RESEARCH ARTICLE

Editorial Process: Submission:03/28/2024 Acceptance:09/03/2024

Short Course Brachytherapy in Locally Advanced Cervical Cancer; Safety and Response Rate

Mahdi Aghili[1], Mohammad Babaei[1,2], Reyhaneh Bayani[1,2]*, Ramin Jaberi[3], Farnaz Amouzegar Hashemi[1], Bita Kalaghchi[1], Saeed Rezaei[1], Fatemeh Jafari[1,2], Mojtaba Vand Rajabpour[1,2], Sorour Garousi[4], Maryam Garousi[5]*

Abstract

Objective: Overall treatment time (OTT) is an important index for local control in patients with locally advanced¬ cervical cancer treated with definitive chemoradiation (External Beam Radiation Therapy (EBRT), Brachytherapy (BT) and concomittant chemotherapy). This study aimed to evaluate the efficiency and safety of reducing OTT by shortening the brachytherapy duration to one week in the intervention group copared to three weeks in the control group. **Method:** The study was a non-randomized open-label phase II clinical trial, carried out on 49 cervical cancer patients (26 in intervention grouop and 23 in control group) who received EBRT concomitant with Cisplatin, followed by brachytherap in order to deliver 60 Gy equivalent total doses in 2-Gy fractions (EQD2) to Intermediate Risk-Clinical Tumor Volume (IR-CTV) and 85-90 Gy EQD2 to High Risk-Clinical Tumor Volume (HR-CTV). In the intervention group, all brachytherapy sessions were performed in 1 week, while for the control group, it was administrated in 3 consecutive weeks. The participants were followed (Minimum follow up time was 6 month and median follow up time was 10 month) to assess response and toxicity of the treatment. **Results:** Overall, more than 95% of study participants had a complete response and more than 4.0% reported partial response, and no treatment failure was observed. The complete response in intervention and control groups was 96.1% and 95.6%, respectively (P value > 0.05). There was no difference in acute toxicity between the two groups. **Conclusion:** considering that short course brachytherapy was non inferior to conventional course from point of Response Rate and Side Effects during follow up time; so this strategy can be considered as an option for reducing the OTT which can at least cause decreasing the costs. Studies with larger sample size and phase 3 are recommended.

Keywords: Brachytherapy- Cervix- Dose-Response- Overrall treatment time

Asian Pac J Cancer Prev, **25 (9)**, 3119-3124

Introduction

Cervical cancer has the fourth greatest global burden of cancer among women for both incidence and mortality [1]. Approximately 6.5% of women developed cervical cancer before the age of 75 [2]. While developed countries have seen a decline in the incidence and mortality of cervical cancer due to extensive perevention and screening programs, cervical cancer still had a high incidence and mortality rate in developing countries [3] .

Corstone of Treatment for early-stage cervical cancer is surgery, although radiotherapy and brachytherapy are key component of treatment for locally advanced patients. in 1999 concomitant chemoradiation (platinum-based chemotherapy concurrent with external beam radiation therapy) followed by brachytherapy (BT) was established as standard of treatment in most patients with locally advanced cervical cancer [4,5].

Reduced overall treatment time (OTT) has been recognized as a fvarable prognostic factor for these patients. The optimal OTT is 7-8 weeks, and increasing the time further is associated with a higher risk of failure and reduced treatment efficacy [6-8]. Other factors affecting prognosis include the volume of high risk clinical target volume (CTV) and dose escalation of high and intermediate CTV. In this study, we aimed to examine the efficiency and safety of reducing OTT through reducing duration of the brachytherapy to one week (intervention arm) versus three weeks (control arm) in locally advanced¬ cervical cancer patients who

*[1]Department of Radiation Oncology, Cancer Institute, Imam-Khomeini Hospital Complex, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. [2]Radiation Oncology Research Center, Cancer Research Institute, Imam-Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran. [3]Radiation Oncology Department, Yas General Hospital, Tehran, Iran. [4]Iran University of Medical Sciences, Tehran, Iran. [5]Radiation Oncology Department, Iran University of Medical Sciences, Tehran, Iran. *For Correspondence: Garousi.m@iums.ac.ir, Bayani.reyhane@yahoo.com*

recieve definitive chemoradiation (EBRT plus BT plus concomittant chemotherapy).

