treatment related factors have impact on disease outcome. So it is very important to assess the patterns of failure & the factors affecting it in a cohort of patients treated in a single institution.

In this retrospective study, we have tried to evaluate recurrence & its patterns, time to recurrence & factors affecting it.

Aims & objectives:-

The aim of this study is to assess the patterns of failure and the factors affecting it in carcinoma of cervix stage IIB to IVA treated with radical / curative intent with Concurrent Chemoradiation and Brachytherapy.

Specific objectives of the study:-

1. To study the distribution, pattern and time to failure in patients of Advanced Ca cervix treated radically with chemoradiation in last 5 years in Medical College, Kolkata.
2. To determine the role of different factors affecting local, regional and distant failures in patients of advanced Ca Cervix treated radically with chemoradiation.
3. To identify various the predictive and prognostic markers for loco regional and distant failures in patients of advanced Ca Cervix treated radically with radiotherapy.

Materials and methods:-

Study area: Department of Radiotherapy, Medical College Kolkata.

Study population: Cases of Cervical carcinoma, stages IIB-IVA, treated radically in the Radiotherapy department of Medical College, Kolkata during the period of January 2009 to January 2014.

Study period: December 2014 to May 2016.

Sample size: Approximately 300 patients are treated with curative intent in the Radiotherapy Department every year, out of which 70% patients i.e. about 200 patients are of in advanced stages in a year. If we take the lost to follow up cases as approx. 50% then we can study 100 patients per year. So for five years a cumulative sample size of approximately 500 such patients will be included in the study.

Sample method: Non probability sampling. All patients of CA Cervix meeting inclusion & exclusion criteria during the defined time frame will be included in the study.

Study design: A retrospective cohort study.

Inclusion criteria:

- a. Females aged 18 & above with diagnosis as per FIGO 2009 staging, treated with curative intent.
- b. Confirmed diagnosis & treated between January 2009 to January 2014.

- c. Received full treatment comprising of external beam radiotherapy with or without concurrent chemotherapy followed by brachytherapy.

Exclusion criteria:

- a. History of concurrent or any other primary malignancy.
- d. Patients who did not complete their full course of treatment.
- e. Patients in whom proper staging and pretreatment metastatic workup data is not available.
- f. Patients who have defaulted and have not come for even a single follow up

Outcome measures:

a. Primary outcome :

- i. Incidence rate of recurrence or progression (local, regional & distant) in the cohort of patients of newly diagnosed Ca Cervix who were treated with curative intent.

ii.

b. Secondary outcomes :

- i. Progression / Recurrence free survival rates.
- ii. Progression / Recurrence free survival times.
- iii. Time to progression & recurrence.
- iv. Clinico-demographic characteristics & clinic-pathological characteristics of the patients affecting recurrence rate and time.
- v. Treatment related factors affecting recurrence rate and time.

Parameters to be studied:-

- i. Socio-demographic character of patients.
- ii. Clinical features as assessed & recorded from history & examination (including initial stage).
- iii. Histopathological characteristics (biopsy & surgical pathology).
- iv. Pretreatment anthropometric parameters.
- v. Pretreatment performance status.
- vi. Pretreatment laboratory parameters.
- vii. Pretreatment radiological parameters.
- viii. Treatment parameters.
- ix. Total treatment period.
- x. Response to treatment by clinical & radiological assessment.
- xi. Recurrence rate/ Incidence .
- xii. Time to progression.
- xiii. Pattern of progression.
- xiv. Response to subsequent therapy & end points.

Additional sources and resources:

- i. Patient's case record proforma, standard haematological, biochemical and radiological test.
- ii. Case files stored at record section of Dept. of Radiotherapy, Medical College, Kolkata.
- lii . Radiotherapy Treatment records
- iv. Brachytherapy treatment records
- v. TPS archives

Study technique:-

A retrospective study of data stored at record section from case files of all proven cases of Carcinoma of cervix, FIGO stages IIB-IVA, treated at Radiotherapy dept. of Medical College, Kolkata from 1st January 2009 to 1st January 2014. The study will be performed by the following steps

- i) Data will be collected according to the individual patient proforma with their history of presentation, age, socio-economic profile, anthropometric assessment.
- ii) Staging according to FIGO staging 2009 by clinical assessment & gynaecological examination done by our department to be mentioned.
- iii) Staging confirmed & corroborated by radiological assessment to be specified i.e., tumour volume, lymph node status, local or distant spread.

- iv) Treatment history to be elaborated i.e. time of treatment initiation, details of dose of EBRT & brachytherapy, technique, TPS data from archive, chemotherapy details.
- v) Response to be assessed by clinical examination & radiological evidences at 6 weeks of treatment completion.
- vi) Follow up data will be taken in respect to control of disease clinically, appearance of recurrence & metastasis. Minimum follow up period is taken as 1 year. Further data for subsequent treatment is received.
- vii) Telephonic contact to be made for information about status & survival of patients.

