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A comparative study on weekly versus three weekly cisplatin based concurrent chemoradiotherapy in treatment of carcinoma cervix; Patient compliance and Feasibility study

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Abstract

Background: This prospective study compare concurrent weekly and three weekly cisplatin based concurrent chemoradiotherapy in locally advanced cervical cancer.Methods: The study was conducted in 40 patients with locally advanced carcinoma cervix randomised into 2 arms. Arm A patients received external beam Radiotherapy (EBRT) to pelvis with concurrent weekly cisplatin at dose of 40 mg/m2 and arm B patients received EBRT to pelvis with concurrent three weekly cisplatin at dose of 75 mg/m2 followed by high dose rate intracavitary brachytherapy (HDR ICBT). Acute gastrointestinal (GI) toxicities being common and worrisome complication and response rates were analysed.**Results:** The patient and disease characteristics were comparable in both arms. There was no significant difference in both arms in terms of lower GI toxicity i.e weekly vs three weekly(75% Vs 80%; *P* = 0.208) . Compliance to chemoradiation was better in three weekly vs weekly (85% vs 70%) cisplatin arms but not statistically significant (p<0.05) After a median follow up of 18 months, tumor control rates in both arms were comparable (85% Vs 90%; *P* = 0.128).**Conclusion:** The present study observations suggest that concurrent weekly or three weekly cisplatin based chemo-radiation therapy is equally effective in treatment of cervical cancer in terms of local tumor control rate,lower GI toxicity and patients compliance to proposed chemoradiotherapy treatment. However randomised trials with larger sample sizes and longer duration of follow up are required.

Keywords: cisplatin, concurrent chemoradiation, carcinoma cervix.

Introduction

Carcinoma of uterine cervix is the most common gynaecological malignancy worldwide and in India.[1,2] Majority of patients present as locally advanced stage in our country unlike the western affluent society due to lack of universal screening and awareness among women.

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Concurrent cisplatin-based chemoradiotherapy (CRT) is the treatment of choice in locally advanced cervical cancer based on five randomised trials.[3-8] Most widely accepted CRT is weekly cisplatin at dose of 40-50 mg/m^2. Several other trials used 3 weekly cisplatin 75–100 mg/m2 because of the ease of administration and improved patients' compliance which shows almost similar toxicity profile and clinical outcome compared to concurrent weekly cisplatin. The present study was conducted to compare and evaluate the compliance, efficacy and toxicity profile especially the gastrointestinal and genitourinary complication between two different dosing schedules of concurrent cisplatin, i.e., once in

three weekly cisplatin (75 mg/m2) with weekly cisplatin (40 mg/m2) in treatment of locally advanced carcinoma cervix.

Patients and Methods

This prospective randomised study was conducted on histopathologically proven locally advanced carcinoma cervix patients from March 2015 to August 2017, A total of sixty patients were screened out of which Forty patients were randomised by computer-generated random number tables; twenty patients to each arm. Arm A (external beam radiotherapy (EBRT) + weekly cisplatin 40 mg/m2 followed by high-dose rate intracavitory brachytherapy (HDR ICBT) and arm B (EBRT + 3 weekly cisplatin 75 mg/m2 followed by HDR ICBT). The study was started after getting approval from the institutional ethics committee. Written
informed consent was taken from the patients before the start of treatment.The International Federation of Gynaecology and Obstetrics staging system was used to stage the patients. The study was conducted on patients meeting eligibility criteria: age ≤65 years, the Eastern Cooperative Oncology Group performance status 0–2, haematologic parameters ([haemoglobin (Hb) ≥10 gms/dl) , total white blood cell count ≥4000/mm3 and platelets ≥100,000/mm3]) and renal function (calculated creatinine clearance ≥60 mL/min).

Radiotherapy was delivered by combination of EBRT and HDR ICBT. All patients were treated with 15 MV photons, EBRT. Patients were treated by two fields (AP/PA)/four-field technique if the anteroposterior-posteroanterior (AP-PA) separation was >20 cm in the supine position. All patients were planned in the supine position without any bladder protocol. The superior border for the AP-PA field was kept at L4 to L5 interspace and inferior border at the inferior border of obturator foramen or lower depending on disease extension to the vagina to cover tumour with a margin of 2 cm. The lateral border was kept 2 cm from the lateral pelvic brim. For lateral fields, the superior and inferior borders were same as AP-PA field. The anterior border was kept just in front of the pubic symphysis, and the posterior border was set to cover the entire sacral hollow. Dose was delivered to the centre of field with isocentric technique.Radiation was delivered by conventional fractionation to a total dose of 46–50 Gy at the rate of 2 Gy per fraction, single fraction per day and five fractions per week in 23–25 fractions over a period of 5–6 weeks.

