Original Article

A Comparative Study of Nab-Paclitaxel versus Cisplatin Concurrent Chemoradiotherapy in Locally Advanced Cervical Cancer

Varsha Mandloi, Veenita Yogi, Om Prakash Singh, Manish Kumar Ahirwar, Suresh Yadav, H. U. Ghori

Department of Radiation Oncology, Gandhi Medical College, Bhopal, Madhya Pradesh, India

Abstract

Background: Approximately, 80%–90% patients presented with locally advanced stage with bulky central disease in our center, thus induction followed by concurrent chemoradiotherapy (CCRT) plays a predominant role in the treatment of cervical cancer. **Aim:** The purpose of this study was to compare the effects, toxicities, treatment response, and progression-free survival (PFS) of nab-paclitaxel and cisplatin in the management of cervical cancer as CCRT. **Materials and Methods:** This was a prospective, observational study performed at a tertiary care hospital. A total of 120 patients of squamous cell carcinoma of cervical cancer had received three cycles of induction chemotherapy (CT), paclitaxel 175 mg/m^2, and cisplatin 75 mg/m^2, three weekly regimen. All patients were divided into two CCRT arm, A and B. In arm A, patients received external beam radiation therapy (EBRT) with weekly cisplatin 40 mg/m^2 plus intracavitary brachytherapy (ICBT). In arm B, patients received EBRT with weekly nab-paclitaxel 70 mg/m^2 plus ICBT. **Results:** In this study, International Federation of Gynecology and Obstetrics Stage III B, 53.33% in arm A and 46.66% in arm B. After EBRT, complete response was 48.33% in arm A and 73.33% patients in arm B, and 51.66% in arm A and 26.66% patients in arm B had partial response. Median duration of follow-up was 33 months (range 24–48). The PFS, $P = 0.0093$ was significant. **Conclusion:** With this study, we can consider the justification for future approach for locally advanced cervical cancer which incorporates induction CT followed by concurrent nab-paclitaxel with EBRT followed by ICBT.

Keywords: *Concurrent chemoradiotherapy, intracavitary brachytherapy, locally advanced cervical cancer, nab-paclitaxel*

Introduction

Cervical cancer remains a considerable health burden worldwide, and it was reported to be the fourth most familiar cause of cancer-related morbidity and mortality among women living in the developing countries.[1] Globally, approximately half a million new cases were diagnosed each year, and 86% of all deaths due to cervical cancer were from developing, low-income, and middle-income countries.[2] Despite widespread use of screening tests, cervical cancer was the second most common cancer in women in India in 2016, with 77,000 diagnosed new cases. The age-standardized incidence rate of cervical cancer decreased considerably by 39.7% in India from 1990 to 2016.[3] According to a study data, it was estimated that by year 2025, the incidence rate in India will increase to 225,000.[4]

Screening is the mainstay of prevention and early diagnosis of cervical cancer. Human papilloma virus (HPV) infection is central cause of carcinogenesis.[5] Globally, the prevalence of HPV in cervical tumors is 99.7%.[6] All three standard treatment modalities: surgery, radiotherapy, and chemotherapy (CT) can be advised either alone or in combination in different stages of cervical cancer. Approximately, 80%–90% patients were presented with locally advanced stage with bulky central disease in our center, thus induction followed by concurrent chemoradiotherapy (CCRT) was a preferred choice for the treatment of cervical cancer. The combination of CT along with external beam radiotherapy (EBRT) followed by intracavitary brachytherapy (ICBT) were accepted treatment modalities in most cases.

CT drugs most oftenly used to treat cervical cancer are cisplatin, 5-fluorouracil, hydroxyurea, carboplatin, paclitaxel, docetaxel, gemcitabine, and mitomycin either alone or in combination.[7,8] Some

How to cite this article: Mandloi V, Yogi V, Singh OP, Ahirwar MK, Yadav S, Ghori HU. A comparative study of nab-paclitaxel versus cisplatin concurrent chemoradiotherapy in locally advanced cervical cancer. Clin Cancer Investig J 2019;8:198-204.

