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Original Research Paper

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CARCINOMA CERVIX PROGNOSTIC SIGNIFICANCE OF TREATMENT DURATION

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ABSTRACT **Aim:** To study prognostic significance of treatment duration in carcinoma cervix. **Materials and methods:** Prospective Analysis of forty patients of carcinoma cervix were analyzed from July 2019 to June 2022. All patients were planned for chemoradiation followed by brachytherapy. Clinical response was assessed (as per WHO criterion) during radiotherapy and every month after radiotherapy for at least 6 months. Collected data was analyzed using standard statistical methods. **Results:** In patients with treatment duration ≤ 8 weeks, residual was observed in 18% (12/66) of patients. While in patients with treatment duration > 8 weeks residual was observed in 57% (8/14) of the patients at end of 6 months after treatment. This difference in duration of treatment for residual is statistically significant (p=0.031). **Conclusion:** Duration of treatment has significant impact in treatment outcome of carcinoma cervix.

KEYWORDS : cervix, carcinoma, treatment, residual, survival, duration

INTRODUCTION

According to GLOBOCAN 2018, it was projected that around 18.1 million people would be diagnosed with cancer and approximately 9.6 million would die from the disease in 2018. Among women globally, cervical cancer ranked as the fourth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths, following breast, colorectal, and lung cancers. The estimated number of new cervical cancer cases each year worldwide is about 570,000, with approximately 311,000 deaths occurring in 2018.[1] Cervical cancer has a much lower mortality rate compared to its incidence, with a mortality-to-incidence ratio of 50.3%.[2] It is leading cause of cancer deaths in Sub-Saharan Africa and South Eastern Asia.

Developing countries bear more than 85% of the global burden of cervical cancer, with the disease accounting for 13% of all female cancers worldwide.[2] Specifically in India, cervical cancer represents 16% of all cancer cases.[3] Cervical cancer is the second most common cancer in developing countries after carcinoma breast, but only the tenth most common in developed countries.

In India, there are significant statistics related to cervical cancer.[4] The female population aged 15 years and above, which is at risk for cervical cancer, is approximately 432.20 million. Annually, there are around 122,844 new cases of cervical cancer reported in the country. Tragically, the disease leads to approximately 67,477 deaths each year. The crude incidence rate of cervical cancer stands at 20.2 cases per 100,000 population per year, while the age-standardized incidence rate is 26.0.

Cervical cancer is rare in women under 30 yrs of age and and it becomes more prevalent as women reach the age of 40 and older. The highest number of fatalities from cervical cancer typically occurs among women in their 50s and 60s,[5] with most women diagnosed in advanced stages. 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.[6,7] A large multinational study on cervical cancer has found that over 90% of all cervical cancer cases worldwide are caused by 8 HPV types: 16, 18, 31, 33, 35, 45, 52, and 58. Among these types, three specifically 16, 18, and 45- are responsible for 94% of cervical adenocarcinomas.[8] The infection of Human Immunodeficiency Virus (HIV) is associated with a five-fold increase in the risk of cervical cancer, likely due to an impaired immune response to HPV (Human Papilloma Virus) infection.[9]

About 85% of cervical cancers are squamous cell cancers and the remainder adenocarcinomas. Endometroid, small cell carcinoma, serous and clear cell carcinoma are rare histological variants of cervical cancer. Adenocarcinoma is reported four times more commonly than squamous carcinoma in cervical stumps.[10]

Many prognostic factors have been recognized in patients with cancer cervix that affects treatment outcome and causes failure. These have been divided into 1) patient related 2) tumor related and 3) treatment related factors. Patient related factors are - age, medical co-morbidities, renal status, blood hemoglobin level, HIV and HPV. Tumor related factors are - stage, lymph node involvement, parametrial extension, hydronephrosis, histology, grade and size of tumor. Treatment related factors are duration of treatment and total radiation dose and concurrent use of chemotherapy.[11-14]

The prognosis for patients with cervical cancer varies depending on the stage of the disease. Generally, the 5-year survival rates are as follows: for stage I, the survival rate is greater than 90%; for stage II, it ranges from 60% to 80%; for stage III, it is approximately 50%; and for stage IV, it is less than 30%.

The treatment of cervical cancer varies with the stage of disease. Concurrent Chemoradiotherapy (CCRT) is now the preferred treatment for more advanced stages of disease (I b-II b, III, and IV a). Stage I and II a tumors can be treated surgically or with radiotherapy, with a five-year survival rate of 80 to 90 percent.[15] In patients with disseminated disease, chemotherapy or radiation provides symptom palliation. The present study aimed to study prognostic significance of treatment duration in carcinoma cervix.

