DOI:10.31557/APJCP.2024.25.4.1333
A Randomized Controlled Trial

RESEARCH ARTICLE

Editorial Process: Submission:12/05/2023 Acceptance:04/12/2024

A Comparative Study of Clinical Outcomes in Locally Advanced Cervical Cancer: External Beam Radiotherapy (EBRT) and Sequential High Dose Rate Intracavitary Brachytherapy (HDRICBT) with or without Concurrent Cisplatin on the Day of ICBT Insertion - A Tertiary Care Center Randomized Controlled Trial in India

Shamila Alim[1]*, Shahid Ali Siddiqui[1], Mohd Akram[1], Seema Hakim[2], Mohd Asif Khan[3]

Abstract

Objective: The current study aimed to delve into the comparative clinical outcomes between external beam radiation therapy (EBRT) and sequential High Dose Rate Intracavitary Brachytherapy (HDRICBT) with or without concurrent cisplatin administration on the day of intracavitary brachytherapy (ICBT) insertion in women with locally advanced cervical cancer. **Methods:** In this study, conducted between January 2017 and July 2018 at a leading institute in India, diagnosed and untreated patients of locally advanced carcinoma cervix were randomized into two groups. Arm 1 received concurrent cisplatin before each course of brachytherapy, while Arm 2 underwent brachytherapy alone. The outcomes were compared in terms of acute and late toxicities, treatment response, and follow-up. Data analysis was performed using SPSS 16, with statistical significance set at $p < 0.05$. **Results:** Both study arms showed similar complete response (CR) rates of 73.3%, with no significant advantage of concurrent cisplatin before brachytherapy. However, a noteworthy trend emerged during follow-up. In the concurrent cisplatin group, the CR rate increased from 73.3% post 1 month of brachytherapy to 86.7% at 3 months and 83.3% at 6 months. Contrastingly, the control group showed CR rates of 73.3% post 1 month, 80% at 3 months, and 76.6% at 6 months. While not statistically significant, this observation suggests a possible enhancement in response rates with concurrent cisplatin and ICBT. **Conclusions:** Future studies focusing on the optimal drug, dosage, scheduling, and combining cisplatin with other agents are recommended to further explore the potential benefits observed in this study.

Keywords: Cancer cervix- concurrent chemotherapy- brachytherapy

Asian Pac J Cancer Prev, **25 (4)**, 1333-1338

Introduction

In the realm of treating women with locally advanced cervical cancer (LACC), the standard of care has transitioned from external beam radiation therapy (EBRT) in isolation to a comprehensive approach involving EBRT combined with brachytherapy and concurrent chemotherapy [1-2]. The American Brachytherapy Society advises specific dose ranges for different stages of cervical cancer, emphasizing the importance of appropriate dosages for optimal treatment outcomes [3]. Notably, the recommended dose limits for critical organs like the bladder, rectum, and sigmoid play a crucial role in treatment planning.

For patients grappling with locally advanced disease, particularly concerning central disease areas (cervix, vagina, and medial parametria), the efficacy of intracavitary brachytherapy (ICBT) dose delivery alongside EBRT remains pivotal. Studies consistently reaffirm the vital role of brachytherapy in boosting survival rates post-EBRT in cervical cancer management [4-8]. As a result, brachytherapy is now firmly established as a cornerstone in the treatment regimen for locally advanced cervical cancer cases ranging from stages IB2 to IVA following external beam radiation. In select instances involving early-stage disease (stages IA to IB1), brachytherapy

*[1]Department of Radiation Oncology, JNMCH, Aligarh Muslim University, Aligarh, Uttar Pradesh, India. [2]Department of Obstetrics and Gynecology, JNMCH, Aligarh Muslim University, Aligarh,Uttar Pradesh, India. [3]Department of Pathology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India. *For Correspondence: shamilazz007@gmail.com*

alone may suffice as the primary therapeutic modality [9].