Address for correspondence:
Dr. Veenita Yogi, Department of Radiation Oncology, Gandhi Medical College, Bhopal, Madhya Pradesh, India.
E-mail: dryogi_vinita@yahoo.co.in

Access this article online

Website: www.ccij-online.org

DOI: 10.4103/ccij.ccij_59_19

Quick Response Code:

studies have suggested the use of nab-paclitaxel as neoadjuvant and adjuvant CT in head and neck, breast, and cervical cancers. Nab-paclitaxel as CCRT used with the perspective to improve the delivery of CT to the tumors while reducing drug dose to normal tissue. The purpose of the present study is to compare the effects, toxicities, treatment response, and progression-free survival (PFS) of nab-paclitaxel and cisplatin in the management of cervical cancer as CCRT.

Materials and Methods

This prospective, observational study has been approved by the Institute's Ethical Committee. The study period was from July 2014 to 2016, and follow-up period was at least 24 months. All the patients included in this study were aged >20 and <70 years, histopathologically proven squamous cell carcinoma, International Federation of Gynecology and Obstetrics (FIGO) Stage IB2-IVA, and Karnofsky Performance Score 80 or more. Patients with any prior surgery, CT, or radiation therapy for the treatment of the same disease have been excluded from this study. A written informed consent has been obtained from all patients followed by pretreatment evaluation which included complete medical history and thorough physical examination, complete hematological and biochemical profile, chest X-ray, abdominal-pelvis ultrasonography (USG), and abdominal-pelvis contrast-enhanced computed tomography (CECT).

A total of 120 patients had received three cycles of induction: CT, paclitaxel 175 mg/m^2, and cisplatin 75 mg/m^2, as three weekly regimens. All patients included in the study were randomly divided into two CCRT arm, A and B. Each arm consists 60 patients. Arm A patients had received EBRT dose of 50 Gy in 25 fractions (with or without midline shield) over 5 weeks with weekly cisplatin 40 mg/m^2 up to five doses plus ICBT. Arm B patients had received EBRT dose of 50 Gy in 25 fractions (with or without midline shield) over 5 weeks with weekly nab-paclitaxel 70 mg/m^2 up to five doses plus ICBT.

Response assessment of induction CT has been done by clinical evaluation, radiologically by USG and CECT of the abdomen and pelvis. During CCRT, patients were reviewed routinely every week for clinical assessment, and complete blood counts were noted. A hemoglobin >8 g/dl, absolute neutrophil count >4000/mm^3, and platelet count >100,000/mm^3 were maintained using oral hematinics and transfusions of whole blood/blood components whenever required. Patients were clinically assessed for ICBT during or after EBRT. All patients had received four or five fractions of high-dose rate (HDR) ICBT using Ir 192 isotope, 1 week apart, a dose of 6 Gy/fraction to point A. Before the procedure started, response was assessed, and this was repeated during all insertions. All applications were carried out using the Fletcher Applicator to assure comparability. In all patients, the treatment was completed within 58 days of starting external radiotherapy.

Response was assessed using the Response Evaluation Criteria in Solid Tumors.[9] Acute toxicities were recorded weekly during CCRT and after completion of treatment at first follow-up. Toxicities were reported using the Common Terminology Criteria for Adverse Events version 3.0.[10] All patients were examined for clinical and radiological response on routine follow-up. Initially, patients were followed up after every month of completion of treatment up to 1 year and thereafter every 3 months. Clinical assessment includes pelvic examination and Papanicolaou smear test. Radiologic assessment of disease was conducted by chest X-ray, abdominal-pelvic USG, abdominal-pelvic CT, or magnetic resonance imaging.

The primary endpoint was PFS which was defined as the interval between the date of start of CCRT to the first documentation of disease recurrence, death, or last follow-up visit. The secondary endpoint was the toxicity of nab-paclitaxel and cisplatin during CCRT.

Statistical analysis was done on the data collected, and result was formulated. Comparisons of patient and tumor characteristics were performed using the Chi-square test. The effect of two different treatment modalities on PFS of patients was investigated using the log-rank test. Kaplan–Meier survival estimates were calculated. $P < 0.05$ was considered as statistically significant. (Epi Info version 7.0 software, CDC-INFO, Atlanta, USA) was used for statistical analysis.

Results

Cervical cancer accounts for approximately 10.9% of all malignancies in our department. In this study, maximum patients belong to fourth to sixth decade of life; mean age was 52.2 years (range 32–68 years). Maximum patients belong to rural areas, 80% in arm A, and 83.33% in arm B; most of the patients were illiterate – 90% in arm A and 86.66% in arm B. Eighty percent patients in arm A and 81.66% in arm B were from low socioeconomic status. Ninety percent of patients were multiparous [Table 1].