Materials and Methods

This study was a non-randomized open-label phase II clinical trial, conducted on 49 patients with locally advanced cervical cancer (26 in intervention group and 23 in control group) who underwent external beam radiotherapy(EBRT) concomitant with Cisplatin, followed by high dose rate (HDR) brachytherap during 2018 to 2019. In the intervention group, all brachytherapy sessions were performed within 1 week, while in the control group, it was administrated in 3 consecutive weeks. The participants were followed for response and treatment related toxicity over a minimum and median followup period of 6 and 10 months, respectively.

Patient selection

We enrolled patients with histologically confirmed squamous cell carcinoma (SCC) or adenocarcinoma of cervix in stage 1B-4A Based on International Federation of Gynecology and Obstetrics system (FIGO) 2018. All of the patients had received EBRT 45-50 Gy to the pelvic concurrent with chemotherapy (Cisplatin 35 mg/ m2 Weekly) then referred to Yas radiation oncology center to receive BT. Exclusions were made for patients with a Karnofsky Performance Status Scale (KPS) below 70, histologies other than SCC and Adenocarcinoma, recurrent or metastasis at peresentation cases, and patients who had perviously received alternative treatments such as surgery.

Patients allocation to treatment groups

Although our study was non randomized, we endeavored to balance the distribution of patients in terms of age and stage across both groups(Table 1).

EBRT protocol

All patients underwent planning Computed Tomography (CT). The CTV encompassed the common, external, and internal iliac lymph nodes, as well as the presacral lymph nodes. EBRT was delivered using a linear accelerator with 6-18 MV photon energy and a four-field (anteroposterior, posteroanterior, and two lateral) three dimentional conformal radiotherapy (3DCRT) technique. Total dose of EBRT was 45-50 Gy administered in 25 fractions (1.8-2 Gy daily) over 5 weeks. They also received Weekly Cisplatin (35 mg/ m2) for five weeks concurrent with EBRT.

BT protocol

After the completion of EBRT, patients were allocated to either the intervention or control groups for brachytherapy. Brachytherapy was adminstered using Cobalt-60 in a Hihg Dose Rate (HDR) Brachytherapy machine - Eckert & Ziegler BEBIG. A total BT dose of 21 Gy, whith a dose per fraction of 7 Gy was administered during one week (Intervention Group) or three weeks (control group).

We used MRI with Intravenous contrast both before and after EBRT to evaluate the response to external Chemoradiation and to choose the appropriate BT applicators (tandem ovoid or tandem cylinder needles).

Following insertion and fixation of applicators in the operating room with spinal anesthesia, patients underwent planning CT Scan with 1 mm thickness slices. The images were then transferred to the SagiPlan® treatment planning software. MRI was employed to contour the HR-CTV , IR-CTV, and organs at risk such as Rectum, Sigmoid, and Bladder according to GEC-ESTRO recommendations [9]. HR-CTV was included residual gross tumor volume (GTV) plus whole cervix, and HR-CTV along with initial GTV were formed IR-CTV.

We calculated the total received dose to HR-CTV and IR-CTV, EQD2:85-90 and EQD2:60-70Gy. Also, the dose constrain for bladder was D2cc less than EQD2:80 Gy and for rectum and sigmoid D2cc less tan EQD2:70Gy.

Toxicity and Response evaluation protocol

We conducted regular patients visit after each session of BT and at the first, third and sixth month post-treatment. The patients were assessed objectively and subjectively for acute toxicities such as: Vaginal hemorrhage, proctitis, and cystitis according to Common Terminology Criteria for Adverse Events version 5 (CTCAE v5). Furthermore, we performed additional MRI three months after treatment for response evaluation based on the Response evaluation criteria in solid tumors (RECIST) [10]. Any suspicious residue identified in the imaging was further evaluated by needle biopsy.

Statistical analysis

We utilized mean and standard deviation (SD) to report continuous variables when comparing groups. We also used a percentage and 95% confidence interval for the dichotomous variable. The mean comparison between intervention and control groups was conducted using an independent T-test, while the distribution of categorical variables across the groups were assessed using Chi-square. All statistical analyses were performed using Stata (Ver 14.1, College Station, Texas, USA).

Results

49 patients were enrolled in this study, and non-randomly placed into two groups, control (23 patients) and intervention (26 patients).

The mean age of all participants was 55.6 (±9.8) years. More than one third of the tumors were stage IIB (36.7%), according to FIGO 2018 followed by stage IIIC1 (32.6%) and stage IB3 (10.2%). There was not significant difference between the age disturbiution and the stage of the disease between the two groups (Table 1). The treatment course was completed for all participants consistent with planned schedule and Over 95.0% of the patients in both intervention and control groups acheived complete clinical response and no statistical difference was observed between the groups (Table 1). Table 1 shows Pathological and Radiological Characteristics of patients. No patient was lost during follow-up time. Table 2 shows Treatment dose characteristics in Control and intervention Group.