Recent years have witnessed an upsurge in the utilization of High Dose Rate Intracavitary Brachytherapy (HDRICBT) owing to its distinctive advantages such as shorter treatment durations, enhanced patient comfort, efficient immobilization techniques, and outpatient-friendly procedures. Despite the global adoption of various dose and fractionation schedules, the optimal regimen for HDRICBT remains a topic of debate [10-14].

The current study aimed to delve into the comparative clinical outcomes between EBRT and sequential HDRICBT with or without concurrent cisplatin administration on the day of ICBT insertion in women with locally advanced cervical cancer. By exploring these treatment modalities, the study sought to shed light on potential avenues for improving patient care and outcomes in the management of this challenging disease.

Materials and Methods

Study Location and Design

This prospective randomized controlled study spanned 18 months, running from January 2017 to July 2018, with a focus on previously untreated patients diagnosed with locally advanced carcinoma cervix at the Department of Radiation Oncology in a tertiary care center in Northern India. The institute serves a substantial population in the region and obtained approval from its ethical committee (646/FM/17.07.2017).

Inclusion and Exclusion Criteria

Cervical carcinoma staging adhered to the 2009 International Federation of Gynecological and Obstetric (FIGO) criteria. Patients meeting the following criteria were included: histologically confirmed cervix carcinoma (FIGO stage IB to IVA), age ≥18 years, Karnofsky Performance Status (KPS) > 60%, and satisfactory hematologic, renal, and liver function parameters. Exclusion criteria comprised patients with severe concomitant illnesses, distant metastasis, pregnancy, breastfeeding, or prior treatment for the same condition.

Treatment Protocol

All patients underwent EBRT using a telecobalt 60 unit, delivering 50 Gy in 25 fractions to the pelvis alongside weekly concurrent cisplatin at 35 mg/m2. Following EBRT completion, patients were randomly assigned to either Arm 1 (study group) or Arm 2 (control group), simulated in a supine position. The standard EBRT field encompassed the pelvis with tailored techniques such as AP-PA fields or a four-field isocentric approach, reaching a dose of 40 Gy. Midline shielding was applied after 44 Gy, culminating in a total 50 Gy dose. Extended field irradiation was considered in cases of para-aortic nodal involvement.

Study Arm Protocol

Post-EBRT completion, patients in the study arm underwent three fractions of HDRICBT at 8 Gy each, spaced a week apart, concurrent with cisplatin at 35 mg/m2 on the day of brachytherapy before applicator insertion. The treatment utilized MicroSelectron HDR with Iridium 192 as the radiation source boasting 10 Curie of nominal activity. Employing Fletcher-Williamson applicators with intrauterine tandems and variously sized shielded vaginal colpostats tailored to individual anatomies ensured precise targeting and treatment delivery.

Control Arm Protocol

Patients in the control arm received only three fractions of HDRICBT at 8 Gy per fraction, totaling 24 Gy to point A. Doses to Point B, rectum, and bladder were meticulously calculated and monitored following the established ICRU 38 method. This involved using a bladder balloon and rectal marker for accurate dose assessment. Semi-orthogonal X-rays were employed to pinpoint the applicator's prescription points and critical structures like the bladder and rectum.

Monitoring toxicity

Weekly monitoring of acute hematological toxicity was conducted throughout treatment via serum examinations and blood cell counts. Patient-reported symptoms such as diarrhea, vomiting, and dysuria were recorded and graded according to the Radiation Therapy Oncology Group (RTOG) criteria [15].

Follow-up

Patients underwent regular evaluations before each chemotherapy course and weekly examinations by a Radiation Oncologist during radiotherapy. Standard investigations like complete blood count (CBC), renal function tests (RFT), and liver function tests (LFT) were performed, with supportive care administered when necessary. Adverse reactions were meticulously documented following the RTOG criteria. Clinical evaluations, including per-vaginal examinations, occurred at 6-8 weeks following treatment completion, followed by assessments at 3 and 6 months, then at three-month intervals throughout the study duration.