Histologically, all cases were squamous cell carcinoma with varying degree of differentiation. Well-differentiated type was the most common, 53.33% in arm A and 51.66% in arm B. Next common grade was moderately differentiated, none of the patients had poorly differentiated carcinoma. Maximum number of patients belong to Stage III B, 53.33% in arm A and 46.66% in arm B. All patients were presented with symptoms, most common was bleeding per vagina. On clinical examination 55% patients in arm A and 46.66% in arm B presented with bilateral parametrium involvement which was suggestive of locally advanced disease. Unilateral parametrium was involved in 25% in arm A and 45% patients in arm B, 85% of them presented with left parametrium involvement [Table 2].

Most common side effects were hematological toxicities, nausea, and vomiting with induction CT. Maximum patients, 83.3% in arm A and 65% in arm B, had Grade I hematological toxicities [Table 3]. Patients were managed with blood transfusion and growth factors as supportive measures. In this study, 85% patients in arm A and 96.6% patients in arm B experienced Grade II nausea and vomiting [Table 4]. All patients were managed with antiemetic drugs and hydration.

Table 1: Patient characteristics

	Arm A	Arm B
Age (years)		
31-40	8	6
41-50	18	27
51-60	20	15
61-70	14	12
Habitat		
Rural	48	50
Urban	12	10
Socioeconomic status		
Middle	8	11
Lower	52	49
Education		
Illiterate	54	52
Literate	6	8
Parity (number of child)		
0	0	1
1-4	34	39
5-8	25	18
9-12	1	2
Menopausal status		
Premenopausal	38	30
Postmenopausal	22	30

Table 2: Disease characteristics

	Arm A	Arm B
Histological differentiation		
WDSCC	32	31
MDSCC	28	29
PDSCC	0	0
FIGO stage		
IB2	3	2
IIA	3	4
IIB	12	13
IIIA	2	3
IIIB	32	28
IVA	8	10
Parametrium involvement		
Unilateral	15	27
Bilateral	33	28
Right	12	12
Left	7	15
Symptoms		
Bleeding	52	46
White discharge	38	37
Abdominal pain	24	19

WDSCC: Well-differentiated squamous cell carcinoma, MDSCC: Moderately differentiated squamous cell carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma, FIGO: International Federation of Gynecology and Obstetrics

As noticed by patients, subjective response was very encouraging in both the arm. Almost every patient had experienced relief from presenting symptoms; this might be due to control of infection, bleeding, and pain. The overall objective response of induction CT in both arms were as follows: complete response (CR) in 26.66% patients in arm A and 43.33% in arm B, and 71.66% patients in arm A and 56.66% in arm B had partial response (PR) [Table 5].

Most common side effects observed during CCRT were hematological, gastrointestinal, and urological. There were marginally higher late rectal toxicities in patients undergoing nab-paclitaxel CCRT arm, than in the standard cisplatin arm. Radiation-induced dermatitis (RID) was observed in both arms after EBRT, 91.66% in arm A and 90% patients in arm B had Grade I, 8.33% patients in both arms had Grade II, and 1.66% patients in arm B had Grade III RID. All patients were managed by local application of gentian violet paint and aloe vera gel. Response after EBRT in both arms was achieved as CR in 48.33% in arm A and 73.33% patients in arm B, and 51.66% in arm A and 26.66% patients in arm B had PR [Table 6]. Complete response was achieved in 53% in arm A, and 68% in arm B patients after ICBT treatment completion [Table 7].

Median duration of follow-up was 33 months (range 24–48). Median PFS for arm A was 30 months (range 22–46) and median PFS for arm B was 33 months (range 22–42). $P = 0.0093$ as a result of comparison of two arms PFS was significant. These results were suggestive that PFS in nab-paclitaxel arm was convincingly better than cisplatin arm [Figure 1].

