Original Research Article

Comparison of outcome of interdigitated versus sequential brachytherapy along with concurrent chemoradiation in locally advanced carcinoma cervix

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ABSTRACT

Background: Carcinoma cervix is a significant health concern, particularly in lower socioeconomic groups. The effectiveness of interdigitated versus sequential brachytherapy, both with concurrent chemoradiation, in treating this condition remains underexplored.
Methods: This quasi-experimental study at Rajshahi Medical College Hospital enrolled 63 patients with biopsy-proven squamous cell cervical cancer. They were randomly divided into two arms: arm a received pelvic EBRT 50 Gy in 25 fractions, followed by HDR brachytherapy (7 Gy weekly $\times$ 3 weeks) starting after 30 Gy of EBRT; arm B received the same pelvic EBRT, followed by HDR brachytherapy (7 Gy weekly $\times$ 3 weeks) starting a week after the completion of EBRT.
Results: Mean age was 47.82±8.45 years (range: 29-64 years). The mean OTT was significantly reduced in arm-A (36.58 days) compared to arm-B (59.5 days). In terms of treatment response, 90.32% of patients in arm-A and 78.12% in arm-B experienced a complete response.
Conclusions: Interdigitated brachytherapy with concurrent chemoradiation significantly reduces treatment time without compromising treatment effectiveness. Despite a shorter treatment duration, the complete response rate was slightly higher in the interdigitated arm.

Keywords: Sequential brachytherapy, Concurrent chemoradiation, Advanced carcinoma cervix

INTRODUCTION

Cervical cancer is a significant global health issue, being the fourth most common cancer among women worldwide.[1] The primary cause of cervical cancer is persistent infection with high-risk human papillomavirus (HPV), particularly HPV types 16 and 18, which are responsible for approximately 70% of all cases.[2-4] Other risk factors include early sexual activity, multiple sexual partners, long-term use of oral contraceptives, and smoking.[5-7] The treatment of early-stage cervical cancer typically involves surgery, often followed by adjuvant radiotherapy or chemoradiation to reduce the risk of recurrence.[8] However, despite these interventions,

recurrence rates remain high, particularly in patients with high-risk factors such as lymph node metastasis, deep stromal invasion, and lymphovascular space involvement.[9] Recent advancements in the treatment of cervical cancer have focused on improving the effectiveness of adjuvant therapies. One such approach is sequential chemoradiation (SCRT), which involves the administration of chemotherapy followed by radiation therapy. This approach has been shown to improve disease-free survival (DFS) and overall survival (OS) compared to radiotherapy alone or concurrent chemoradiation (CCRT) in patients with early-stage cervical cancer.[9] However, the optimal adjuvant treatment for early-stage cervical cancer remains a subject of ongoing debate. While some studies have shown a survival benefit with SCRT, others have found no significant difference between SCRT and CCRT or radiotherapy alone.[9,10] Furthermore, the choice of adjuvant treatment may be influenced by factors such as patient characteristics, tumor features, and the availability of resources.[8] The aim of the present study is to compare the outcomes of two different treatment approaches for locally advanced cervical cancer: interdigitated and sequential brachytherapy, both in conjunction with concurrent chemoradiation. The study seeks to evaluate the effectiveness of these treatment modalities in terms of local disease control, acute toxicity, and patient survival. Furthermore, it aims to contribute to the existing body of knowledge by providing insights into the potential benefits and drawbacks of these treatment approaches, thereby aiding clinicians in making informed decisions about the most suitable treatment plan for their patients. Ultimately, the goal is to improve the quality of life and survival outcomes for women diagnosed with locally advanced cervical cancer.