Response Assessment

Post-treatment, all patients were scrutinized for treatment response and acute toxicity. Response evaluation was carried out three months after completing the full treatment regimen via clinical and radiological examinations, including per-vaginal assessments and pelvic MRI scans.

Statistical analysis

Data analysis was performed using SPSS (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, IL, USA). The data were presented using proportions and frequency tables for categorical variables, while continuous variables were summarized using means and standard deviations. The Chi-square test was utilized to examine associations between variables, with statistical significance set at a p-value of less than 0.05. Comparative analyses of treatment responses and acute and late toxicities between the study arms were conducted upon completion of the study.

Results

A total of sixty-five patients were initially enrolled in the study. Response assessments were conducted one month after the completion of the last (third) fraction of ICRT. Unfortunately, five patients defaulted during EBRT due to radiotherapy-related toxicities, disease progression, and death (three, one, and one patient, respectively). The remaining sixty patients were then randomized into the study group (Arm 1) and control group (Arm 2), with patient characteristics summarized in Table 1.

Upon the completion of EBRT, thirty patients were included in each group, where none of them defaulted during ICRT, resulting in the successful completion of treatment per protocol for all sixty patients. The follow-up duration ranged from a minimum of 3 months to a maximum of 21 months, with a mean follow-up period of 8 months (Figure 1).

In the concurrent cisplatin before brachytherapy (CCBT) arm, the complete response (CR) rate was 73.3% (22/30) at one-month-post-brachytherapy, escalating to 86.7% (26/30) at 3 months and sustaining at 83.3% (25/30) at 6 months. Conversely, the control arm exhibited CR rates of 73.3% at one month, 80% at 3 months, and 76.6% at 6 months (Table 2) with corresponding p-values of 1, 0.55, and 0.73 at 1 month, 3 months, and 6 months, respectively. Grade III toxicity post-ICBT was documented in 20% (6/30) of patients in the study group, with manifestations including vaginal, gastrointestinal tract, hematological, and skin reactions (Table 3). Late reactions were observed during the final follow-up: the study arm had 13.3% (4/30) development of late reactions, encompassing proctitis, cystitis, and vaginitis, while the control arm saw 6.6% (2/30) late reactions (Table 4).

Regarding disease progression, 10% (3/30) of patients in the study arm experienced progression, while 16.6% (5/30) in the control arm exhibited disease progression (Table 5).

Discussion

The current study aimed to assess the impact of CCBT on the outcomes of patients with locally advanced Carcinoma cervix. The incorporation of concurrent chemotherapy with EBRT in such patients is a well-established practice, with cisplatin being a commonly utilized radiosensitizer in this context [2, 4-6]. While the concurrent use of radiosensitizers or chemotherapy agents with brachytherapy remains a relatively nascent area, it holds significant promise due to its sound theoretical foundations and potential efficacy for patients with locally advanced cervical cancer.

In cervical cancer treatment, the delivery of a boost dose to the uterine cervix and parametria is primarily achieved through brachytherapy, necessitating precise treatment planning to achieve optimal doses to the rectum and bladder [5-8]. Given these considerations, it is intriguing to contemplate the optimal timing of