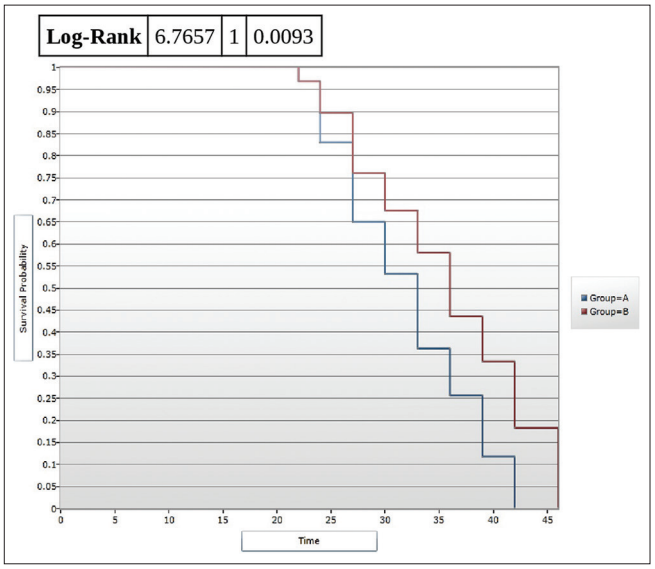

Figure 1: Graph depicting progression-free survival

Table 3: Hematological toxicity after induction chemotherapy

Grade	Number of patient (%)	
	Arm A	Arm B
0	5 (8.3)	3 (5)
I	50 (83.3)	39 (65)
II	5 (8.3)	18 (30)

Table 4: Nausea and vomiting after induction chemotherapy

Grade	Number of patient (%)	
	Arm A	Arm B
0	6 (10)	0
I	51 (85)	58 (96.6)
II	3 (5)	2 (3.3)

Table 5: Response after induction chemotherapy

Grade of response	Number of patient (%)	
	Arm A	Arm B
Complete response	16 (26.66)	26 (43.33)
Partial response	43 (71.66)	34 (56.66)
Progressive disease	1 (1.66)	0

Table 6: Response after concurrent chemoradiotherapy

Grade of response	Number of patient (%)	
	Arm A	Arm B
Complete response	29 (48.33)	44 (73.33)
Partial response	31 (51.66)	16 (26.66)

Table 7: Overall response

Grade of response	Number of patient (%)	
	Arm A	Arm B
Complete response	32 (53)	41 (68.33)
Partial response	22 (36.66)	13 (21.66)
Progressive disease	6 (10)	6 (10)

On follow-up, late complications of ICBT were recorded in terms of vaginal fibrosis, hydrometra, and pyometra in patients of both the arms. Three patients had developed vesicovaginal fistula (VVF) during follow-up due to progressive disease.

Discussion

Cervical cancer is the prevalent malignancy seen among the Indian women. In the present study, maximum patients belong to fourth to sixth decade of life. It was also revealed from the study of rural India by Thulaseedharan *et al*. that the maximum number of cervical cancers were diagnosed in the fourth and fifth decade of life.[11] In our study maximum patients belong to rural areas and most of them were illiterate and from low socioeconomic status. So, these results explained that cervical cancer is associated with illiteracy and low socioeconomic status in developing countries. This group of Indian population is less aware about health, especially female health, and because of this ignorance, most cases came with late stage of disease, while in developed countries, where Pap's smear based screening of population is in trend and health awareness is prompt, patients of cervical cancer report with early stage.

During induction CT, maximum number of patients had Grades I and II hematological toxicities in our study, in contrast to the study by Moore *et al*.; they reported Grade III–IV anemia and neutropenia with paclitaxel and cisplatin combination neoadjuvant CT.[12,13]

Overall objective response after induction CT were as follows: 26.66% patients in arm A and 43.33% patients in arm B had CR though 71.66% patients in arm A and 56.66% patients in arm B had PR. This was comparable to the study by Papadimitriou *et al*.; they reported 95% objective response with induction CT.[14] Study by Park *et al*. suggested that cisplatin and paclitaxel regimen have overall response rate in 90.7% patients, and downstaging was seen in 72.1% patients. The 3–5 years' disease-free survival rate in complete or PR group were 95% and 83%, respectively, whereas in stable disease group were 33% and 0%, respectively.[15]

There were studies which have been suggested that cisplatin as CCRT had a higher rate of PFS and overall survival rate than EBRT alone.[16,17] Peter *et al*, found that PFS and overall survival were significantly improved with CCRT (80%), in comparison to RT (63%) alone in patients of cervical cancer. CCRT arm patients had frequent grade III and IV haematological and gastrointestinal toxicities.[18] Another study by Eifel supported this study and revealed that the overall survival rate for patients treated with CCRT was significantly higher than that for patients treated with EBRT alone (0.7% vs. $P < 0.001$). Overall reduction in the risk of disease recurrence was 51% (95% confidence interval [CI], 31%–63%) for patients who received CCRT.[19]