METHODS

A total of 68 patients were initially enrolled in this quasi-experimental study, a design that allows for comparison between groups but lacks random assignment, at the department of radiotherapy, Rajshahi Medical College Hospital, Rajshahi, from January 2020 to December 2020. Each arm initially had 34 patients. However, three patients from arm A were excluded due to the failure of the ICRT instrument to be introduced in the cervix. In arm B, one patient was excluded due to nephrotoxicity development, and another patient did not receive the 3rd fraction of ICRT. The final analysis was conducted on 63 patients, with 31 in arm A and 32 in arm B, who completed the treatment as per protocol. Patients with locally advanced squamous cell carcinoma of the uterine cervix (FIGO stage IIB–IVA) who visited the department of radiation oncology during the study period were included using purposive sampling, a non-random technique where subjects are selected because of their unique characteristics. Data collection utilized a semi-structured form, and the sample size was determined based on previous study responses, with a final size of 34 patients in each arm, calculated at a significance level of 5% and 80% power. Exclusion criteria covered patients with hysterectomy, prior carcinoma cervix treatment, ECOG performance status 3 or 4, serious medical illnesses, distant metastasis, pregnant or lactating women, and patients aged below 18 years or above 70 years. Treatment planning allocated patients to two arms: arm A received concurrent chemoradiation with EBRT and HDR-brachytherapy (7 Gy weekly × 3 weeks) starting after 30 Gy of EBRT, while arm B received concurrent chemoradiation with EBRT and HDR-brachytherapy (7 Gy weekly × 3 weeks) starting one week after completing EBRT. Both groups received weekly injection cisplatin 40 mg/m² with hydration, and treatment response was evaluated using RECIST 1.1 criteria. The treatment technique involved manually delineated EBRT fields with 50 Gy in 25 fractions over 5 weeks (2 Gy per fraction) for both arms, using a constant bladder filling protocol. HDR brachytherapy was delivered using Co-60 after loading technique with specific dose prescriptions for each arm. Throughout treatment, patient assessment, response criteria evaluation, symptom relief, quality of life improvement, and toxicity reporting were conducted. Follow-up examinations were performed at 4th, 8th, and 12th weeks after completing therapy. Data analysis and interpretation were carried out using IBM statistical package for the social sciences (SPSS) software version 25.0. Unpaired 't' tests were used for continuous variables to compare means between two unrelated groups, and χ^2 tests were used for categorical variables to test the independence of two variables, with a significance level of $p<0.05$. Ethical considerations involved obtaining approval from the institutional review board and ethical committee of Rajshahi Medical College. Informed consent was obtained from all patients, ensuring confidentiality of their information. The study was conducted in accordance with the declaration of Helsinki, and all participants were informed of their rights to withdraw from the study at any time without any consequences.

RESULTS

The mean age of patients in arm-A (interdigitated brachytherapy with concurrent chemoradiation) was 46.77±7.80 years, while in arm-B (sequential brachytherapy with concurrent chemoradiation), it was 48.84±9.04 years, with an overall mean age of 47.82±8.45 years. The difference in mean age between the two arms was not statistically significant (p=0.434). Regarding the residence, the majority of patients in both arms came from rural areas, constituting 74.19% in arm-A and 78.12% in arm-B, with a total of 76.19%. The difference in residence distribution between the two arms was not statistically significant (p=0.714). Regarding education status, the highest proportion of patients in both arms were categorized as illiterate, accounting for 45.16% in arm-A and 50% in arm-B, making up 47.61% of the total. The education status distribution did not show a significant difference between the two arms (p=0.729). Regarding occupation, the majority of patients in both arms were housewives, making up 80.64% in arm-A and 75% in arm-B, with a total of 77.77%. The distribution of occupation

did not show a significant difference between the two arms (p=0.428). Regarding socio-economic status (monthly income), the highest proportion of patients in both arms fell into the income bracket of <12,260 Taka, accounting for 61.29% in arm-A and 71.87% in arm-B, comprising 66.66% of the total. The socio-economic status distribution did not show a significant difference between the two arms (p=0.491). The statistical analysis for categorical variables was done using the Chi-squared test (χ^2), while the t-test was used to determine the significance of the difference in mean age between the two arms. Among the patients 26 (46.03%) were in between 41-50 years. There was no significant difference of age in between patients of two arms (p=0.512).