High dose rate intracavitary brachytherapy (HDR ICBT) was performed by using with Ir^{192} isotope with an interval of one week between two fractions. Patient was assessed for ICBT fitness after completion of 15-20 fractions of EBRT. ICBTwas planned when the os was able to sound. Modified Fletcher suit applicator – Central intrauterine tandem and paired ovoids or a tandem and ring of different sizes were used according to individual patient's anatomy. The prescribed dose was 600-800 cGy per fraction in 3-4 fractions to point A.

Chemotherapy cisplatin was given concurrently with EBRT once weekly (40 mg/m2) for a total of five cycles in arm A and once in 3 weeks (75 mg/m2) for a total of two cycles in arm B during the course of EBRT. Pre-chemotherapy hydration was administered 500 ml of 0.9% saline (NS) over 1 h followed by prophylactic antiemetic medication with injection dexamethasone 16 mg intravenous (IV), injection palonosetron 0.25 mg IV and injection ranitidine 50 mg in 100 ml of 0.9% NS over half hour. Cisplatin 40 mg/m2 was given in 500 mL of 0.9% NS over 2 h in arm A patients. The total dose of cisplatin in arm B patients who received cisplatin 75 mg/m2 was calculated and given in 500 ml 0.9% NS over 2 h. It was followed by RT within 1 h after completion of the infusion. Post-chemotherapy (CT) patients received 2 ampoules (300 mg) potassium chloride in 500 ml of 0.9% NS over 1hr followed by 2 ampoules of 50% w/v magnesium sulphate in 500 mL of 5% dextrose over 1 h. Post-chemohydration with 500 mL of 0.9% NS over 1 h was given. On fourth day post chemotherapy laboratory investigations such as serum electrolytes such as sodium, potassium, calcium and magnesium and serum creatinine were sent and hemogram sent one week after chemotherapy.

During their entire treatment course, all patients were examined weekly or earlier whether they had developed acute gastrointestinal and genitourinary toxicities were assessed as per the Common Terminology Criteria for Adverse Events (CTCAE) Version 4 formulated by the NCI. [13] Antiemetics were given on day of chemotherapy and for 2 days after CT. Any delay causing treatment interruption was noted and appropriate gap corrections were done. Response assessment was done as per Response Evaluation Criteria In Solid Tumors (RECIST) criteria.[14] All responses were measured clinically. Responses to therapy were classified as complete, partial, stable or progressive.

Follow up of all patients was asked for the first time, 6 weeks after completion of treatment. Patients were planned to follow up every one month for 1st three months, every three monthly for 9 months then for every 4 months for two years. Follow-up procedures include general, systemic and pelvic examination,

palpation of inguinal and supraclavicular nodes. Imaging studies, such as radiograph, computer tomography, ultrasonography, and bone scan were done when required.

Statistical Analysis

All informations collected in the approved proforma was recorded in a master chart in MS EXCEL 2007 . Data analysis was done with the help of computer using SPSS software version 20 **(**IBM SPSS Statistics, Somers NY, USA)**.** Using this software, range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. All the descriptive statistical values were presented in the form of mean ± standard deviation. Student independent 't' test was used to compare the means of different continuous variables. Pearson's chi square test was performed to assess the association among different categorical variables. A 'p' value less than 0.05 is taken to denote statistically significant relationship.

Results

Patients with histopathologically diagnosed carcinoma of cervix during the study period were (n =60) screened for inclusion into the study. Of these n =20 were excluded from the study for several reasons such as patients with early cervical cancer, metastatic disease at presentation, post operative cases fit for adjuvant therapy, dual malignancies and recurrent cases. After exclusion n = 40 patients were in locally advanced stages who are eligible for concurrent CRT. All these patients were recruited into study and patients were divided into two arms with 20 patients each. Arm A patients received RT along with concurrent weekly cisplatin and arm B patients received RT along with concurrent three weekly cisplatin followed by HDR-ICBT (Figure 1).

All the patient and disease characteristics like age, stage, size of tumor, uni or bilateral parametrial involvement were comparable in both arms.