A study by Pearcey *et al*. in which 253 patients were analyzed with median follow-up of 82 months suggested that the patients with FIGO Stage IB_2 to IIB who received cisplatin-based CCRT had better overall and disease-free survival than those treated with EBRT ($P < 0.001$) alone, with no significant difference found in PFS ($P = 0.33$). No significant difference in 3- and 5-year survival rate were found (69% vs. 66% and 62% vs. 58% respectively, $P = 0.42$). The hazard ratio for survival arm A and arm B were 1.10 (95% CI, 0.75–1.62).[20]

In a study by Thomas , the estimated curative rates of survival at 5 years were 73% among patients treated with RT alone ($P = 0.004$). Cumulative rate among patients with combined therapy were 67%, and 40% among patients in RT alone group. The rates of both distant metastasis ($P < 0.001$) and locoregional recurrence ($P < 0.001$) were significantly higher among treated with RT alone.[21,22]

The gynecologic oncology group and added studies concluded that paclitaxel is active in patient with squamous cell carcinoma of cervix and is well tolerated in CCRT schedule with granulocyte colony-stimulating factor support. The recommended concurrent dose of paclitaxel 40 mg/m^2 or 60 mg/m^2 weekly is feasible and well tolerated.[23] There was no literature available regarding nab-paclitaxel as a concurrent CT in cancer, although it has been used as neoadjuvant and adjuvant CT agent in head and neck, breast, and cervical cancer.

Nab-paclitaxel is a solvent-free, homogenizing paclitaxel with 3%–4% albumin form nanoparticle of 130 nm with a large volume of distribution and more concentration of circulating, free drug which accumulates in tumor by the enhanced permeability and retention effect. A preclinical study concluded that nab-paclitaxel showed strong antitumor efficacy with radiotherapy in a supra-additive manner without increased normal tissue toxicity.[24]

Clinical studies have shown that nab-paclitaxel is significantly more effective than cremophor-based paclitaxel, with almost double the response rate, increased time to disease progression, and increased survival. Nab-paclitaxel showed better tolerance in women with gynecological malignancies those who have experienced cremophor-based paclitaxel hypersensitivity reactions. The absence of cremophor is also associated with decreased neutropenia and peripheral neuropathy. Nab-paclitaxel can be administered in higher doses than cremophor based paclitaxel.[25,26] Nab-paclitaxel showed better results in patients with squamous histology.[27] In our study, we have used 70 mg/m^2 dose of nab-paclitaxel, which was well tolerated by all patients with minimal toxicities.

Long *et al*., reported Grade III–IV adverse events with CCRT, which were hyponatremia (14%), neutropenia (10%), lymphopenia (4%), and thrombocytopenia (2%); however, no such severe events were reported in our study.[28] No dose limiting toxicities were reported in our study in both arms as compared to other CCRT regime.[29]

In our study, most common side effects with CCRT were hematological, gastrointestinal, and urological. Eighty percent in arm A and 70% in arm B had grade I haematological and gastrointestinal toxicities. Skin reactions were developed in both the groups after EBRT. 91.66% in arm A and 90% in arm B patients had Grade I skin reaction which were managed by local application of gentian violet paint and aloe vera gel.

International brachytherapy practice guidelines recommended standard management for Stage IB–IVA cervical cancer. They recommended HDR brachytherapy fractionation regimens according to stage for Stage IB–IIA, 6 Gy × 5 fractions or 6 Gy × 4 fractions or 7 Gy × 3 fractions, for Stage IIB–IVA, 6 Gy × 5 fractions or 7 Gy × 4 fractions or 7 Gy × 3 fractions. The mean combined external beam and brachytherapy equivalent dose 2 is 81.1 Gy (standard deviation 10.16).[30] In our study, the patients were given 6 Gy for four or five fractions (depends on midline shielding during EBRT) to point A. In a Japanese study, they have used low cumulative dose by administering lower external beam dose with higher brachytherapy dose to the cervix with less late toxicities, which were comparable to our study.[31] Wang *et al*. reported 5-years pelvic tumor control rates which were 94%, 87%, and 72% for Stages IIA, IIB–IIIA, and IIIB–IVA, respectively. Five-year actuarial survival rates were 79%, 59%, and 41%, respectively. Sixty-six patients (38%) had rectal complications, and 19 (11%) had bladder complications. The 5-year actuarial rectal complication rates were 15%, 4%, and 3% for Grades II, III, and IV, respectively. More number of HDR intracavitary fractions with low dose per fraction were recommended.[32]

