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To study the treatment outcome in post-operative cervical cancer patients availing radiotherapy and/or chemotherapy at a Rural Hospital.

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BACKGROUND: Carcinoma of the uterine cervix is one of the most common gynecological malignancies among women especially in the developing countries. In India cervical cancer is the second most common cancer after breast cancer. The management of early-stage cervical cancer includes surgery in select cases with or without adjuvant chemoradiation. Locally advanced stages are managed by external beam radiotherapy with or without chemotherapy along with brachytherapy.

ABSTRACT

AIM: To study the treatment outcome in post-operative cervical cancer patients availing radiotherapy and/or chemotherapy at a Rural Hospital**.**

METHODOLOGY:25 post-operative cervical cancer patients, fitting the inclusion criteria were enrolled in the study. Patients were then evaluated by detailed history, followed by general, systemic & local examination. Presence of any residual growth, was documented and a thorough hematological and radiological investigations done prior to the initiation of treatment. Based on the risk factors patients were stratified, high risk and intermediate risk group patients received adjuvant EBRT with or without concurrent chemotherapy to a total dose of 50Gy in 25 fractions at 2Gy per fraction. Patients were then planned for either EBRT boost or Vaginal brachytherapy. EBRT boost was delivered using 3D CRT or IMRT technique. Acute and late toxicities were assessed based on CTCAE version 5.0 and response evaluation done by RECIST criteria version 1.1.

RESULTS: The most common age group of presentation noted was between61-70 years 33.3%(8) followed by 51-60 years 28%(7). The risk factors noted in the present study included 56%(14) patients were illiterate, 72%(18) belonged to the lower socio-economic class, age at menarche 13-14 years in 68%(17), para >3 in 52% (13), age at first child birth < 18 years was in 56%(14) and poor birth spacing (<2 years) was in 60%(15). Overlap of complaints wasnoted with most common complaint being PV discharge 64%(16). 80%(20) patients did not have pre-operative staging and surgery was performed irrespective of age of patient without adequate radiological and histopathological investigations. 92%(23) patients had undergone surgery at other Centre's and 44%(11) patients had residual disease and/or metastatic lymph node in the post operative CT scan. Other pathological risk factors such as deep stromal invasion 40% (10), tumor size >4cm 24% (6), lymphovascular space invasion 20% (5) positive lymph nodes 16% (4) and positive margins 8% (2) were noted in the present study. Out of 25 patients 17 patients after completion of their treatment, achieved complete response and had disease free survival at the end of 6 months. Only one post operative patient did not require adjuvant treatment and was kept on regular observation.

CONCLUSION: Although the management of early-stage cervical cancer is surgery and is the preferred mode of treatment, choice of surgery should be based on patient and tumor related factors. Patients who would require adjuvant treatment, should be considered for definitive radiotherapy with concurrent chemotherapy, to

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avoid compounding treatment related morbidity. It is observed that the use of dual modality of treatment increases the risk of morbidity several folds.

Keywords: Cervical cancer, uterine cervical neoplasm/surgery, postoperative adjuvant therapy.

I. INTRODUCTION

Cancer of the cervix is a common malignancy among women worldwide.In India cervical cancer is the second most common cancer after breast cancer, with 123,907 new cases diagnosed according to GLOBOCAN 2020[1] and second, in deaths due to cervical cancer, accounting for 9.1% of the total deaths.The disproportionately high burden of cervical cancer in developing countries is largely due to a lack of screening that allows detection of precancerous and early-stage cervical cancer[2,3]. The high burden of cervical cancer in India and Southeast Asian countries is linked to poor to moderate living standards, a high prevalence of HPV (more than 10% in women aged more than 30 years) and due to lack of screening[4].In addition to HPV infection, co-factors such as parity, early age of marriage, genital hygiene, use of oral contraceptives, smoking, immune suppression (e.g. HIV), infection with other sexually transmitted agents and poor nutrition have been associated with the development of cervical cancer[5,6].The last 20 years have led to numerous advances in the medical management of early-stagecervical cancer, including preventive vaccination, various surgical techniques,chemoradiation, and neoadjuvant chemotherapy.Present study is to observe the risk factors, pre-operative staging, different surgical procedures, post-operative stagingand treatment response in early-stage post operative cervical cancer.