Patients in the arm A received a mean dose of 50.5 mg per cycle, whereas patients in the arm B received a mean dose of 105.75 mg per cycle. The total cumulative dose in both the cycles was statistically similar with a mean of 230 mg in arm A versus 194 mg in arm B (*P* = 0.9) [Table 1].All patients were evaluated for different toxicities according to NCI CTCAE version 4.0 There were no treatment related deaths. No dose limiting toxicities were recorded. Patterns of acute toxicities – haematological toxicity (anemia, neutropenia, leukopenia), upper gastrointestinal toxicity (nausea, vomiting), lower gastrointestinal toxicity(diarrhoea) and nephrotoxicity and electrolyte imbalances were evaluated between 2 arms and represented in [Table 2]. All the patients in the study were assessed for treatment response 6 weeks after the completion of treatment using RECIST criteria. Responses were assessed clinically. 17(85%) patients of Arm A, 19 (95%) patients of Arm B had complete response and 3 patients of Arm A and 1 of Arm B had partial response (*P* =.195) after 6 weeks of completion of treatment (Table 3)
After a median follow up of 12 months in arm A, 19 patients of arm A had complete response and 1 patient had progressive disease. After a median follow up of 11.5 months in arm B, 1 patient in arm B lost to follow up, 4 patients had progressive disease manifested as distant metastasis. Sites of progression are bone metastasis in 2 patients, 2 with supraclavicular lymph node recurrence.

The results of the present study is compared with another similar study in Korea by Ryu etal [9]] is shown in [Table 4].

Table 1: Details of chemotherapy in both arms

Variable	Arm A	Arm B	*P*-value
Dose per cycle (mg)	50.5±5.1	105.75±10.9	**0.004**
Total cumulative dose (mg)	230±34.8	194±38.1	0.9

Table 2: Pattern of acute toxicities of cisplatin in two arms

Variable	Arm	Grade 1	Grade 2	Grade 3	Grade 4	*P*- value
Anemia	Arm A	12 (60)	4 (20)	1(5)	0	0.659
	Arm B	12 (60)	6 (30)	0	0	
TLC	Arm A	0	5 (25)	0	0	0.197
	Arm B	3 (15)	4 (20)	0	0	
ANC	Arm A	3 (15)	2 (10)	0	0	0.195
	Arm B	0	2 (10)	0	0	
Nausea	Arm A	16 (80)	4 (20)	0	0	0.344

	Arm B	14 (70)	4 (20)	2 (10)	0	
Vomiting	Arm A	8 (40)	5 (25)	0	0	0.208
	Arm B	6 (30)	10 (50)	0	0	
Diarrhea	Arm A	11 (55)	3 (!5)	1 (5)	0	0.643
	Arm B	14 (70)	2 (10)	0	0	
Nephrotoxicity	Arm A	2 (10)	0	0	0	0.212
	Arm B	5 (25)	0	0	0	
Hyponatremia	Arm A	2 (10)	0	0	0	0.114
	Arm B	6 (30)	0	0	0	
Hypokalemia	Arm A	2 (10)	0	0	0	0.513
	Arm B	1 (5)	1 (5)	0	0	
Weight loss	Arm A	6 (30)	2 (10)	0	0	0.633
	Arm B	8 (40)	3 (15)	0	0	

TLC = Total leukocyte count; ANC = Absolute neutrophil count

Table 3: Response to treatment in both arms

Variable	No of pts in arm A	No of pts in arm B	*P*-value
Complete response	17 (85%)	19 (95%)	0.128
Partial response	3 (15%)	1 (5%)	
Stable disease	0	0	
Progressive disease	0	0	

Table 4: Comparison of patient characteristics and toxicities of present study with Korean study

Variable	**RYU** [9]		**Present study**	
Publication	2011		-	
Place of study	Korea		Tirupati, India	
Type of study	Prospective		Prospective	
No. Studied	104		40	
Radiotherapy schedule	EBRT – 50 Gy in 1.8-2 Gy per fraction. (^{137} Cs) LDR ICBT – 30-40 Gy in 1-2 fractions.		EBRT: 46-50 Gy in 2 Gy per fraction. HDR ICBT 24 Gy in 3-4 fractions with a gap of 1 week between fractions.	
Chemotherapy schedule (cisplatin)	Arm A: weekly (40mg/m2) for 6 cycles Arm B: triweekly (75mg/m2) for 3 cycles		Arm A: weekly 40mg/m2 for 5 cycles. Arm B: three weekly 75 mg/m2 for 2 cycles.	
Mean Age (yrs) ± SD	54.4 ±1.3	51.9 ±1.3	45.45 ± 8.6	51.75 ± 5.6
Patients in each arm	51	53	20	20
Histology	SCC- 46 (90.2) Adeno- 5 (9.8)	47 (88.7) 6 (11.3)	20 (100) 0	20 (100) 0
FIGO stage	IIB - 28 (54.9) III -19 (37.3) IVA - 4 (7.8)	34 (64.2) 19 (30.2) 3 (5.7)	12 (60) 8 (40) 0	8 (40) 12 (60) 0
Compliance to chemotherapy	44 (86%)	49 (92.5%)	14 (70%)	17 (85%)
Toxicities	NCI CTCAE		NCI CTCAE	
Anemia	ND	ND	Grade 1-2: 16 (80%) Grade 3-4: 1 (5%)	Grade 1-2 : 18 (90%)
Leucopenia	ND	ND	Grade 1-2 : 5 (25%)	Grade 1-2 : 7 (35%)