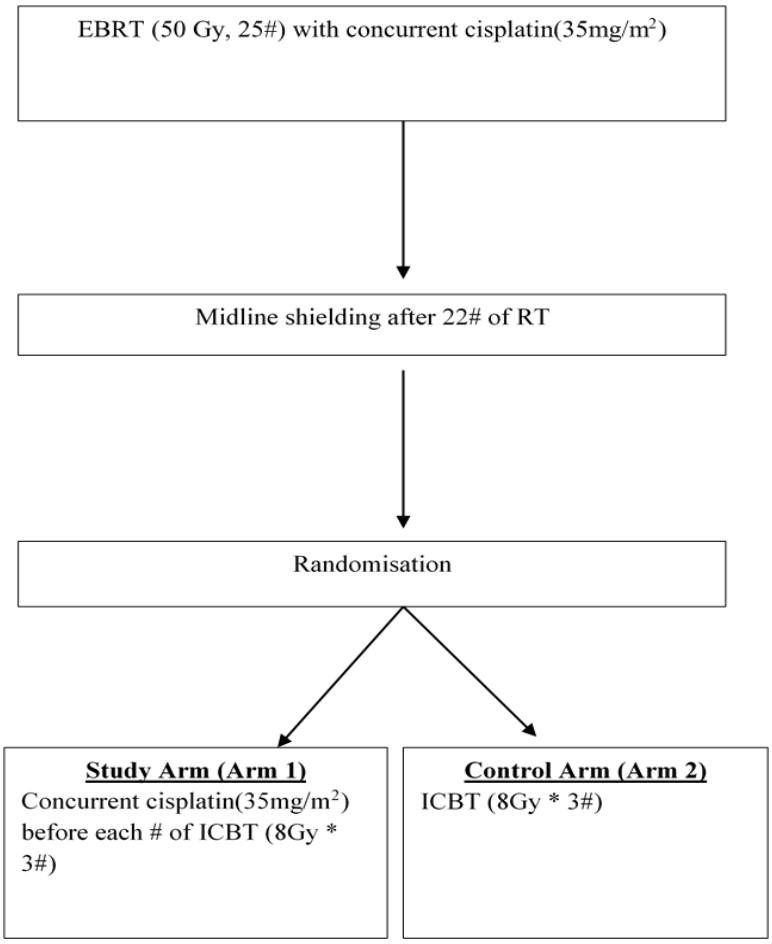

Figure 1. Flowchart of Study

Table 1. Patient Characteristics

Patient Characteristics	Study Arm (Concurrent CDDP with ICBT) (no. along with percent)	Control Arm (Only ICBT) (no. along with percent)
Median Age	49.89 (±7.89)	51.83(+_8.91)
Stage		
IB2	1 (3.3)	2 (6.7)
IIA	2 (6.7)	3 (10)
II B	13 (43.3)	13 (43.3)
IIIA	8 (26.7)	6 (20)
III B	8 (26.7)	6(20)
IVA	3 (10)	2(6.7)
Menstrual Profile		
Pre-Menopausal	15 (50)	10 (33.33)
Post-Menopausal	15 (50)	20 (66.67)
Residence Profile		
Urban	13 (43.3)	13 (43.3)
Rural	17 (56.7)	17 (56.7)
Socioeconomic status		
Lower	8 (26.7)	13 (43.3)
Lower middle	10 (33.3)	11 (36.7)
Upper middle	3 (10)	1 (3.3)
Middle	8 (26.7)	3 (10)
Upper	1 (3.3)	2 (6.7)
Parity		
Nulliparous	1 (3.3)	3 (10)
Multiparous	29 (96.7)	27 (90)

CDDP, Cisplatin; ICBT, Intracavitary brachytherapy

Table 3. Post ICBT Toxicity (Early Radiation Toxicity)

Toxicity (Post ICBT)	Study Arm (no.along with percent)	Control Arm (no.along with percent)
Grade I and II skin	29 (96.7)	29 (96.7)
Grade III Skin	1 (3.3)	1 (3.3)
Grade I and II vaginal	28 (93.4)	30 (100)
Grade III Vaginal	2 (6.6)	0
Grade I and II Gastrointestinal	28 (93.4)	30 (100)
Grade III Gastrointestinal tract	2 (6.6)	0
Grade I and II Hematological	29 (96.7)	30 (100)
Grade III Hematological	1(3.3)	0

ICBT, Intracavitary brachytherapy

Table 4. Late Radiation Toxicity (Post 6 Months Treatment)