II. METHODOLOGY

Post-operative cervical cancer patientsavailing radiotherapy and/or chemotherapy at Department of Radiation Oncology, at our Institutewere enrolled in the study after receiving IEC approval from the ethics committee. Patients were enrolled as per the inclusion criteria,post-operative cervical cancer patients on radiotherapy and/or chemotherapy with normal hemogram, renal function tests and liver function tests and post-operative patients who were ready to give written informed consent for the study. Exclusion criteria included all metastatic cervical cancers and patients above the age of 70 years.

Patients were then evaluated by detailed history, general, systemic & local examination followed by hematological and relevant radiological investigations. Detailed history included the age of the patient, presence of any risk factor, pre-operative staging, type of surgery performed, lymph nodal dissection if done, histopathological report and if adjuvant treatment was advised, were assessed. Based on the clinical assessment and presence of post operative histopathological risk factors, patients were planned for adjuvant treatment with radiotherapy with or without chemotherapy. Patients with high risk factors were planned for adequate radiation dose delivery, after EBRT, using either vaginal brachytherapy or EBRT boost using 3D CRT or IMRT technique. During and after treatment patients were assessed for acute and late treatment toxicities using CTCAE version 5.0. After completion of treatment patients were followed up, first follow up after one and a half months and there after every three monthly up to 6 months. On each follow up patients were evaluated by clinical examination, hematological investigations and radiological investigations.Thereafter, the disease outcome of each patient was assessed and response evaluation done by RECIST Criteria version 1.1.

III. RESULTS

In our study, about 56% (14) of the study population was illiterate, having received no formal education and 72% (18) belonged to the lower socio-economic class thereby indicating an increased incidence of cervical cancer among lower socio-economic class.

The most common age group at presentation in present study was 61-70 years contributing to 33.3% (8) and 51-60 years contributing to 28% (7).This indicated surgery was performed irrespective of the age of the patientThe risk factors found in the present study, were 56% (14) of the study population had first child birth before 18 years, indicating early age at first coitus, parity >3 was seen in 52% (13) of study participants and 68% (17) patients had menarche at 13-14 years. Table 1 shows the risk factors among the study participants in the present study.

In the present study, 64% (16) participants had whitish PV discharge as the chief complaint, followed by 56% (14) PV bleed and 28% (7) with lower abdominal pain. An overlap of symptoms among a few patients was noted. 44% (11) patients had residual disease or radiologically detected pelvic lymph nodes on evaluation after surgery, due to inadequate preoperative staging of cervical cancer as per FIGO. Figure 1 shows residual disease on marker CT scan, in a post operative cervical cancer patient treated at our institute.

About 92% (23) of the study participants were referred from other centres after surgery for adjuvant treatment to our centre

The most common histopathology noted was Moderately differentiated Squamous cell carcinoma 52% (13) among the study participants. Deep stromal invasion was seen in 40% (10) post operative patients and 24% (6) patients had tumor size more than 4cm on histopathological reports, in the present study. 16% (4) of the study participants had lymph nodal metastasis and positive cut margins were seen in 8% (2) patients making it a high-risk factor. All such patients in the study, received adjuvant radiotherapy with or without chemotherapy.Table 2 indicates the clinical profile with histopathological risk factors among the study participants.

24 out of 25 post operative cervical cancer patients in the present study required adjuvant radiotherapy and/or chemotherapy after radical surgery. 76% (19) patients received EBRT with concurrent chemotherapy, 52% (13) patients received EBRT with vaginal brachytherapy and 28% (7) patients received EBRT boost. Only one post operative cervical cancer patient had no risk factors and hence was kept on close observation. This patient was followed up at regularly timed intervals and a thorough pelvic examination, Pap smear and ultrasound was done on every visit at 3 monthly intervals to monitor the disease-free survival. On completion of 6 months post-surgery, patient was disease free. Table 3 and graph 1 show the distribution of treatment modalities delivered among the study participants.