Table 1. Study Participants Pathological and Radiological Characteristicsm (add statical analysis)

Variable	Control	Intervention	Overall	P-value
Age, Mean (SD)	56.1 (±10.2)	55.2 (±9.7)	55.6 (±9.8)	0.7
Brachytherapy time, Mean (SD)	5.9 (±1.2)	21.5(±3.7)	13.26 (±26.4)	0.01
Median Follow up Months (IQR)	11.96 (±7.73)	14.13(±5.6)	13.83 (±5.4)	0.7
Stage, n (%)				
1b2	1 (4.3%)	0 (0)	1 (2%)	
1b3	1 (4.3%)	4 (15.3%)	5 (10.2%)	
2a	0 (0)	1 (3.8%)	1 (2%)	
2b	8 (34.7%)	10 (38.4%)	18 (36.7%)	
3a	2 (8.6%)	1 (3.8%)	3 (6.1%)	
3b	1 (4.3%)	1 (3.8%)	2 (4%)	
3c1	9 (39.1%)	7 (26.9%)	16 (32.6%)	
4a	1 (4.3%)	2 (7.6%)	3 (6.1%)	0.5
Pathological diagnosis, n(%)				
ADC, n (%)	3 (13.0%)	2 (7.6%)	5 (10.2%)	
Poor differentiated SCC, n (%)	3 (13.0%)	5 (19.2%)	8 (16.3%)	
Well differentiated SCC, n (%)	17 (73.9%)	19 (73.4%)	36 (73.4%)	0.7
Treatment response				
Partial response	1 (4.35%)	1 (3.8%)	2 (4.2%)	
Complete response	22 (95.6%)	25 (96.1%)	47 (95.7%)	0.9
Total	23 (100)	26 (100)	49 (100)	

The evaluated toxicities (proctitis, cystitis, vaginal hemorrhage, and hematuria) in all time checkpoints (3, 30. 90, and 180 days after treatment) showed no significant differences between two groups (Tables 3-6). It was only the proctitis 30 days after treatment being significantly higher in control group (Table 3). And also proctitis followed by cyctitis were the most prevalent side effect which occurred during the study in both groups (Tables 3, 4).

Most of the vaginal hemorrhages occured in first 3 days after treatment mainly due to the trauma in inserting the applicators (Table 5).

All vaginal hemorrhage reported after 30 days from the end of treatment were post coital and they were not

Table 2. Treatment Dose Characteristics in Control and Intervention Group

Variable	Control	Intervention	P-value
External dose(Gy), mean(SD)	49.9 (0.8)	50.2 (2.6)	0.286
Total dose (Gy) to HRCTV*, Mean (SD)	89.8 (3.5)	90.2 (2.3)	0.212
High Risk volume**,Mean (SD)	24.8 (8.8)	26.0 (9.1)	0.329
Total dose (Gy) to IRCTV***, Mean (SD)	68.9 (4.7)	69.3 (3.8)	0.514
Intermediate Risk volume**, Mean (SD)	67.5 (18.1)	68.1 (19.2)	0.459
Total dose (Gy) to Bladder 1cc, Mean (SD)	85.9 (11.7)	83.4 (10.0)	0.22
Total dose (Gy) to Rectum 1cc, Mean (SD)	76.3 (7.9)	75.6 (6.4)	0.374
Total dose (Gy) to Rectum 2 cc, Mean (SD)	66.9 (5.9)	64.9 (3.7)	0.079
Total dose (Gy) to Sigmoid 1 cc, Mean (SD)	74.3 (9.5)	77.0 (10.1)	0.179
Total dose (Gy) to Sigmoid 2 cc, Mean (SD)	63.7 (6.3)	65.8 (5.0)	0.099

*, High Risk Clinical Target Volume; **, Volume by Mililiter (ml); ***, Intermediate Risk Target Volume

Table 3. Frequency of Grade I and II Proactitis after Brachytherapy

	Intervention	Control	Pvalue
Before brachytherapy	11 (42.31%)	8 (34.78%)	0.59
3 days after brachytherapy	14 (53.85%)	13 (56.52%)	0.851
30 day after brachytherapy	6 (23.08%)	12 (52.17%)	0.035
90 day after brachytherapy	3 (11.54%)	7 (30.43%)	0.101
180 day after brachytherapy	2 (9.52%)	4 (26.67%)	0.174