At last Follow Up (August 2019)	Study Arm (no.along with percent)	Control Arm (no.along with percent)	p value
Post RT Proctitis	2 (6.6)	0	
Post RT Colitis	0	0	
Post RT Cystitis	1 (3.3)	1 (3.3)	
Post RT Cervicitis	0	0	
Post RT Vaginitis	1 (3.3)	1 (3.3)	
Recto-Vaginal fistula	0	0	
Vesico-Vaginal fistula	0	0	
Total	4/30 (13.3)	2/30 (6.6)	0.38

p value refers to significance level($p<0.05$ is statistically significant)

integrating chemotherapy during the radiotherapy course, particularly concurrent with brachytherapy insertions. Two key rationales support this notion. Firstly, the radiation dose administered during each brachytherapy session significantly surpasses that of external beam radiation, suggesting a synergistic effect of combining brachytherapy with chemotherapy. Secondly, the reduction in dose rate with brachytherapy application, governed by the inverse-square law, may potentially minimize toxicity to surrounding healthy tissues. Therefore, following the successful integration of chemotherapy with EBRT, extending the same approach to brachytherapy appears theoretically promising and could lead to improved treatment outcomes.

The concept of radiosensitizing high-dose brachytherapy with concurrent chemotherapy in a localized manner holds the potential for enhanced treatment response and minimal toxicity to neighboring structures given the decay in dose rate with brachytherapy. While the available data addressing this question is

Table 2. Post Treatment (Radiotherapy and Brachytherapy) Response

	Study Arm (Concurrent CDDP with ICBT))(no. along with percent)	Control Arm (Only ICBT)) (no. along with percent)
Response after ICBT		
CR	22 (73.3)	22 (73.3)
PR	8 (26.7)	8 (26.7)
SD	0	0
PD	0	0
Status at 3 months follow up		
CR	26 (86.7)	24 (80)
PR	1 (3.3)	2 (6.7)
SD	0	0
PD	3 (10)	4 (13.3)
Status at 6 months follow up		
CR	25 (83.33)	23 (76.66)
PR	0	0
SD	2 (6.7)	2 (6.7)
PD	3(10)	5 (16.6)

CR, Complete response; PR, Partial Response; SD, Stable disease; PD, Progressive disease

Table 5. Disease Progression (Local and Distant) in Study and Control Arms

At last follow up (August 2019)	Study Arm (no.along with percent)	Control Arm (no.along with percent)	p value
Local (Cervicitis/Pelvic)	1(3.3)	3(10)	
Distant metastasis	2(Lung)(6.6)	2 (Lung and brain) (6.6)	
Local and distant	0	0	
Total	3(10)	5(16.6)	0.83

p value refers to significance level ($p<0.05$ is statistically significant)

currently limited, the evolving nature of this concept is evident. Although existing studies predominantly consist of phase I/II trials or retrospective analyses, their collective findings support the feasibility and potential benefits of CCBT in locally advanced cervical cancer cases [11-14, 16]. Further exploration through robust research endeavors is warranted to elucidate the full scope of this treatment approach and its impact on patient outcomes in this challenging clinical scenario.

One of the primary concerns associated with the use of cisplatin in CCBT is the potential for increased toxicity, encompassing both hematological issues and systemic effects. Hematological toxicity has the potential to delay CCBT sessions, consequently impacting the timely insertion of ICBT and extending the overall treatment duration. Moreover, skin and vaginal toxicities that manifest post-EBRT may be exacerbated with the addition of CCBT. Nevertheless, existing literature indicates a notably promising response rate in cervical carcinoma with the adoption of concurrent chemoradiation (EBRT followed by brachytherapy) [11-14].

In our study, a similar outcome was observed with a 73.33% complete response rate alongside mostly grade 1 and 2 acute toxicities, assessed one-month-post-treatment completion. At this juncture, responses were comparable between the study and control groups. Both arms exhibited a 73.3% CR rate and a 26.7% partial response (PR) rate. Notably, the initial evaluation at one-month-post-treatment did not demonstrate a clear advantage of employing CCBT. However, over subsequent follow-up periods, intriguing results emerged favoring the utilization of CCBT. Specifically, in the CCBT arm, the CR rate rose from 73.3% one-month-post-brachytherapy to 86.7% at 3 months and maintained at 83.3% at 6 months, while the control arm showed slightly lower CR rates at these time points.