The distribution of risk factors in arm-A (interdigitated brachytherapy with concurrent chemoradiation) and arm-B (sequential brachytherapy with concurrent chemoradiation) was analyzed. For the risk factor "age of marriage," 70.96% of patients in arm-A and 75% in arm-B got married before 18 years of age, while 29.03% in arm-A and 25% in arm-B got married at or after 18 years. The difference in the age of marriage between the two arms was not statistically significant (p=0.718). Regarding the risk factor "parity," the majority of patients in both arms had a parity of 1-3, constituting 25.80% in arm-A and 35.29% in arm-B, with a total of 30.15%. Patients with a parity of 4-6 were 64.51% in arm-A and 58.82% in arm-B, comprising 61.90% of the total. Only a small percentage of patients in both arms had a parity greater than 6, with 9.67% in arm-A and 5.88% in Arm-B, making up 7.93% of the total. The distribution of parity did not show a significant difference between the two arms (p=0.710). Regarding the risk factors "tobacco use (SLT user)," "H/O OCP," and "poor personal hygiene," the majority of patients in both arms exhibited these risk factors, with 74.19%, 83.87%, and 80.64% in arm-A, and 81.25%, 87.5%, and 84.37% in arm-B, respectively. The distributions of these risk factors did not show a significant difference between the two arms, with p values of 0.501, 0.681, and 0.697, respectively. For the risk factor "multiple sexual partner (due to more than 1 marriage)," only a small percentage of patients in both arms reported having multiple sexual partners due to more than one marriage, with 12.90% in arm-A and 15.62% in arm-B, making up 14.28% of the total. The difference in this risk factor between the two arms was not statistically significant (p=0.758). Regarding the risk factor "age of first pregnancy," 70.96% of patients in arm-A and 78.12% in arm-B experienced their first pregnancy before 18 years of age, while 29.03% in arm-A and 21.87% in arm-B had their first pregnancy at or after 18 years. The difference in the age of first pregnancy between the two arms was not statistically significant (p=0.514).

The majority of patients in both arms were at stage IIB, constituting 64.70% in arm A and 55.88% in arm B, with a total of 60.29%. Patients at stage IIIA accounted for 19.35% in arm A and 25% in arm B, making up 22.22% of the total. For patients at stage IIIB, the percentage was

11.76% in arm A and 14.70% in arm B, totaling 11.11% of the patients. There was only one patient at stage IVA, which was observed in arm B, representing 3.125% of this arm and 1.58% of the total. The distribution of disease stages did not show a significant difference between the two arms, with a p value of 0.652, as determined by the Chi-squared test (χ^2).

In the per-speculum examination, the majority of patients in both arms exhibited bleeding (80.64% in arm A and 81.25% in arm B), with a total of 80.95%. Additionally, all patients showed growth in this examination in both arms, accounting for 100% of the total study subjects. Regarding the per-speculum discharge, 83.87% in arm A and 87.5% in arm B had this symptom, making up 85.71% of the total. Similarly, in the per-vaginal examination, most patients experienced bleeding (80.64% in arm A and 81.25% in arm B), totaling 80.95%. All patients demonstrated growth in this examination in both arms, comprising 100% of the total subjects. Moreover, in the per-vaginal discharge, 83.87% in arm A and 87.5% in arm B exhibited this finding, constituting 85.71% of the total. For the bimanual, per rectal, and rectovaginal examination, all patients (100%) in both arms displayed growth, and a high proportion of patients showed parametrium involvement (93.54% in arm A and 93.75% in arm B), with a total of 93.65%.

The mean OTT in arm A was significantly reduced to 36.58 days, ranging from 35 to 42 days, whereas in arm B, it was 59.5 days, ranging from 56 to 63 days (p<0.001). The unpaired t-test was employed to determine the p value, which indicated a highly significant difference in the overall treatment time between the two arms. The implementation of interdigitated brachytherapy with concurrent chemoradiation in arm A led to a considerable reduction in the treatment duration compared to sequential brachytherapy in arm B, making it a more efficient and promising approach for the patients.

Response assessment was done 3 months after the completion of treatment by imaging (CT scan of whole abdomen and pelvis). In arm A, 28 (90.32%) patients experienced complete response (CR) and 3 (9.67%) had partial response (PR). While in arm B, CR was experienced by 25 (78.12%) of patients, whereas 7 (21.87%) had PR. No patient in both the groups observed stable or progressive disease. The difference was not statistically significant (p>0.05) between two groups.

There were no significant differences in treatment response between the two arms for most symptoms. Pervaginal discharge showed a treatment response of 80.76% in arm A and 78.57% in arm B (p=0.943). Per vaginal bleeding had a treatment response of 80.64% in arm A and 81.25% in arm B (p=1). Symptoms of anemia showed a response rate of 77.77% in arm A and 70% in arm B (p=0.905), while anorexia had a response rate of 66.66% in arm A and 65% in arm B (p=0.964). Weight loss had a treatment response of 81.81% in arm A and

77.77% in arm B (p=0.064). Pelvic pain showed a response rate of 85.71% in arm A and 80% in arm B (p=0.974). Urinary symptoms had a response rate of 100% in arm A and 50% in arm B (p=0.709). Overall, there were no significant differences in treatment response based on symptoms between the two arms.