Table 4. Frequency of Grade I and II Cystitis after Brachytherapy

	Intervention	Control	P value
Before brachytherapy	9 (34.62%)	7 (30.43%)	0.755
3 days after brachytherapy	12 (46.15%)	11 (47.83%)	0.907
30 day after brachytherapy	5 (19.23%)	5 (21.74%)	0.828
90 day after brachytherapy	2 (7.69%)	1 (4.35%)	0.626
180 day after brachytherapy	2 (9.52%)	0 (0.0%)	0.219

Table 5. Frequency of Grade I and II Vaginal Hemorrhage after Brachytherapy

	Intervention	Control	P value
Before brachytherapy	0	0	1
3 days after brachytherapy	11 (42.31%)	6 (26.09%)	0.234
30 day after brachytherapy	0 (0.0%)	2 (8.70%)	0.125
90 day after brachytherapy	0 (0.0%)	2 (8.70%)	0.125
180 day after brachytherapy	3 (14.29%)	1 (6.67%)	0.473

Table 6. Frequency of Grade I and II Hematuria after Brachytherapy

	Intervention	Control	P value
Before brachytherapy	0 (0.0%)	1 (4.35%)	0.283
3 days after brachytherapy	2 (7.69%)	1 (4.35%)	0.626
30 day after brachytherapy	0 (0.0%)	0 (0.0%)	1
90 day after brachytherapy	0 (0.0%)	0 (0.0%)	1
180 day after brachytherapy	1 (4.76%)	0 (0.00%)	0.391

related to recurrence or residue. In addition no fistula, ureteral stricture or vaginal stenosis was detected during follow up time. All reported side-effects in both groups were mild or moderate and no grade 3 or grade 4 toxicity was detected .

Discussion

Impact of overall treatment time on local control and cancer specific survival has been demonstrated in a number of retrospective studies [7,11-13]. Time tresholds such as 50 days, 55 days, and 7-8 weeks have been suggested in these studies. Accelerated repopulation of surviving tumor clonogens during the course of RT has been hypothesized to contribute to the poorer outcomes found in the setting of extended treatment duration [14]. Although most of these studies conducted in the era before concomitant chemotherapy. After establishing the survival benefit due to adding chemotherapy to radiation, concurrent chemoradiation has been considered as the standard treatment for locally advanced cervical cancer patients [15,16]. Also it is noteworthy to mention that most studies which treated patients with chemoradiathion reported detrimental effect of prolonged OTT on pelvic control too[17-19]. Although it was argued that the observed decrease in local control might be biased due to the hypothesis that more extensive tumors technically require prolongation of the course of irradiation; thus decreased tumor control and survival in these patients may not necessarily be the result of time/dose factor. But a study conducted in 372 patients proved that the effect of OTT was present regardless of tumor size [11].

Considering the importance of the OTT in the mentioned studies, efforts were made to shorten the treatment time. For example in a study conducted by Alam et al 82 patients randomly assign to two groups. The study group received EBRT 50 Gy/25 fractions with interdigitated HDR BT 8 Gy/fraction weekly a total of three fractions and patients in the control group received EBRT 50 Gy/25 fractions with sequential HDR intracavitary BT 8 Gy/fraction weekly a total of three fractions. Median follow-up duration was 10 months. Treatment interruption due to treatment-related toxicity was slightly higher in the study group than the control group, but it was statistically insignificant. Interdigitated HDR BT has equivalent response and toxicities as sequential HDR BT with the advantage of significant reduction in OTT [20]. Our study had similar or even better acute and three months post treatment toxicity compared to the Alam et al.'s. In another study by Kumara et al. OTT have decreased by merging the BT with EBRT, in this report Fifty patients of carcinoma cervix (FIGO-I B/III B) were randomly divided into two groups: the study group treated with concomitant EBRT and HDR-ICBT (EBRT = 50–50.4 Gy/25–28 Fr, HDR 7 Gy in 3 Fr during the 3rd, 4th, and 5th weeks), and the control group treated with EBRT followed by HDR-ICBT and weekly cisplatin [21]. In comparing our finding with this study the bladder and rectal complications was lower in our study. This might be due to using MRI and 3D planning and, consequently, more precise contouring

to reduce the dose of organ at risk or using brachytherapy after the end of EBRT and better applicators insertion (using tandem-cylinder- needles) for dose coverage and organs saving. Also in this study vaginal hemorrhage in both arms was more commom in 3 days after treatment which is spposed to be due to the trauma in inserting the applicators, similar to ours study.