In the present study, 68% (17) patients had Grade I skin toxicity while 62% (15) participants had Grade I gastro-intestinal in 66% (16) and grade I genito-urinary toxicities in 41% (10). Table 4 and Graph 2 shows the toxicities seen in the present study. Six months after completion of treatment 68% (17) patients had complete response, 16% (4) patients had disease progression and 16% (4) patients in the study were lost to follow up.Table 5 and graph 3 show response after 6 months of treatment.

IV. DISCUSSION

The incidence of cervical cancer is higher in the rural population where the majority of women are socio-economically disadvantaged, with no formal education and no awareness of the risk factors associated with development of the disease.

Based on a case control study on 273 patients, by Pragati Sharma and Pattanshetty S.M, at a tertiary care Centre in Karnataka, parity of >3, age at 1st coitus <18 years and age at menarche of 13-14 years, are important risk factors of cervical cancer[7]. Similar results were observed in the present study.

Saibishkumar et al in 105 Invasive cervical carcinoma patients treated with external beam RT with or without intracavitary RT after having undergone total/subtotal hysterectomy, clinically visible residual disease was present in 81 patients. Inadequate and inappropriate surgery in invasive cervical cancer with resulting gross residual disease is common in India. Factors such as the use of intracavitary RT, the correction of anaemia, and a shorter gap between surgery and RT will enable postoperative RT to achieve acceptable results with minimal morbidity[8].Theduration between surgery and adjuvant treatment was more than 6 weeks in 44% (12) patients and between 4 to 6 weeks in 32% (8)in the present study among the participants.

Jain et al. in a study on significance of pre-operative diagnosis and staging in carcinoma cervix, stated the importance of pre-operative staging to reduce the surgical trauma, reduce financial burden and delay in initiation of radiation treatmentin cervical cancer patients unfit for surgery[9].

Sharma et al in 83 patients with cervical carcinoma treated with post operative radiotherapy (PORT) following hysterectomy, treated with pelvic external beam radiation therapy (EBRT) followed by intravaginal brachytherapy (IVBT). It was observed, PORT provides greater clinical benefit in patients who had undergone Radical and Simple Hysterectomy for early stage invasive cervical carcinoma[10].

Appropriate staging and disease mapping prior to surgery helps in the management of cervical cancer, as management of cervical cancer is stratified according to the stage of the disease. Inadequate preoperative documentation of clinical disease and disease mapping, was seen in most cases included in the study. As a result, it was difficult to ascertain the pre-operative stage in the cervical cancer patients referred to our Centre for adjuvant therapy.

The absence of adequate surgical notes describing the method/type of surgery the patient underwent and lymph nodal dissection if done, lead to difficulty in stratifying the high-risk patients. Such patients required thorough clinical and radiological examination post operatively to rule out any residual disease.

The present study also gives an idea, that a standard surgical histopathology reporting with emphasis on possible risk factors such as tumor

size, margin status, parametrial invasion, lymph node status, stromal invasion, and lymphovascular space invasion is required, to categorize the patients and plan for adjuvant treatment.

Based on the Histopathological reports, surgical resection and clinical judgement, the treating surgeon, must refer patients for adjuvant therapy at the earliest without delay. This would help in achieving better overall survival in post-operative cervical cancer patients.

Adequate radiation dose with or without chemotherapy must be delivered especially in the high-risk patients. Adequate dose delivery in post operative patients is difficult due to distorted anatomy as a result of surgical interventions. Patients with short vagina and with residual/recurrent disease, require high dose delivery locally, which can be delivered byinterstitial brachytherapy only, which requires expertise and specialized facility.

V. CONCLUSION

Completepre-operative clinical stagingwith radiological investigations forms the main stay in the management of cervical cancer, as the treatment for cervical cancer is stratified based on FIGO staging.Plan for surgery should be decided with the stage of disease and patient related parameters.Adequate radiation dose with or without chemotherapy must be delivered especially in the high-risk post operative cervical cancer patients. Adequate dose delivery in post operative patients is difficult due to distorted anatomy as a result of surgical interventions. The combination of surgery and radiotherapy increases the risk of post-treatment morbidities several-fold.