Plan for statistical analysis of data:-

To be analysed following standard statistical methods. Analyses will be done based on the cohort of patients with proper follow up. All P values will be two sided. A significance level of 95% will be considered. The Chi-Square test will be used to compare categorical baseline characteristics and proportions. T-tests and ANOVA will be used for comparing numerical variables.

Results:-

From December 2014 to May 2016 a total of 518 case study with full treatment & follow up history is analysed thoroughly. The patients were treated for the carcinoma cervix of stage IIB to IVA with conventional Chemoradiation or radiotherapy alone followed by Brachytherapy in curative intent between January 2009 & January 2014 in the department of radiotherapy of Medical College & Hospital. Results were analyzed in June 2016. Eight cervical cancer patients were died due to other co morbid condition and the patients who were lost to follow up are not included in the study. So the total no of eligible patients was 510. 70.6% of patients are treated with chemoradiation & 29.4% with radiotherapy alone. Median age of presentation was **53 years**. Patients with age >55years have poorer 3 year survival (39.1%) than <55years (75%). Total 210 patients (41.2%) died due to cervical cancer after palliative chemotherapy & 300 patients (58.8%) had three year overall survival. Stage wise analysis shows maximum patients (43.1%) presented with stage IIB. 3 year survival is better in stage **IIB (80%)**, poorer in stage **IIIB (54.5%)** & **stage IVA (20%)**. 3 year OS is better in patients with **chemoradiation (63.9%)** than only radiotherapy (46.7%). Better 3year OS in overall treatment time < 56 days (87.5%) than >56 days (10.5%). Median value of pre-treatment Hb was 10 gm/dl. Patients presented with pretreatment Hb <11 gm/dl had poorer 3 year survival.

240 patients had recurrence either local or distant with median disease free survival of 38 months. Distant recurrence (58.33%) is more than local recurrence (41.66%). Recurrence is minimum (20%) in **stage IIB** with all being local recurrence, recurrence is more in advanced stages with more distant pattern i.e stage IIIB (distant 45.5%) & stage IVA (distant 80%). In 260 Patients presented with either pelvic or para-aortic L.N 76.9% had recurrence, more with para-aortic nodes (100%) than pelvic nodes (68.4%). Distant pattern of failure is more also in patients presented with nodes (Distant 60%), in Pelvic L.N (Distant 42.1%) & with para-aortic L.N (Distant 57.1%). Recurrence is also more in patients treated with only RT (66.7%).

Variables	3 yr survival(counts)	Chi sq value	P value
1. Age(>55yr)	90	67.07	< 0.0001
2. Parity	60		
2	150		< 0.0001
3	60	311.14	
4	20		
5	10		
6	0		
3.Contraception			
IUCD	100		
OCP	290	159.31	< 0.0001
NONE	120		
4.Diagnostic			
Delay(month)	250		
1	180	285.89	
2	70		< 0.0001
3	10		
4			

5.Initial tumour vol < 4cm > 4 cm	190 110	59.73	< 0.0001
6 .Para involved None One para involved Both para involved	50 160 90	86.08	< 0.0001
7. LN involvement None Pelvic Para aortic	220 70 10	183.09	< 0.0001
8. STAGE II B III A III B IV A	120 50 120 10	60.94	< 0.0001
10. Histology Squamous Non squamous	280 20	11.13	< 0.0001
11. Treatment type CTRT RT	230 70	12	< 0.0001
12.Over all treatment time < 56 day >56 day	280 20	11.67	< 0.0001

Table 1:- Association of Prognostic factors with 3year Survival

In multivariate analysis by Cox regression of shows the following factors are significant for prognosis. The factors are age at presentation (p=0.005, **hazard ratio 1.031**), L.N involvement (p=0.000), overall treatment time >56 days (p=0.000, **hazard ratio 2.525**).

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
stage			3.947	3	.267			
stage(1)	-.481	.282	2.906	1	.088	.618	.356	1.075
stage(2)	-.139	.250	.310	1	.578	.870	.533	1.420
stage(3)	-.069	.204	.114	1	.736	.933	.626	1.393
AGE	.030	.011	7.843	1	.005	1.031	1.009	1.053
L.N.involvement			19.097	2	.000			
L.N.involvement(1)	-1.092	.267	16.674	1	.000	.335	.199	.567
L.N.involvement(2)	-.097	.160	.369	1	.544	.908	.664	1.241
Tt TIME	.926	.184	25.416	1	.000	2.525	1.761	3.619
TREATMENT TYPE	.052	.215	.059	1	.808	1.054	.692	1.604

Table 2:- Multivariate analysis with Cox regression with of factors of covariates i) Age at presentation, ii) Pelvic or Para-aortic L.N involvement iii) Overall treatment time, iv)treatment type, v) stage

Kaplan Meier survival curve with Disease free survival shows significant difference in (fig 1) survival in case of age (log rank value 86.39, p<0.0001), stage (log rank value 119.39, p<0.0001), pelvic/ para-aortic node involvement

(log rank value 294.14, $p < 0.0001$), both parametrium (log rank value 121.70, $p < 0.0001$), overall treatment time (log rank value 449.56, $p < 0.0001$), treatment type (log rank value 15.52, $p < 0.0001$).