The overall treatment time (OTT) in our study was 58 days. Prolongation of OTT is associated with decreased local control and survival.[33] Patel *et al*. compared the two dose schedule of ICBT and observed the 3-year actuarial local control was 81.35% with 9 Gy versus 65.18% with 6.8 Gy (P = 0.04). The 3-year actuarial risk of developing any Grade 3 or worse late toxicity was 7.47% with 9 Gy and 3.57% with 6.8 Gy (P = 0.3); significant P value was comparable with our study which supported low dose per fraction (6 Gy).[34]

Late complications of ICBT were recorded in terms of vaginal fibrosis, hydrometra, and pyometra in patients of both the arms, which was indicated that patients need frequent vaginal dilatation, antibiotic, and antifungal coverage during follow-up. Three patients had developed VVF during follow-up due to progressive disease not as a complication of therapy.

This study revealed that maximum patients who achieved CR with induction CT also achieved CR with CCRT.

Conclusion

This study shows the superiority of nab-paclitaxel as concurrent CT in cervical cancer with higher percentage of overall response, PFS, drug tolerance, and manageable toxicities with higher doses than cremophor-based paclitaxel. With this study, we can consider the justification for future approach for locally advanced cervical cancer which incorporates induction CT followed by concurrent nab-paclitaxel with EBRT followed by ICBT.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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;68:394-424.
2. Arbyn M, Castellsagué X, de Sanjosé S, Bruni L, Saraiya M, Bray F, *et al.* Worldwide burden of cervical cancer in 2008. Ann Oncol 2011;22:2675-86.
3. India State-Level Disease Burden Initiative Cancer Collaborators. The burden of cancers and their variations across the states of India: The global burden of disease study 1990-2016. Lancet Oncol 2018;19:1289-306.
4. Yeole BB, Kumar AV, Kurkure A, Sunny L. Population-based survival from cancers of breast, cervix and ovary in women in Mumbai, India. Asian Pac J Cancer Prev 2004;5:308-15.
5. Bosch FX, Lorinez A, Munoz N, Meijer CJ, Shah KV. The causal relationship between human papillomavirus and cervical cancer. J Clin Pathol 2002;55:241-2.
6. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, *et al.* Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189:12-9.
7. Green J, Kirwan J, Tierney J, Vale C, Symonds P, Fresco L, *et al.* Concomittant chemotherapy and radiation therapy for cancer of the uterine cervix. Cochrane Systematic Review Intervention 2005. http:doi.org/10.1002/14651858CD002225.pub2. [Last accessed on 2018 Feb 06].
8. Candelaria M, Garcia-Arias A, Cetina L, Dueñas-Gonzalez A. Radiosensitizers in cervical cancer. Cisplatin and beyond. Radiat Oncol 2006;1:15.
9. 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.
10. Common Terminology Criteria for Adverse Events; 2017. Available from: http://www.rtog.org/ResearchAssociates/AdverseEventsReporting/AcuteRadiation Morbidity Scoring Criteria. [Last accessed on 2018 Feb 06].
11. Thulaseedharan JV, Malila N, Hakama M, Esmy PO, Cheriyan M, Swaminathan R, *et al.* Socio demographic and reproductive risk factors for cervical cancer – A large prospective cohort study from rural India. Asian Pac J Cancer Prev 2012;13:2991-5.
12. Moore DH. Neoadjuvant chemotherapy for cervical cancer. Expert Opin Pharmacother 2003;4:859-67.
13. Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda Jo, *et al.* Phase III study of cisplatin with or without paclitaxel in stage IV B recurrent, or persistent squamous cell carcinoma of the cervix: A gynaecologic oncology group study. J Clin Oncol 2004;22:3113-9.