VI. LIMITATION

Limitations of the study were small sample size, imperfect assessment of pre-operative cervical cancer stage, lack of central pathology review and shorter follow up among the patients as a result of which long term follow up record could not be maintained.In view of global pandemic of COVID 19 many patients could not report to hospitals at the onset of symptoms which resulted in many locally advanced cervical cancer cases being presented.

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TABLES, FIGURE AND GRAPHS

Table 1: Risk factorsamong the study participants

Age group	Number of Patients	%
35-40 years	4	16.0
41-50 years	6	24.0
51-60 years	7	28.0
61-70 years	8	33.3
Socio-economic Status		
Lower	10	40.0
Upper Lower	8	32.0
Lower Middle	5	20.0
Upper Middle	2	8.0
Age at Menarche 13-14 years	17	68.0
Para > 3	13	52.0
Age at first child birth < 18 years	14	56.0
Birth spacing < 2 years	15	60.0
Multiple sexual partners	2	8.0
Oral Contraceptive Use	1	4.0

Table 2: Clinical profile among the study participants

Chief complaints	Number of Patients	%
Whitish PV discharge	16	64.0

PV Bleed/ PV spotting	14	56.0
Post coital Bleed	4	16.0
Lower abdominal pain	7	28.0
Place of surgery		
At our institute	2	8.0
Referred from other centers	23	92.0
Pathological risk factors		
Tumor Size > 4cm	6	24.0
Positive Cut Margins	2	8.0
Positive LN's	4	16.0
Deep Stromal invasion	10	40.0
Lymphovascular space invasion	5	20.0
Duration between surgery and adjuvant treatment	12	44.0
Residual lesion and/or Lymph node present on post op investigation	11	44.0

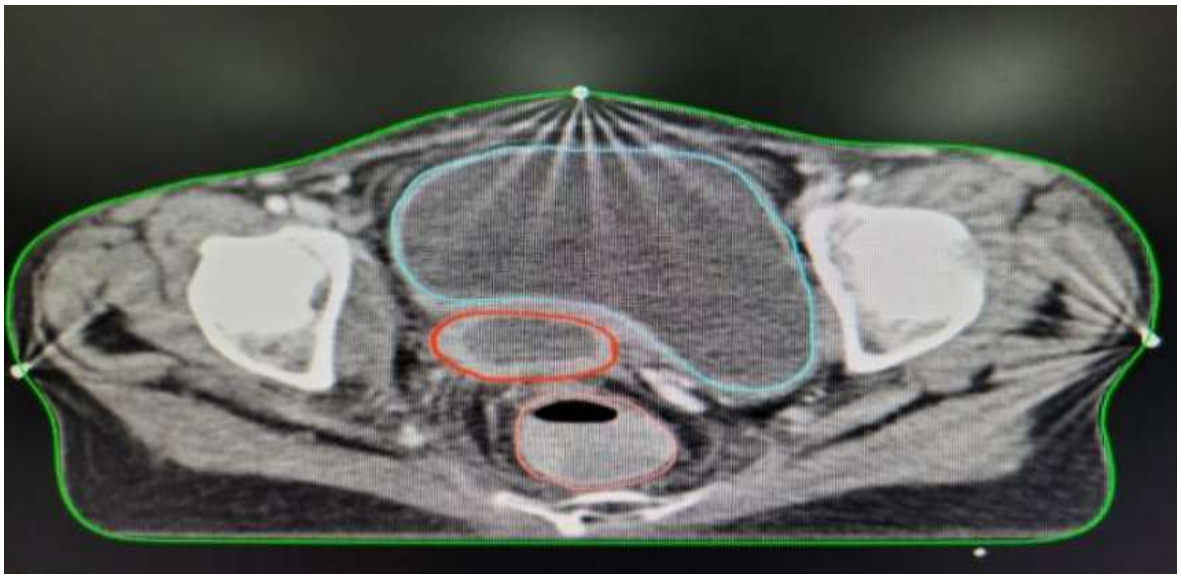

Figure 1: Gross residual lesion on marker CT in a post operative cervical cancer patient treated at our institute.