MATERIAL AND METHODS

Prospective Analysis of forty patients of carcinoma cervix were analyzed who were treated in the Cancer Department J. A. Hospital Gwalior. Study Duration was July 2019 to June 2022. Inclusion criteria includes biopsy proven cancer cervix, Age above 18 years, Karnofsky performance scale above 70, stage IA to IIIB, No history of previous malignancy, Hepatic, renal and cardiopulmonary functions were adequate. Exclusion

criteria includes Carcinoma of the cervix FIGO stage IV patients, Metastatic disease, Any previous pelvic surgery, Any previous chemotherapy, Previous pelvic radiotherapy.

All patients were planned and delivered by 3- Dimensional Conformal radiotherapy using four field box technique. Radiotherapy dose delivered to pelvic area was 50 Gy in 25 fractions at 200cGy/day. This was followed by intracavitary brachytherapy either 4 applications of 6Gy/fraction or 3 applications of 7Gy/fraction each as per departmental protocol. Total duration of the treatment is less than 8 weeks. Patients received cisplatin 35mg/m^2 weekly intravenous for a total of 5 cycles or 75mg/m^2 triweekly intravenous for a total of 2 cycles.

Clinical response was assessed (as per WHO criterion) during radiotherapy and every month after radiotherapy for at least 6 months. Collected data was analyzed using standard statistical methods (Chi Square test) and software to calculate level of significance using "p" value. Statistical significance considered with p-value of <0.05

RESULTS

At the end of 6 months, outcome of treatment of patients were analyzed in terms of WHO response criteria. Table 1 showed baseline characteristics. The mean age at diagnosis was 52 years. The majority of the patients had FIGO stage IIIB (n = 57; 71.2%).

Table – 1 Clinical Characteristics Of Patients With Cervical Cancer

Characteristics	Number of patients (N=80)
Age (years)	52 (2.5)
BMI (kg/m2)	23.5 (4.2)
Blood leukocyte count (cells/mm3)	9697 (4572)
Serum albumin level (g/dL)	3.37 (0.6)
FIGO staging, n (%)	
Stage IA	2 (2.5)
Stage IIA	15 (18.8)
Stage IIIA	6 (7.5)
Stage IIIB	57 (71.2)
Data shown as mean (SD), unless otherwise specified.	

At end of 6 months, outcome of treatment of patients were analyzed in terms of WHO response criteria. In our study out of total 80 cases studied, 75% (60/80) of patients had complete response, 20% (16/80) had partial response and 5% (4/80) of patients had progressive disease (Figure 1).

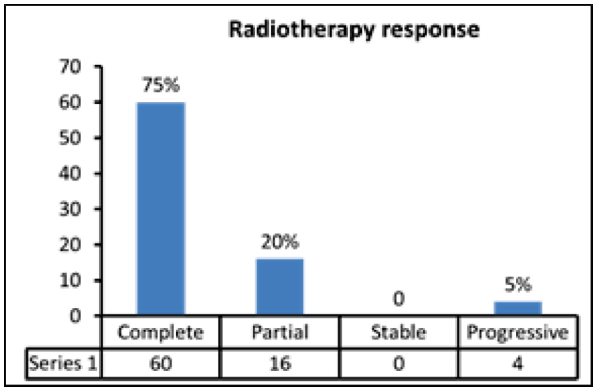

Figure – 1 Outcome Of Treatment Of Patients At End Of 6 Months

In patients with treatment duration ≤ 8 weeks, residual was observed in 18% (12/66) of patients (Table 2). While in patients with treatment duration > 8 weeks residual was observed in 57% (8/14) of the patients at end of 6 months after treatment. This difference in duration of treatment for residual is statistically significant (p=0.031).

Table – 2 Duration Of Treatment Vs. Response At 6 Months

Duration Of Treatment	Total number of patients	Patients disease free at 6 months follow up, n (%)	Patients with residual at 6 months follow up, n (%)	p-value
≤ 8 weeks	66	54 (82)	12 (18)	0.031
> 8 weeks	14	6 (43)	8 (57)	

The mean (SD) cause specific survival (CSS) and overall survival (OS) times in the subgroups with overall treatment duration of ≤ 8 weeks compared with > 8 weeks were 72.4 (1.5) and 62.2 (1.1) months versus 65.8 (0.7) and 56.8 (0.8) months, respectively (Table 3). The crude hazard ratios (HRs) for CSS and OS in the subgroup of patients with an overall treatment duration of > 8 weeks were 1.78 (95% confidence interval, CI = 1.51-1.89, p < 0.001) and 1.53 (95% CI = 1.28-1.65, p < 0.001), respectively.