Although statistically nonsignificant, these findings provide promising insights supporting our study's foundational concept that concurrent cisplatin with ICBT may boost response rates. Additionally, a longer follow-up duration revealed a more favorable trend towards complete response rates, evident at the 6-month mark. Furthermore, the observation of metastasis incidence highlights an intriguing trend, with a lower occurrence in the CCBT arm possibly attributed to the heightened overall radiosensitization compared to the control arm. This underscores the concept of spatial cooperation, reinforcing the idea that chemotherapy integration with radiation may be more efficacious in combating micro-metastases.

Evaluation of the therapeutic index in our study suggests that the addition of chemotherapy did not significantly escalate local, hematological, or systemic toxicities. However, notable limitations exist within our study, including the relatively short observation period and an average follow-up duration of only 8 months. Results were assessed over a limited follow-up period of a maximum of one year, signaling the need for future investigations with extended monitoring periods to glean more conclusive insights into the long-term efficacy and safety of CCBT in locally advanced cervical cancer management.

Addressing feasibility and patient compliance within the framework of our study is paramount. Operated within a government setting with predominantly economically disadvantaged patients, the rationale behind utilizing single-agent cisplatin resonates with the patients' financial realities. Remarkably, our study highlights good patient compliance with this regimen, streamlined by the drug's easy administration alongside ICBT on the same day. This condensed treatment approach contributed to enhanced patient adherence by minimizing hospital visits.

The authors affirm that the successful integration of chemotherapy with brachytherapy not only proves feasible but also yields encouraging response rates, accompanied by manageable toxicity profiles and commendable patient adherence. Nonetheless, the need persists for extensive, prolonged follow-up involving a larger patient cohort to solidify the evidence supporting this therapeutic approach. The application of CCBT in locally advanced carcinoma cervix demands further scrutiny through controlled randomized trials to elucidate its full potential. Explorations into refining the optimal drug selection, dosing, integration schedules, and synergistic combinations of cisplatin with other agents emerge as pivotal areas for future investigation.

In conclusions, the study underscores that the integration of chemotherapy with brachytherapy stands as a viable strategy, yielding reassuring response rates, manageable toxicity profiles, and commendable patient adherence in locally advanced Cervical Cancer. Yet, to cement the significance of this therapeutic approach, extensive, long-term follow-up involving a larger patient cohort is indispensable. The continued exploration of CCBT in the management of locally advanced cervical cancer warrants meticulous investigation through controlled randomized trials to unveil its full therapeutic potential. The suggestions for future studies include refining the optimal drug selections, dosages, integration schedules, and exploring synergistic combinations of cisplatin with other complementary agents to optimize therapeutic outcomes in this challenging clinical scenario.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

I would like to thank Dr Rafey Abdul Rahman and Dr Muniba Alim for their help in proofreading.

References

1. Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: A systematic review and meta-analysis. Lancet. 2001;358(9284):781-6. https://doi.org/10.1016/s0140-6736(01)05965-7.
2. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM,