Neutropenia	Grade 1-2 20 (39%) Grade 3-4 20 (39%)	Grade 1-2 23(43%) Grade 3-4 12 (23%)*	Grade 1-2 : 5 (25%)	Grade 1-2: 2 (10%)
Nausea	Grade 1-2: 43 (84%) Grade 3-4: 2 (4%)	Grade 1-2: 46 (87%) Grade 3-4: 2 (4%)	Grade 1-2 : 20 (100%)	Grade 1-2: 18 (90%) Grade 3-4: 2 (10%)
Vomiting	Grade 1-2 12 (24%)	Grade 1-2 11 (21%)	Grade 1-2 13 (65%)	Grade 1-2 16 (80%)
Nephrotoxicity	Grade 1-2 8 (15.7%)	Grade 1-2 15 (28.3%)	Grade 1-2 2 (10%)	Grade 1-2 5 (25%)

EBRT – External beam radiotherapy; LDR – Low dose rate; HDR – High dose rate; ICBT – Intracavitary brachytherapy; SCC – Squamous cell carcinoma; FIGO – International federation of gynecology and obstetrics; NCI – National cancer institute; CTCAE – Common terminology criteria for adverse events; ND – Not described.

Discussion

In our country most of the cervical cancers are being diagnosed in locally advanced or metastatic stages due to socioeconomic problems, illiteracy, lack of effective implementation of screening programmes, late presentation and irregular follow-up.[12,13,14] After the NCI statement in 1992 concurrent cisplatin based chemoradiation became the standard of choice for locally advanced carcinoma cervix.

CRT in all stages of carcinoma cervix either with platinum based or non platinum based drugs improved 5 years Overall Survival (OS) by 6% and decreased the risk of death by 19%. There was no evidence to suggest that the benefit of CRT varied according to length of cycle, dose intensity of cisplatin but the benefit decreases with increasing stage of disease. [15] Cisplatin in combination regimens did not gain popularity due to greater toxicities. [11, 15,16]

Weekly cisplatin provides radiosensitisation, by inhibiting potentially lethal and sub-lethal damage repair and smaller individual doses of cisplatin may lead to less chemotherapy-induced morbidity without compromising efficacy. Three weekly cisplatin is popular in head and neck cancers. It was assumed that tumor biology of squamous cell carcinoma of the cervix and head/neck are similar. High-dose chemotherapy may also help in preventing distant metastasis by neutralising occult micrometastasis apart from radiosensitisation. [16]

In the present study, the planned RT treatment was completed in 100% of patients in both the arms. Scheduled five cycles of concurrent weekly cisplatin was completed by only of the 14 patients (70%) in arm A and scheduled 2 cycles of concurrent 3 weekly cisplatin was completed by 17 (85%) patients in arm B. Most common reason for incomplete treatment was hematologic toxicity. One patient in arm B had treatment interruption. In the study by Ryu et al [9] comparing weekly versus triweekly cisplatin based CRT; the two regimens were tolerated very well, with 86.3% and 92.5% completion of scheduled CT cycles for the weekly and triweekly arms, respectively. There was no statistically significant difference of compliance between the two arms (P >0.05). According to the study by Chumworathayi et al [11] 70% had incomplete treatment in the three-weekly group and 15% in the weekly cisplatin group.This high rate of incomplete treatment was seen for 3rd cycle of CT.

It was observed by patterns of care and survival study (POCSS) conducted by ICMR that better survival was seen in patients who received optimal RT and 150 mg or more of cisplatin and complications increase with increasing dose of cisplatin above 150mg. [16]

Acute toxicities, principally neutropenia and gastrointestinal toxicities were more common with CRT but were transient. All patients were evaluated and graded for different toxicities according to NCI CTCAE.