Table – 3 Impact Of The Duration Of The Entire Course Of Treatment According To Cox's Proportional Hazards Model

	Mean survival time (months)			95% (CI)		Cox's proportional hazards	
	Total	Death	Mean (SD)	Lower bound	Upper bound	HR (95% CI)	p-value
OS							
≤ 8 weeks (ref.)	66	15	62.2 (1.1)	58.7	68.5	1.00	0.001
> 8 weeks	14	6	56.8 (0.8)	55.9	62.9	1.53 (1.28–1.65)	
CSS							
≤ 8 weeks (ref.)	66	11	72.4 (1.5)	70.8	73.7	1.00	0.001
> 8 weeks	14	4	65.8 (0.7)	63.4	67.8	1.78 (1.51–1.89)	

CCRT: curative concurrent chemoradiotherapy; CI: confidence interval; CSS: cancer-specific survival; HR: hazard ratio; OS: overall survival; RT: radiotherapy; SE: standard error.

DISCUSSION

In this study, it was observed that the majority of patients (n = 60, 75%) achieved a complete response to the radiotherapy treatment. This indicates a relatively positive response to radiotherapy, although the response rate was slightly higher than that reported in a previous study conducted in 2018 by Rahakbauw E and Winarto H (68.29% complete response in 84 patients).[16] The variance in response rates between the studies could be attributed to factors such as differences in sample size and duration of observation. However, another study conducted by Amin et al. at Dr Soetomo Hospital in Surabaya yielded similar results, with 70.4% of patients achieving a complete response and no complete response observed in 29.6% of patients.[17]

Eifel et al. concluded that better results are achievable when the treatment is completed in 8 weeks or less.8 Expected 1% decrement in local control for every additional day beyond 56 days.[18-21] Vishma B.K.[22] conducted a study among the 380 cervical cancer patients and concluded that age at diagnosis, performance status at presentation, staging and treatment duration were the prognostic factors for cervical cancer. In a study of Ruta Grigienė,[23] 162 patients were analyzed, the radiotherapy duration had showed significant influence on overall survival (p=0.045), disease free survival (p=0.006) and local control (p=0.033).

Several retrospective studies have found a correlation between a prolonged overall treatment time and lower rates of pelvic control and CSS in cervical cancer patients who undergo definitive radiation therapy without concurrent chemotherapy. In a retrospective study by Petereit et al., it was observed that an overall treatment time exceeding 55 days was a negative factor for pelvic control and CSS in a cohort of 209 cervical cancer patients treated with external beam radiotherapy and low-dose rate brachytherapy.[24] Similarly, Chen et al. reported that an overall treatment time longer than 63 days was linked to reduced pelvic control and 5-year cause-specific survival in their series of cervical cancer patients receiving external beam radiotherapy and high-dose rate brachytherapy.[25] However, it should be noted that these studies were conducted before concurrent chemoradio therapy became the standard treatment approach for cervical carcinoma.[26]

In present study, residual was observed in 18% of the patients with treatment duration ≤ 8 weeks. While in patients with treatment duration > 8 weeks residual was observed in 57% of the patients. This difference in duration of treatment for residual is statistically significant (p=0.031). The duration of treatment plays a crucial role as a prognostic factor that significantly influences treatment outcomes. When the duration of treatment is prolonged, it can have an impact on the overall prognosis and effectiveness of the treatment. Factors such as adherence to treatment protocols, timely adjustments or modifications to the treatment plan, and patient compliance can all contribute to the duration of treatment. In correlation with Eifel et al study and Ruta Grigiene study, our study concluded that prolonged duration of treatment is a significant prognostic factor that affects treatment outcome.

CONCLUSIONS

The duration of treatment in cervical cancer patients was found to be a significant factor impacting disease-free survival in the present study. This highlights the importance of optimizing treatment protocols and minimizing delays to ensure timely and effective management of cervical cancer. Further research and interventions aimed at reducing treatment duration and improving treatment efficiency may lead to better outcomes for patients with cervical cancer.

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