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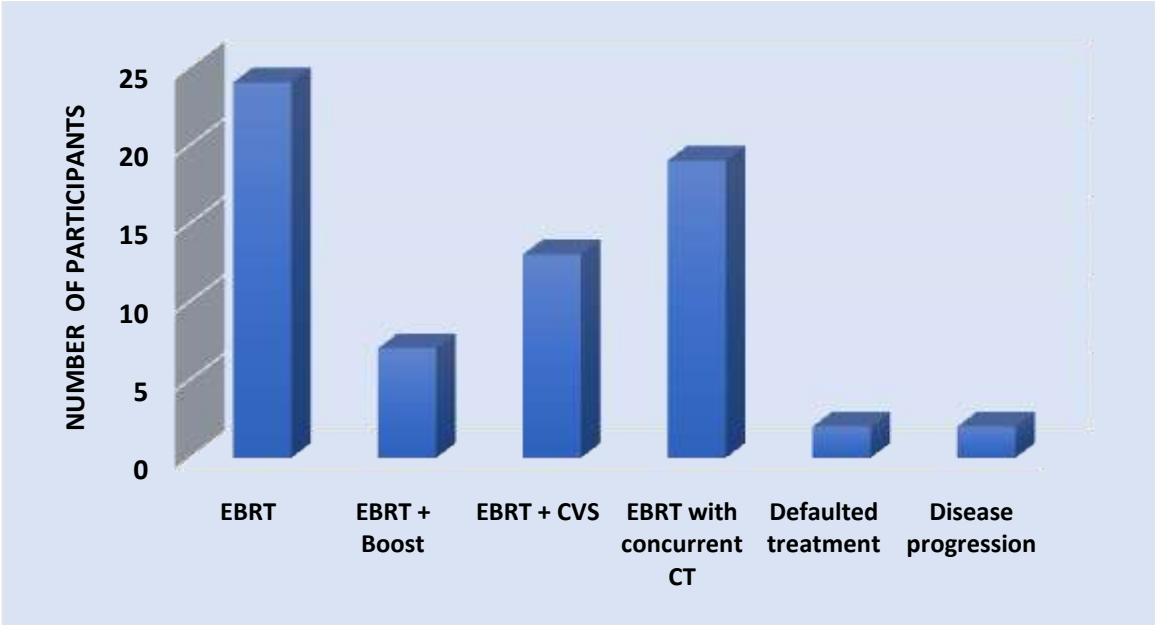
Treatment:

Table 3: Modalities of treatment deliveredamong the study participants

Treatment	Frequency(n)	%
EBRT	24	96.0
EBRT + BOOST	7	28.0
EBRT + CVS	13	52.0
EBRT + Concurrent CT	19	76.0
Defaulted Treatment	2	8.0
Disease Progression	2	8.0



Graph 1: Modalities of treatment deliveredamong the study participants

Acute toxicities according to CTCAE criteria Version 5.0:

Table 4: Treatment toxicityamong the study participants

Toxicity	Skin	%	GI	%	GU	%
GradeI	15	62.5	16	66.6	10	41.6
GradeII	9	37.5	8	33.3	4	16.6
GradeIII	0	0.0	0	0.0	0	0.0
GradeIV	0	0.0	0	0.0	0	0.0
GradeV	0	0.0	0	0.0	0	0.0