In the current study we scheduled to initiate BT after end of EBRT and we prescribed all three session of brachytherapy over one week in order to decrease the OTT. To the best of our knowledge, this is the first study that cervical cancer brachytherapy is being prescribed in this way)three fractions of 7 Gy over one week). The study conducted by Toita et al. assessed outcome and adverse effects of concurrent chemoradiation followed by HDR brachytherapy in patients with cervical cancer with the mean follow up of 37 month. Thirty-eight (95%) patients received whole pelvic EBRT with 40 Gy/20 fractions followed by HDR-ICBT with 18 Gy/3 fractions to point A. Subsequently, additional pelvic EBRT with 10 Gy/5 fractions was delivered with a midline block. Grade 3/4 leukopenia was the most common acute side effect (83%). Unlike our study, 15% of patients experienced acute grade 3-4 diarrhea during the treatment which may be due to the 2D planning and schedule of cisplatin administration (20 mg/m2 for five days every three weeks) and concomitan administration of chemotherapy with BT in 50% of patients. Eight (20%) patients suffered late gastrointestinal complications (all grades) [22].

At least from the point of acute toxicity, our study is safe in comparison with aforementioned reports but has not enough power for assessing long term outcomes. A prospective randomize study with longer follow up is encouraged to confirm these findings.

In conclusion, according to our findings, short course brachytherapy (three session with 7 Gy/fr in one week) in cervical cancer patients is not associated with higher short term complication rates or decreased treatment efficacy in terms of tumor response. Although previous studies have shown that reducing OTT is associated with more favorable local control but the optimal OTT is to be determined. More randomized trials with larger sample sizes and longer follow-up are required to determine the optimal OTT for the patients with locally advanced cervical cancer.

Author Contribution Statement

Mahdi Aghili: Conceptualization; data curation; project administration. Mohammad babaei:Data curation. Reyhaneh Bayani: writing original draft, Data curation; review and editing. Ramin Jaberi: review and editing. Farnaz Amouzegar Hashemi: Data curation; supervision and editing. Bita Kalaghchi: Supervision.Fatemeh Jafari: review and editing. Saeed Rezaei: review and editing. Mojtaba vand Rajabpour: review and editing. Maryam Garousi: writing original draft,Data curation

Acknowledgements

We would like to thank all staff at the Cancer Institute of Iran, who helped us in data gathering.

Data availability statement

The data that support the findings of this study are available from the corresponding authors upon reseanable request.

Ethical Considration

Study protocol and implementation approved by ethics committee of Tehran University of Medical Science(IR.TUMS.IKHC.REC.1397.085). This study registerd and approved in Iraninan Registry of Clinical Trials (IRCT20200617047815N1). All of the study participants signed the informed consent form.

Conflict of interest statement

The authors whose names are listed above declare that there is no confilict of interest regarding the puplication of this article.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. https://doi.org/10.3322/caac.21492.
2. Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: A worldwide analysis. Lancet Glob Health. 2020;8(2):e191-e203. https://doi.org/10.1016/s2214-109x(19)30482-6.
3. Akinyemiju TF. Socio-economic and health access determinants of breast and cervical cancer screening in low-income countries: Analysis of the world health survey. PLoS One. 2012;7(11):e48834. https://doi.org/10.1371/journal.pone.0048834.
4. Trimble E, Gius D, Harlan LC. Impact of nci clinical announcement upon use of chemoradiation for women with cervical cancer. J Clin Oncol. 2007;25. https://doi.org/10.1200/jco.2007.25.18_suppl.5537.
5. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999;340(15):1144-53. https://doi.org/10.1056/nejm199904153401502.
6. Girinsky T, Rey A, Roche B, Haie C, Gerbaulet A, Randrianarivello H, et al. Overall treatment time in advanced cervical carcinomas: A critical parameter in treatment outcome. Int J Radiat Oncol Biol Phys. 1993;27(5):1051-6. https://doi.org/10.1016/0360-3016(93)90522-w.
7. Fyles A, Keane TJ, Barton M, Simm J. The effect of treatment duration in the local control of cervix cancer. Radiother Oncol. 1992;25(4):273-9. https://doi.org/10.1016/0167-8140(92)90247-r.
8. Mazeron R, Castelnau-Marchand P, Dumas I, del Campo ER, Kom LK, Martinetti F, et al. Impact of treatment time and dose escalation on local control in locally advanced cervical cancer treated by chemoradiation and image-guided pulsed-dose rate adaptive brachytherapy. Radiother Oncol. 2015;114(2):257-63. https://doi.org/10.1016/j.radonc.2014.11.045.
9. Dimopoulos JC, Petrow P, Tanderup K, Petric P, Berger D, Kirisits C, et al. Recommendations from gynaecological (gyn) gec-estro working group (iv): Basic principles and