There was no statistically significant difference between hematological toxicities in both arms (anemia, leukopenia) and these toxicities were not described in Korean study.[9] There was no statistically significant difference in neutropenia(25% VS 10%, P=0.195) in between both arms. No grade 3-4 toxicities were

observed in this study. In the study by Ryu and collegues, grade 1-2 neutropenia was seen in 40% patients in both arms and grade 3-4 neutropenia was seen in 39% patients in weekly cisplatin arm and 23% patients in three weekly cisplatin arm (P = 0.03). [11] The lower percentage of neutropenia in this study may be due to less cumulative dose of cisplatin given to the patients/ less no of cycles of cisplatin. Lee et al compared weekly cisplatin and triweekly combination chemotherapy as concurrent adjuvant CRT in post-operative cases, reported that the weekly cisplatin group showed incidence of leucopenia in nearly 85% of the cases. Nearly 96% of the patients in triweekly group had leucopenia. [10]

In this study all patients had experienced nausea. 8 patients of arm A, 6 patients of arm B had grade 1 vomiting. 5 (25%) patients of arm A and 10 (50%) of arm B had grade 2 vomiting (P = 0.208). Arm B patients had more vomiting than arm A patients but there was no statistically significant difference. According to Ryu et al upper GI toxicity grade 1-2 was seen in nearly 80% of the patients in both the weekly and three weekly arms. [9] (Table 6).

In present study, 2 (10%) patients of arm A, 5 (25%) patients of arm B had grade 1 nephrotoxicity (P = 0.212). More patients of arm B experienced nephrotoxicity. On comparison to Korean study, 8 (15.7%) patients of weekly cisplatin arm and 15 (28.3%) patients of 3 weekly cisplatin arm experienced grade 1-2 nephrotoxicity which is comparable to this study.

Many analysis in squamous cell carcinoma of head and neck and cervix pointed that accelerated repopulation occurs after 4th week of start of RT and this repopulation starts early in a fractionated RT. The mean duration of treatment should be below 8 weeks as suggested by American Brachytherapy Society. [14] Prolonged treatment time had an adverse effect on outcome because of accelerated repopulation of tumor. Any planned or unplanned interruptions or delays should be avoided.

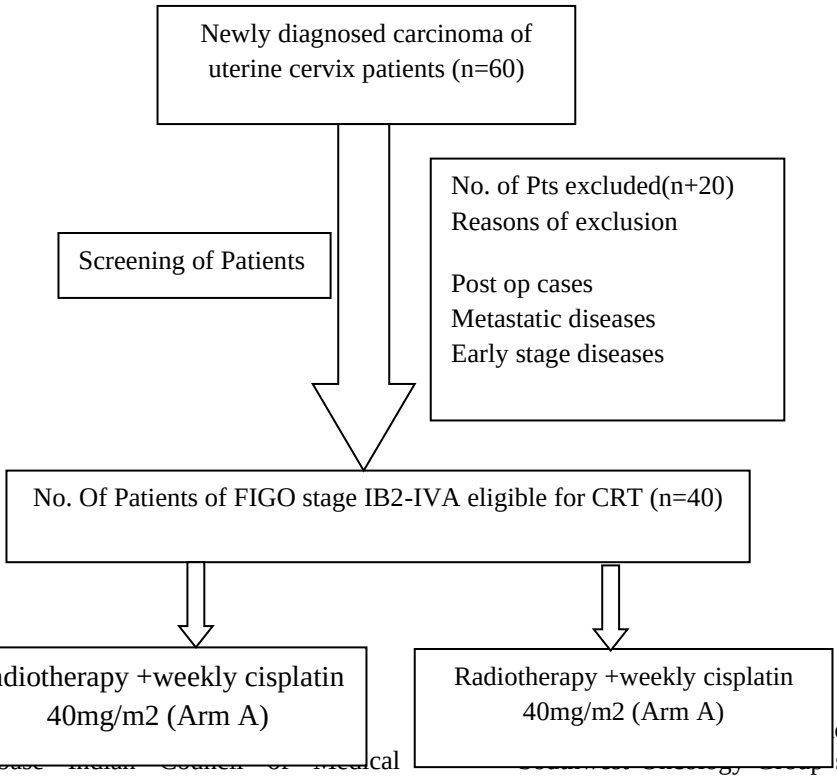
The OTT in this study for both arms ranged from 35-62 days, with a median of 46 days in arm A and 45 days in Arm B. It was statistically similar in both arms. In the Korean study, treatment delay was observed in 2 patients in weekly arm and 1 patient in three weekly arm. The treatment delay was defined as delay of radiation period (56 days) by 1 week. In this study 1 patient in each arm had treatment delay due to acute hematological and gastrointestinal toxicity. Minor interruptions for 1-2 days resulted from acute treatment related toxicities, the RT machine breakdown, patient and tumor related factors and the gap between EBRT to first HDR ICBT and subsequent fractions of ICBT.