The results showed that there were no significant differences in treatment response between the two arms for all three clinical examination categories. In both arms, the majority of patients exhibited complete response rates, with 83.87% in arm A and 68.75% in arm B for per-vaginal examination, 83.87% in arm A and 68.75% in arm B for per-speculum examination, and 83.87% in arm A and 68.75% in arm B for bimanual, per rectal and rectovaginal examination (p=0.630 for all categories). The percentage of patients showing partial response was lower in both arms, with 16.12% in arm A and 31.25% in arm B for per-vaginal examination, 16.12% in arm A and 31.25% in arm B for per-speculum examination, and 16.12% in arm A and 31.25% in arm B for bimanual, per rectal and rectovaginal examination (p=0.630 for all categories). Overall, there were no significant differences in treatment response based on clinical examination between the two arms.
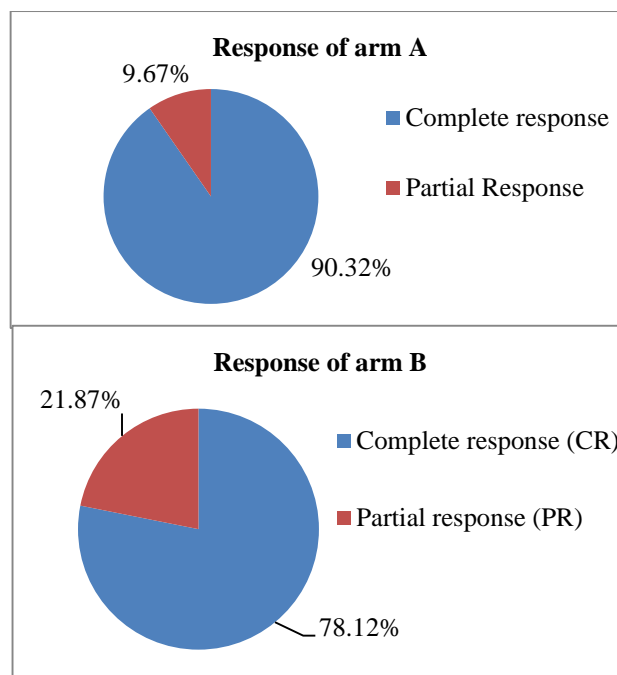

Figure 1: Response of the patients of both arms.

Table 1: Socio-demographic profile of patients (N=63).

Socio-demographic profile	Arm-A (n=31) No. (%)	Arm-B (n=32) No. (%)	Total (N=63) No. (%)	P value*
Mean age (years)	46.77±7.80	48.84±9.04	47.82±8.45	0.434
Residence				
Rural	23 (74.19)	25 (78.12)	48 (76.19)	0.714
Urban	08 (25.80)	07 (21.87)	15 (23.80)	
Education status				
Illiterate	14 (45.16)	16 (50)	30 (47.61)	0.729
Below SSC	12 (38.70)	13 (40.62)	25 (39.68)	
SSC	4 (12.90)	3 (9.37)	7 (11.11)	
HSC and above	1 (3.22)	0 (0)	1 (1.58)	
Occupation				
Housewife	25 (80.64)	24 (75)	49 (77.77)	0.428
Day labour	5 (16.12)	8 (25)	13 (20.63)	
School teacher	1 (3.22)	0 (0)	1 (1.58)	
Socio-economic status (monthly income) (Taka)				
<12,260	19 (61.29)	23 (71.87)	42 (66.66)	0.491
12,260-31,640	09 (29.03)	08 (25)	17 (26.98)	
>31,640	3 (9.67)	1 (3.12)	4 (6.34)	

Table 2: Risk factors among the patients of both arms (N=63).

Risk factors	Arm-A (n=31) No. (%)	Arm-B (n=32) No. (%)	Total (N=63) No. (%)	P value*
Age of marriage (years)				
Before 18	22 (70.96)	24 (75)	46 (73.01)	0.718
At or after 18	9 (29.03)	8 (25)	17 (26.98)	
Parity				
1-3	08 (25.80)	11 (35.29)	19 (30.15)	0.710
4-6	20 (64.51)	19 (58.82)	39 (61.90)	
>6	3 (9.67)	2 (5.88)	5 (7.93)	

Risk factors	Arm-A (n=31) No. (%)	Arm-B (n=32) No. (%)	Total (N=63) No. (%)	P value*
Tobacco use (SLT user)	23 (74.19)	26 (81.25)	49 (77.77)	0.501
H/O OCP	26 (83.87)	28 (87.5)	54 (85.71)	0.681
Poor personal hygiene	25 (80.64)	27 (84.37)	52 (82.53)	0.697
Multiple sexual partner (due to more than 1 marriage)	4 (12.90)	5 (15.62)	9 (14.28)	0.758
Age of first pregnancy (years)				
Before 18	22 (70.96)	25 (78.12)	47 (74.60)	0.514
At or after 18	9 (29.03)	7 (21.87)	16 (25.39)	

Table 3: Distribution of patients according to stage of disease (N=63).