parameters for mr imaging within the frame of image based adaptive cervix cancer brachytherapy. Radiother Oncol. 2012;103(1):113-22. https://doi.org/10.1016/j.radonc.2011.12.024.
10. Padhani AR, Ollivier L. The recist (response evaluation criteria in solid tumors) criteria: Implications for diagnostic radiologists. Br J Radiol. 2001;74(887):983-6. https://doi.org/10.1259/bjr.74.887.740983.
11. Perez CA, Grigsby PW, Castro-Vita H, Lockett MA. Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. Int J Radiat Oncol Biol Phys. 1995;32(5):1275-88. https://doi.org/10.1016/0360-3016(95)00220-s.
12. Petereit DG, Sarkaria JN, Chappell R, Fowler JF, Hartmann TJ, Kinsella TJ, et al. The adverse effect of treatment prolongation in cervical carcinoma. Int J Radiat Oncol Biol Phys. 1995;32(5):1301-7. https://doi.org/10.1016/0360-3016(94)00635-x.
13. Chen SW, Liang JA, Yang SN, Ko HL, Lin FJ. The adverse effect of treatment prolongation in cervical cancer by high-dose-rate intracavitary brachytherapy. Radiother Oncol. 2003;67(1):69-76. https://doi.org/10.1016/s0167-8140(02)00439-5.
14. Huang Z, Mayr NA, Gao M, Lo SS, Wang JZ, Jia G, et al. Onset time of tumor repopulation for cervical cancer: First evidence from clinical data. Int J Radiat Oncol Biol Phys. 2012;84(2):478-84. https://doi.org/10.1016/j.ijrobp.2011.12.037.
15. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL, 3rd, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage ib cervical carcinoma. N Engl J Med. 1999;340(15):1154-61. https://doi.org/10.1056/nejm199904153401503.
16. Eifel PJ, Winter K, Morris M, Levenback C, Grigsby PW, Cooper J, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: An update of radiation therapy oncology group trial (rtog) 90-01. J Clin Oncol. 2004;22(5):872-80. https://doi.org/10.1200/jco.2004.07.197.
17. Song S, Rudra S, Hasselle MD, Dorn PL, Mell LK, Mundt AJ, et al. The effect of treatment time in locally advanced cervical cancer in the era of concurrent chemoradiotherapy. Cancer. 2013;119(2):325-31. https://doi.org/10.1002/cncr.27652.
18. Monk BJ, Tian C, Rose PG, Lanciano R. Which clinical/pathologic factors matter in the era of chemoradiation as treatment for locally advanced cervical carcinoma? Analysis of two gynecologic oncology group (gog) trials. Gynecol Oncol. 2007;105(2):427-33. https://doi.org/10.1016/j.ygyno.2006.12.027.
19. Tanderup K, Fokdal LU, Sturdza A, Haie-Meder C, Mazeron R, van Limbergen E, et al. Effect of tumor dose, volume and overall treatment time on local control after radiochemotherapy including mri guided brachytherapy of locally advanced cervical cancer. Radiother Oncol. 2016;120(3):441-6. https://doi.org/10.1016/j.radonc.2016.05.014.
20. Alam N, Akram M, Siddiqui SA, Hussain MAB. Interdigitated versus sequential high-dose-rate intracavitary brachytherapy with external beam radiotherapy in locally advanced carcinoma cervix. J Cancer Res Ther. 2019;15(6):1254-9. https://doi.org/10.4103/jcrt.JCRT_301_17.
21. Pandu Ranga Kumari M, Nagarjun Reddy B, Sanjeeva Kumari C, Rama Krishna M. Comparison between concurrent ebrt and ica with conventional ebrt followed by ica in cervical cancer. J Obstet Gynaecol India. 2016;66(4):263-73. https://doi.org/10.1007/s13224-014-0661-x.
22. Toita T, Moromizato H, Ogawa K, Kakinohana Y, Maehama T, Kanazawa K, et al. Concurrent chemoradiotherapy using high-dose-rate intracavitary brachytherapy for uterine cervical cancer. Gynecol Oncol. 2005;96(3):665-70. https://doi.org/10.1016/j.ygyno.2004.11.046.