14. Papadimitriou CA, Sarris K, Moulopoulos LA, Fountzilas G, Anagnostopoulos A, Voulgaris Z, *et al.* Phase II trial of paclitaxel and cisplatin in metastatic and recurrent carcinoma of the uterine cervix. J Clin Oncol 1999;17:761-6.
15. Park DC, Suh MJ, Yeo SG. Neoadjuvant paclitaxel and cisplatin in uterine cervical cancer: Long – Term results. Int J Gynaecol Cancer 2009;19:943-7.
16. 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 Eng J Med 1999;340:1144-53.
17. Rose PG, Concurrent chemoradiation for locally advanced carcinoma of the cervix: Where are we in 2006. Ann Oncol 2006;17:224-9.
18. Peter 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.
19. Eifel PJ. Concurrent chemotherapy and radiation therapy as the standard of care for cervical cancer. Nat Clin Pract Oncol 2006;3:248-55.
20. Pearcey R, Brundage M, Drouin P, Jeffery J, Johnston D, Lukka H, *et al*. Phase III trial comparing radical radiotherapy with or without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol 2002;20:966-72.
21. Thomas GM. Improved treatment for cervical cancer – Concurrent chemotherapy and radiotherapy. N Engl J Med 1999;340:1198-200.
22. Thomas GM. Concurrent chemotherapy and radiation for locally advanced cervical cancer: The new standard of care. Semin Radiat Oncol 2000;10:44-50.
23. Walker JL, Morrison A, DiSilvestro P, von Gruenigen VE; Gynecologic Oncology Group. A phase I/II study of extended field radiation therapy with concomitant paclitaxel and cisplatin chemotherapy in patients with cervical carcinoma metastatic to the para-aortic lymph nodes: A gynecologic oncology group study. Gynecol Oncol 2009;112:78-84.
24. Wiedenmann N, Valdecanas D, Hunter N, Hyde S, Buccholz TA, Milas L, *et al.* 1 30-nm albumin –bound paclitaxel enhances tumor radiocurability and therapeutic gain. Clin Cancer Res 2007;13:1868-74.
25. Gradishar WJ. Albumin-bound paclitaxel: A next-generation taxane. Expert Opin Pharmacother 2006;7:1041-53.
26. Desai N, Trieu V, Yao Z, Louie L, Ci S, Yang A, *et al.* Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor – Free, albumin – Bound paclitaxel, AB-007, compared with cremophor-based paclitaxel. Clin Cancer Res 2006;12:1317-24.
27. Cecco S, Aliberti M, Baldo P, Giacomin E, Leone R. Safety and efficacy evaluation of albumin – bound paclitaxel. Expert Opin Drug Safety 2014;13:511-20.
28. Long HJ 3rd, Bundy BN, Grendys EC Jr., Benda JA, McMeekin DS, Sorosky J, *et al.* Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: A gynecologic oncology group study. J Clin Oncol 2005;23:4626-33.
29. Rao GG, Rogers P, Drake RD, Nguyen P, Coleman RL. Phase I clinical trial of weekly paclitaxel, weekly carboplatin, and concurrent radiotherapy for primary cervical cancer. Gynecol Oncol 2005;96:168-72.
30. Viswanathan AN, Creutzberg CL, Craighead P, McCormack M, Toita T, Narayan K, *et al.* International brachytherapy practice patterns: A survey of the gynecologic cancer intergroup (GCIC). Int J Radiat Oncol Biol Phys 2012;82:250-5.
31. Toita T, Kitagawa R, Hamano T, Umayahara K, Hirashima Y, Aoki Y, *et al.* Phase II study of concurrent chemoradiotherapy with high dose rate intracavitary brachytherapy in patients with locally advanced uterine cervical cancer: Efficacy and toxicity of a low cumulative radiation dose schedule. Gynecol Oncol 2012;126:211-6.

32. Wang CJ, Leung SW, Chen HC, Sun LM, Fang FM, Changchien CC, *et al.* High-dose-rate intracavitary brachytherapy (HDR-IC) in treatment of cervical carcinoma: 5-year results and implication of increased low-grade rectal complications on initiation of HDR-IC fractionation scheme. Int J Radiat Oncol Biol Phys 1997;38:391-8.
33. 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;67:69-76.
34. Patel FD, Kumar P, Karunanidhi G, Sharma SC, Kapoor R. Optimization of high-dose-rate intracavitary brachytherapy schedule in the treatment of carcinoma of the cervix. Brachytherapy 2011;10:147-53.