Staging	Arm A (n=31) No. (%)	Arm B (n=32) No. (%)	Total (N=63) No. (%)	P value*
IIB	22 (64.70)	19 (55.88)	41 (60.29)	0.652
IIIA	6 (19.35)	8 (25)	14 (22.22)	
IIIB	3 (11.76)	4 (14.70)	7 (11.11)	
IVA	0	1 (3.125)	1 (1.58)	

Table 4: Examination findings of study subjects (N=63).

Clinical examination	Arm-A (n=31) No. (%)	Arm-B (n=32) No. (%)	Total (N=63) No. (%)
Per-speculum examination			
P/S bleeding	25 (80.64)	26 (81.25)	51 (80.95)
P/S growth	31 (100)	32 (100)	63 (100)
P/S discharge	26 (83.87)	28 (87.5)	54 (85.71)
Per-vaginal examination			
P/V bleeding	25 (80.64)	26 (81.25)	51 (80.95)
P/V growth	31 (100)	32 (100)	63 (100)
P/V discharge	26 (83.87)	28 (87.5)	54 (85.71)
Bimanual, per rectal and rectovaginal examination			
Growth	31 (100)	32 (100)	63 (100)
Parametrium involvement	29 (93.54)	30 (93.75)	59 (93.65)

Table 5: OTT (overall treatment time) of the patients of both arms (N=63).

OTT (days)	Arm A (n=31)	Arm B (n=32)	P value *
Mean	36.58	59.5	<0.001
Range	35 to 42	56 to 63	

Table 6: Assessment of response according to symptoms (after 4th week of treatment) (N=63).

Symptoms and response	Arm-A (n=31) No. (%)	Arm-B (n=32) No. (%)	Total (N=63) No. (%)	P value*
Per-vaginal discharge				
Persist	5 (19.23%)	6 (21.42)	11 (20.37)	0.943
Treatment response	21 (80.76%)	22 (78.57)	43 (79.62)	
Per vaginal bleeding				
Persist	00	00	00	1
Response	25 (80.64)	26 (81.25)	51 (80.95)	
Symptoms of anemia				
Persist	4 (22.22)	6 (30)	10 (26.31)	0.905
Response	14 (77.77)	14 (70)	24 (63.15)	
Anorexia				
Persist	6 (33.33)	7 (35)	13 (34.21)	0.964

Continued.

Symptoms and response	Arm-A (n=31) No. (%)	Arm-B (n=32) No. (%)	Total (N=63) No. (%)	P value*
Response	12 (66.66)	13 (65)	25 (65.78)	
Weight loss				
Persist	2 (18.18)	2 (22.22)	4 (20)	0.064
Response	9 (81.81)	7 (77.77)	16 (80)	
Pelvic pain				
Persist	2 (14.28)	3 (20)	5 (17.24)	0.974
Response	12 (85.71)	12 (80)	24 (82.75)	
Urinary symptom (dysuria, frequncy, nocturia)				
Persist	00	1 (50)	1 (33.33)	0.709
Response	1 (100)	1 (50)	2 (66.67)	

Table 7: Assessment of response according to clinical examination (after 4th week of treatment) (N=63).

Clinical examination and response	Arm-A (n=31) No. (%)	Arm-B (n=32) No. (%)	Total (N=63) No. (%)	P value*
Per-vaginal examination				
Complete response	26 (83.87)	22 (68.75)	48 (76.19)	0.630
Partial response	5 (16.12)	10 (31.25)	15 (23.80)	
Per-speculum examination				
Complete response	26 (83.87)	22 (68.75)	48 (76.19)	0.630
Partial response	5 (16.12)	10 (31.25)	15 (23.80)	
Bimanual, per rectal and rectovaginal examination				
Complete response	26 (83.87)	22 (68.75)	48 (76.19)	0.630
Partial response	5 (16.12)	10 (31.25)	15 (23.80)	