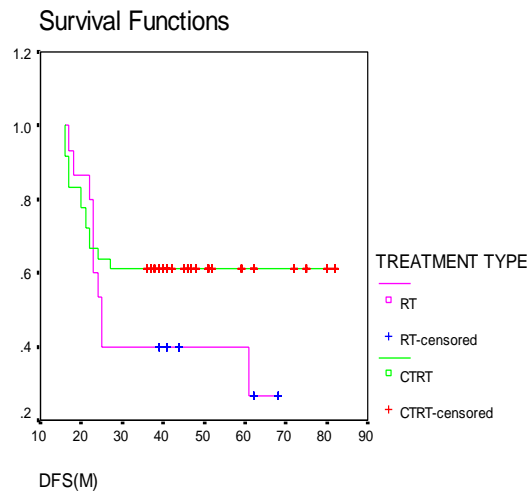


fig (1)

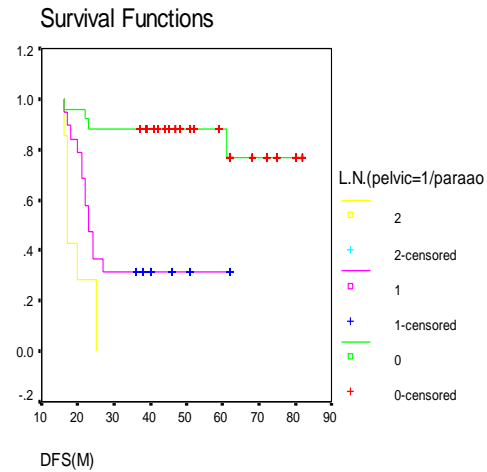


fig (2)

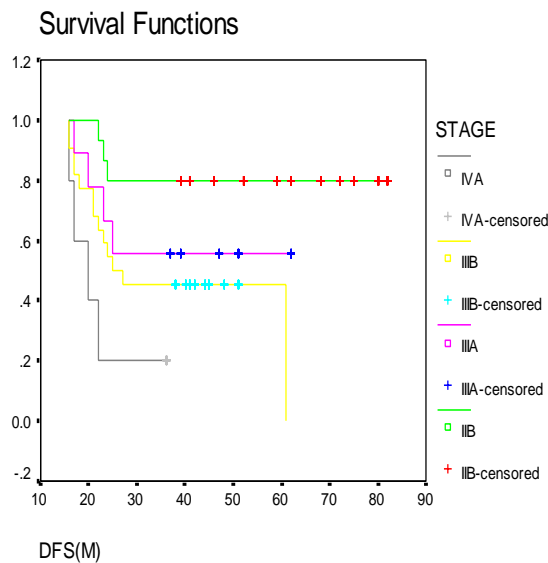


fig (4)

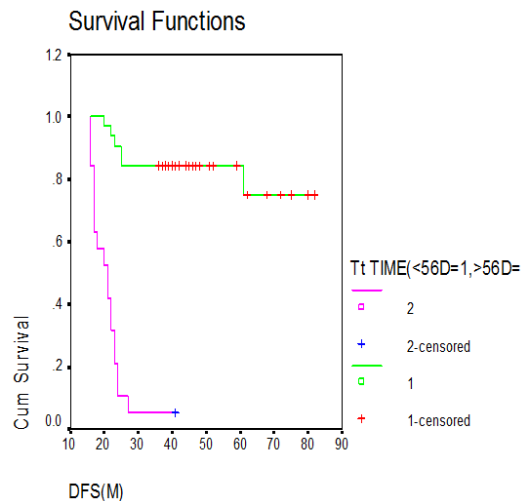


fig (3)

Fig (1,2,3,4):- Survival curve by Kaplan-Meier analysis of Disease free survival with Treatment type, LN involvement, overall treatment time & stage.

Discussion:-

In this single institutional retrospective cohort study shows 3 year OS, DFS, recurrence, recurrence pattern in cervical cancer patients of stages IIB to IVA . Factors i.e age at presentation, age at marriage, age of 1st child birth, parity, tobacco addiction, other co-morbid medical conditions, Pre-treatment Hb% < 11gm/dl, treatment type (RT alone), overall treatment time(>56D), Tumour volume (>4cm), Both parametrium involvement, Delay in diagnosis, Gap between EBRT & ICRT, Gross residual tumour after EBRT have significant association with recurrence, recurrence pattern & 3 year survival. Among them age at presentation, L.N involvement, overall treatment time are found as significant prognostic factor in multivariate analysis.

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. Some other important factors like role of HPV, SCC Antigen could not be assessed. We also failed to get the history of multiple sex partners of the patients or her husbands. Socioeconomic factors except anaemia are not discussed in details poor detailing.

However, the findings of this study are not conclusive as a result of the small sample size & single institutional study. Further multicenter, controlled, randomized phase III trials will be needed to prove the factors affecting the treatment failure.

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