On assessment during 1st follow up, complete response was seen in 17 (85%) patients of arm A , 19 (95%) patients of arm B and 3 patients of arm A and 1 patient of arm B had partial response (P = 0.195). This study did not show any difference in terms of response between the two arms. According to Ryu et al, patients in the three weekly cisplatin arm fared better survival wise with 88.7% OS at 5 years v/s 66.7% for the weekly cisplatin arm. [9] The present study has fewer patients and short median follow up of 12 months. Longer follow up is required for survival comparison.

Conclusion

The above findings from the present study, it can be concluded that either concurrent weekly or three weekly cisplatin along with radiotherapy can be equally effective in the treatment of cervical cancer in regard to gastrointestinal and genitourinary toxicities and patients compliance towards both chemotherapy regimens used concurrently with radiotherapy in treatment of locally advanced carcinoma cervix. However, further randomised trials with larger sample sizes and longer duration of follow up are required to reach a consensus.

Figure 1: Study plan



References

1. Open Database Indian Council of Medical Research (Database on Internet) India. http://www.icmr.nic.in/ncrp/PBCR_ Report2009_2011/ALL_CONTENT/ALL_PDF/ Chapter 2.pdf. [Last accessed on 2014 Oct 10].
2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. Globocan 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No 11. Lyon, France: International Agency for Researchon Cancer; 2013. Available from: http://www.Globocan.iarc.fr. [Last accessed on 2017 Dec 18].
3. Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler WC Jr., et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph
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;340:1144-53.
6. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999;340:1137-43.
7. 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;340:1154-61.

8. Peters WA 3rd, Liu PY, Barrett RJ 2nd, Stock RJ, Monk BJ, Berek JS, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18:1606-13.

9. NCI Clinical Announcement. Concurrent Chemoradiation for Cervical Cancer (Report). U.S. Department of public health; 1999.

10. Ryu SY, Lee WM, Kim K, Park SI, Kim BJ, Kim MH, et al. Randomized clinical trial of weekly vs. triweekly cisplatin-based chemotherapy concurrent with radiotherapy in the treatment of locally advanced cervical cancer. Int J Radiat Oncol Biol Phys 2011;81:e577-81.

11. Lee HN, Lee KH, Lee DW, Lee YS, Park EK, Park JS, et al. Weekly cisplatin therapy compared with triweekly combination chemotherapy as concurrent adjuvant chemoradiation therapy after radical hysterectomy for cervical cancer. Int J Gynecol Cancer 2011;21:128-36.

12. Chumworathayi B, Suprasert P, Charoenkwan K, Srisomboon J, Phongnarisorn C, Siriaree S, et al. Weekly versus three-weekly cisplatin as an adjunct to radiation therapy in high-risk stage I-IIA cervical cancer after surgery: A randomized comparison of treatment compliance.J Med Assoc Thai 2005;88:1483-92.

13. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 2009;105:103-4.13. National Cancer Institute-Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events. Version 4.0.201.

14. DCTD, NCI, NIH, NHHH. Available from: http://www.cteo.cancer.gov. [Last accessed on 2017 Dec 18].

15. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47. 15. Mathew A, George PS. Trends in incidence and mortality rates of squamous cell carcinoma and adenocarcinoma of cervix – Worldwide. Asian Pac J Cancer Prev 2009;10:645-50.

16. Vizcaino AP, Moreno V, Bosch FX, Muñoz N, Barros-Dios XM, Borras J, et al. International trends in incidence of cervical cancer: II. Squamous-cell carcinoma. Int J Cancer 2000;86:429-35.

17. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: A systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol 2008;26:5802-12.

18. Kim YS, Shin SS, Choi EK, Kim JH, Ahn SD, Lee SW, et al. A preliminary results of a randomized trial comparing monthly 5-flourouracil and cisplatin to weekly cisplatin alone combined with concurrent radiotherapy for locally advanced cervical cancer. Cancer Res Treat 2005;37:37-43.