DISCUSSION

The study involved two treatment arms for carcinoma cervix: arm-A (interdigitated brachytherapy with concurrent chemoradiation) and arm-B (sequential brachytherapy with concurrent chemoradiation). The mean age of patients in arm-A was 46.77±7.80 years, while in arm-B, it was 48.84±9.04 years. The difference in mean age between the two arms was not statistically significant (p=0.434). This suggests that age did not significantly influence the assignment of patients to the treatment arms, which is consistent with the findings of a study by Haritha et al.[11] In terms of socioeconomic status, the highest proportion of patients in both arms fell into the income bracket of <12,260 Taka, accounting for 61.29% in arm-A and 71.87% in arm-B, comprising 66.66% of the total. This indicates that the majority of the patients were from a lower socioeconomic background, which is a significant factor to consider in the treatment and management of carcinoma cervix. The study also analyzed various risk factors, including age of marriage, parity, tobacco use, history of oral contraceptive pills (OCP), poor personal hygiene, multiple sexual partners due to more than one marriage, and age of first pregnancy. For instance, for the risk factor "age of marriage", 70.96% of patients in arm-A and 75% in arm-B got married before 18 years of age. This suggests that early marriage could be a potential risk factor for carcinoma cervix, which aligns with the findings of a study by Daripa et al.[12] This was also supported by multiple other studies.[13-15] One of the major findings of the study was the significant reduction in the overall treatment time (OTT) in arm-A compared to arm-B. The mean OTT in arm-A was significantly reduced to 36.58 days, ranging from 35 to 42 days, whereas in arm-B, it was 59.5 days, ranging from 56 to 63 days (p<0.001). This suggests that interdigitated brachytherapy with concurrent chemoradiation can lead to a considerable reduction in the treatment duration, making it a more efficient approach for patients.[16] This is supported by a study by Shewalkar et al, which also reported that dose-escalated intensity-modulated radiotherapy resulted in a satisfactory outcome with reasonably low levels of treatment-related acute gastrointestinal and genitourinary toxicities.[17] In terms of treatment response, in arm A, 28 (90.32%) patients experienced complete response (CR) and 3 (9.67%) had partial response (PR). While in arm B, CR was experienced by 25 (78.12%) of patients, whereas 7 (21.87%) had PR. This suggests that both interdigitated and sequential brachytherapy with concurrent chemoradiation can be effective in treating carcinoma cervix, although the complete response rate was slightly higher in arm A. Interestingly, despite the significant reduction in overall treatment time in arm-A, the treatment response showed no significant difference between both treatment methods. This indicates that the efficiency of the treatment method does not compromise the effectiveness of the treatment outcome. This is a crucial finding as it suggests that patients can benefit from a shorter treatment duration without sacrificing the quality of the treatment response. Moreover, the shorter treatment time in arm-A and no significant difference in treatment outcome after interdigitated brachytherapy with concurrent chemorad-

iation makes it a more beneficial method overall. This is particularly important in the context of patient comfort and healthcare resource utilization.

A shorter treatment duration can potentially reduce the burden on healthcare facilities and improve patient compliance and satisfaction. In conclusion, the study provides valuable insights into the comparative effectiveness of interdigitated and sequential brachytherapy with concurrent chemoradiation in treating carcinoma cervix. The findings suggest that interdigitated brachytherapy with concurrent chemoradiation, despite its shorter treatment duration, can lead to a similar treatment response as sequential brachytherapy. This makes it a promising approach for the treatment of carcinoma cervix, offering benefits in terms of both treatment efficiency and patient experience.

CONCLUSION

This study presents a comparative analysis of interdigitated and sequential brachytherapy, both with concurrent chemoradiation, for treating carcinoma cervix. The results indicate that interdigitated brachytherapy significantly reduces overall treatment time without compromising treatment effectiveness. Despite a shorter treatment duration, the complete response rate was slightly higher in the interdigitated arm, though not significantly different from the sequential arm. In conclusion, interdigitated brachytherapy with concurrent chemorad-iation emerges as a promising, efficient approach for carcinoma cervix treatment. It offers potential benefits in healthcare resource utilization and patient experience, warranting further research to validate these findings and explore long-term outcomes.

Recommendations

Interdigitated brachytherapy along with CCRT could be effective treatment option with limited toxicities and shorter duration of treatment. The study should be continued to see overall survival and late toxicities of the treatment.

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