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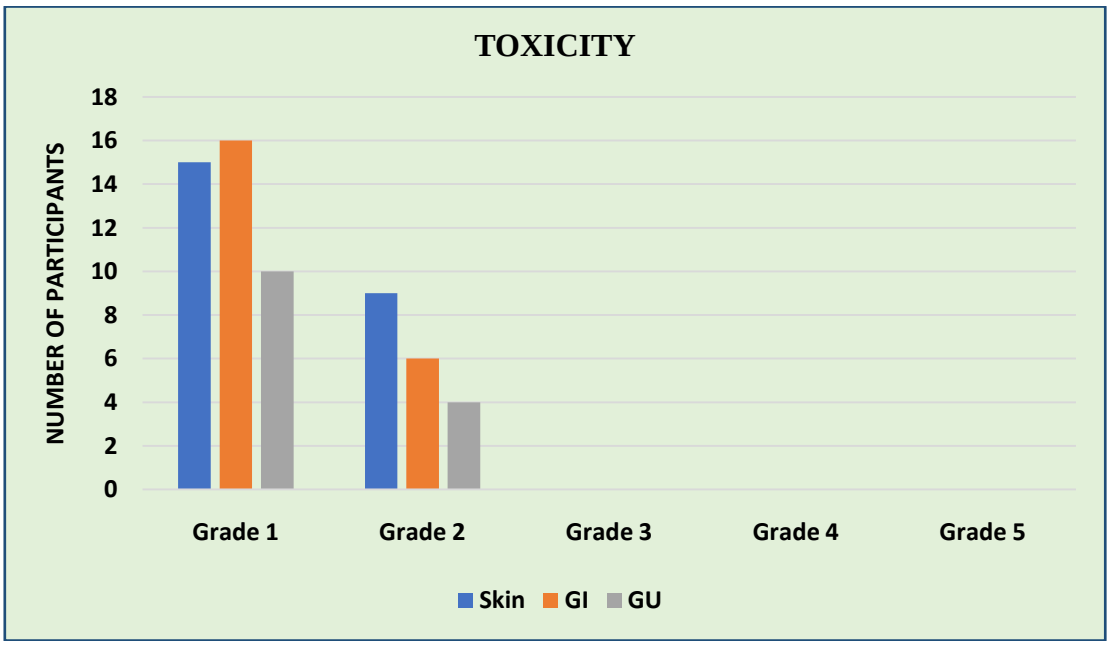


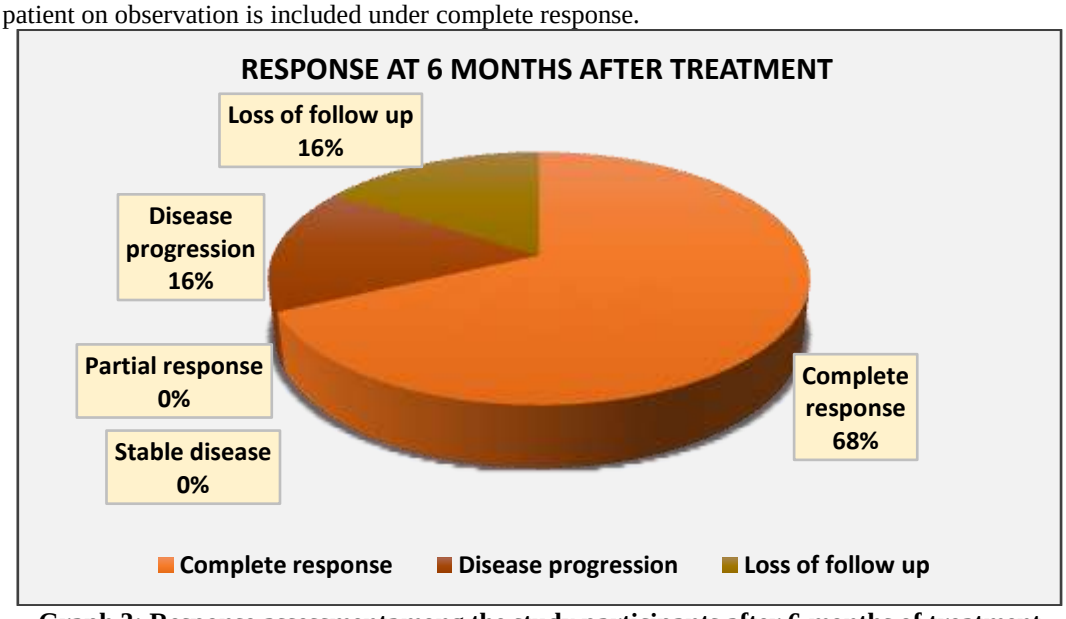
Graph2: Treatment toxicityamong the study participants

Response assessment after 6 months of treatment:

Table 5: Response assessmentamong the study participants after 6 months of treatment

Response	Frequency(n)	%
Complete response	17*	68.0
Partial response	0	0.0
Stable disease	0	0.0
Disease progression	4	16.0
Loss of follow up	4	16.0

*One patient on observation is included under complete response.



Graph 3: Response assessmentamong the study participants after 6 months of treatment