Cho KR, et al. Cervical cancer, version 3.2019, nccn clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2019;17(1):64-84. https://doi.org/10.6004/jnccn.2019.0001.
3. Nag S, Erickson B, Thomadsen B, Orton C, Demanes JD, Petereit D. The american brachytherapy society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys. 2000;48(1):201-11. https://doi.org/10.1016/s0360-3016(00)00497-1.
4. Hanks GE, Herring DF, Kramer S. Patterns of care outcome studies. Results of the national practice in cancer of the cervix. Cancer. 1983;51(5):959-67. https://doi.org/10.1002/1097-0142(19830301)51:5<959::aid-cncr2820510533>3.0.co;2-k.
5. Montana GS, Fowler WC, Varia MA, Walton LA, Mack Y. Analysis of results of radiation therapy for stage ii carcinoma of the cervix. Cancer. 1985;55(5):956-62. https://doi.org/10.1002/1097-0142(19850301)55:5<956::aid-cncr2820550507>3.0.co;2-v.
6. Lanciano RM, Martz K, Coia LR, Hanks GE. Tumor and treatment factors improving outcome in stage iii-b cervix cancer. Int J Radiat Oncol Biol Phys. 1991;20(1):95-100. https://doi.org/10.1016/0360-3016(91)90143-r.
7. Lanciano RM, Won M, Coia LR, Hanks GE. Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: A final report of the 1973 and 1978 patterns of care studies. Int J Radiat Oncol Biol Phys. 1991;20(4):667-76. https://doi.org/10.1016/0360-3016(91)90007-q.
8. Montana GS, Martz KL, Hanks GE. Patterns and sites of failure in cervix cancer treated in the u.S.A. In 1978. Int J Radiat Oncol Biol Phys. 1991;20(1):87-93. https://doi.org/10.1016/0360-3016(91)90142-q.
9. Viswanathan AN, Thomadsen B. American brachytherapy society consensus guidelines for locally advanced carcinoma of the cervix. Part i: General principles. Brachytherapy. 2012;11(1):33-46. https://doi.org/10.1016/j.brachy.2011.07.003.
10. Units I. Measurements: dose and volume specification for reporting intracavitary therapy in gynecology; Repr. International commission on radiation units and measurements. Icru report series 38. Bethesda, md: Icru (ed): Icru, USA; 1985. March 1.
11. Gupta S, Giridhar P, Sharma D, K PH, P KJ, Rath GK. Can chemotherapy be integrated with brachytherapy in locally advanced carcinoma cervix- a proof of principle study. Asian Pac J Cancer Prev. 2019;20(9):2653-7. https://doi.org/10.31557/apjcp.2019.20.9.2653.
12. Koumantakis E, Haralambakis Z, Koukourakis M, Mazonakis M, Haldeopoulos D, Papageorgiou N, et al. A pilot study on concurrent platinum chemotherapy and intracavitary brachytherapy for locally advanced cancer of the uterine cervix. Br J Radiol. 1998;71(845):552-7. https://doi.org/10.1259/bjr.71.845.9691902.
13. Kuske RR, Perez CA, Grigsby PW, Lovett RD, Jacobs AJ, Galakatos AE, et al. Phase i/ii study of definitive radiotherapy and chemotherapy (cisplatin and 5-fluorouracil) for advanced or recurrent gynecologic malignancies. Preliminary report. Am J Clin Oncol. 1989;12(6):467-73. https://doi.org/10.1097/00000421-198912000-00002.
14. Aghili M, Andalib B, Karimi Moghaddam Z, Maddah Safaie A, Amoozgar Hashemi F, Mousavi Darzikolaie N. Concurrent chemo- radiobrachytherapy with cisplatin and medium dose rate intra- cavitary brachytherapy for locally advanced uterine cervical cancer. Asian Pac J Cancer Prev. 2018;19(10):2745-50. https://doi.org/10.22034/apjcp.2018.19.10.2745.
15. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (rtog) and the european organization for research and treatment of cancer (eortc). Int J Radiat Oncol Biol Phys. 1995;31(5):1341-6. https://doi.org/10.1016/0360-3016(95)00060-c.
16. Vrdoljak E, Omrcen T, Novaković ZS, Jelavić TB, Prskalo T, Hrepić D, et al. Concomitant chemobrachyradiotherapy with ifosfamide and cisplatin followed by consolidation chemotherapy for women with locally advanced carcinoma of the uterine cervix--final results of a prospective phase ii-study. Gynecol Oncol. 2006;103(2):494-9. https://doi.org/10.1016/j.ygyno.2006.03.060.

This work is licensed under a Creative Commons Attribution-Non Commercial 4.0 International License.