



Prospective Study to Compare Chemoradiation plus Concomitant weekly HDR ICRT with Sequential HDR ICRT in the management of Carcinoma Cervix

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Abstract

Background: Cervical Cancer is among the most commonly diagnosed cancers in women worldwide. It is 4th most common cancer in women worldwide. HPV (Human Papilloma Virus) infection is the major risk factor for Cervical Cancer. Treatment of Early-stage Cervical Cancer - Stage IA₁, IA₂ → Surgery or ICRT Alone. Stage IB₁ → Surgery or EBRT + ICRT. Stage IB₂ / IIA → Surgery + Post op RT. Advanced stage Cervical Cancer - Stage IIB, III, IV → Conc. Chemoradiotherapy.

Objective: This study seeks a) To evaluate efficacy & toxicity of a concomitant weekly brachytherapy regimen of Carcinoma Cervix b) To compare locoregional response in two arms; two months after completion of treatment & at the end of six months of radiotherapy.

Materials & Methods: Forty-five patients of Ca. Cervix were enrolled who have not undergone surgery. They were randomized in two arms. **Arm A** received Radiotherapy 46 Gy / 23 # + Conc. Inj. Cisplatin weekly followed by HDR ICRT 7 Gy/fraction twice weekly for total 3 fractions. **Arm B** received Radiotherapy 46 Gy / 23 # + Conc. Inj. Cisplatin weekly along with Concomitant weekly HDR ICRT 7 Gy/fraction for total 3 fractions.

Results: 81.81% (18) in Arm A & 83.33% (15) in Arm B had complete response -18.18% patients (4) in Arm A & 16.67% (3) in Arm B had Partial Response - 2 months after Treatment Completion

Conclusion: Concomitant HDR ICRT Brachytherapy sessions along with EBRT & Conc. Cisplatin administration resulted in better Complete Response Rates, toxicity profile, shortened overall Treatment time, decreased hospital stay & can be considered as a reasonable alternative to sequential HDR ICRT.

Keywords: Bilateral Salpingo-oophorectomy, External Beam Radiotherapy, High Dose Rate, Intra Cavitory Radiotherapy, Overall Treatment time, Complete Response, Partial Response.

Introduction

Cancer of the cervix has undergone crucial transitions, both in incidence and in treatment in the recent times. Cancer of cervix uteri is the 4th most common cancer among women worldwide, with an estimated 569,847 new cases and 311,365 death (7.5%) per year (GLOBOCAN 2018).

Estimates indicate that more than 90% cervical cancer are related to presence of HPV infection and are contracted via sexual intercourse.

Four types of standard treatment options are used: surgery, radiation therapy, chemotherapy & targeted therapy.

Concomitant chemo-radiation (CRT) with weekly cisplatin has become the “standard of care” for treatment of advanced cases of carcinoma cervix. Several retrospective analyses suggest that prolonged RT treatment duration has an adverse effect on outcome. Extending the overall treatment beyond 6 to 8 weeks can result in approximately a 0.5% to 1% decrease in pelvic control and cause specific survival for each extra day of overall treatment time. Thus, although no prospective randomized trials have been performed, it is generally accepted that the entire RT course (including both external-beam RT and brachytherapy components) is completed in a timely fashion (within 8 weeks); delays or splits in the radiation treatment is avoided whenever possible.

Brachytherapy forms an integral part of the radiation therapy in cancer cervix. Brachytherapy is performed using an intracavitary approach, with an intrauterine tandem and vaginal colpostats. Depending on tumor anatomy, the vaginal component of brachytherapy may be delivered using ovoids, ring, or cylinder brachytherapy. When combined with EBRT, brachytherapy is usually initiated towards the latter part of treatment, when sufficient tumor regression has occurred to permit satisfactory brachytherapy geometry. In highly selected very early disease (stageIA2), brachytherapy alone may be an

option.

The once-weekly HDR intracavitary applications combined with properly adjusted external beam pelvic irradiation is a safe and effective treatment for patients with uterine cervix cancer.^{6} Twice-weekly HDR regimen may improve the local control rate with fewer complications.

My study aimed to go forward in one of the directions for this subject by comparing concomitant versus sequential HDR ICRT regimens with respect to locoregional control rates and toxicities.

Materials and Methods

The subjects for this study will be selected from the patients registered at the J. K. cancer institute, Kanpur between the time period of January 2019 to July 2020. Histologically proven Squamous cell carcinoma patients will be investigated and the eligible patients would be randomized into two arms.

Pre-Treatment Evaluation

The pre treatment evaluation in all patients will include

- Complete history, general physical examination complete systemic examination
- BSA
- The assessment of general condition will be done by using karnofsky performance status
- Hematological assessment will be done by complete hemogram including Hb, TLC, DLC.
- Biochemical assessment to assess the kidney and liver function will be done by blood urea, serum creatinine, creatinine clearance, SGOT, SGPT levels.
- Radiological assessment includes Chest X-ray – PA view and USG whole abdomen will be done in all patients.
- Whenever clinically indicated CT/MRI pelvis will be done.
- The patients will be staged according to FIGO 2018 staging system.

Inclusion Criteria

Based on the above assessment the patients for the study will be selected depending on the following criteria:

1. Histologically proven cases of squamous cell carcinoma of Ca cervix of stage Ib to IIb presenting to OPD of J.K. Cancer Institute, Kanpur.
2. Age between 35-65 years.
3. Karnofsky Performance Status > 70. (Annexure-4)
4. Complete hemogram with Hb>10gm/dL; TLC>4000/cmm, Platelet count >100,000/cmm
5. Renal function tests with Blood urea < 40mg/dL and Serum creatinine< 1.5mg/dL.
6. Liver function tests with SGOT < 35 IU/L and SGPT < 40 IU/L.
7. Patients who sign the informed consent and are ready to be on follow up as required

Exclusion Criteria

The patients having any of the following conditions will be excluded from the study:

1. Prior radiation, surgery or chemotherapy for the disease.
2. Poor G.C. with Karnofsky Performance Status of <70.
3. Distant metastasis.
4. Pregnant or lactating patient
5. Associated medical condition such as renal disease, liver disease or heart disease
6. Histopathology other than squamous cell carcinoma.

Methodology

Patients fulfilling the above inclusion criteria with carcinoma cervix reporting to JK Cancer Institute, Kanpur January 2019 to July 2020 will be randomly divided into two groups.

Arm-A

EBRT/46Gy/23#/2Gy per Fraction/5 fraction per

week/4.5 weeks with concurrent Inj cisplatin 40mg/m² weekly followed by HDR ICRT 7 Gy per fraction twice weekly for total 3 fractions.

Arm-B

EBRT/46Gy/23#/2 Gy per fraction/5 fraction per week/4.5 weeks with concurrent Inj. cisplatin 40mg/m² weekly along with CONCOMITANT weekly HDR ICRT 7 Gy per fraction for total 3 fractions.

End Points of Study

- Patient response rates

Assessment during Treatment

1. From the commencement of treatment, all the patients included in the study will be carefully and regularly assessed.
2. Detailed clinical evaluation for the tolerance of each patient to the delivered treatment will be done by thorough local examination of the patient for local disease status along with observation of acute toxic side effects of radiation.
3. Tumor response (both primary and nodal response) will be assessed by RECIST 1.1 criteria. (Annexure-2)
4. Response to be assessed 2 months after completion of RT by clinical examination as well as radiological assessment.
5. The major study endpoints will be tumor response.

Assessment at the Completion of Treatment

- All the patients were assessed two weeks after the completion of treatment, to detect acute complications like mucositis, skin reaction.
- The tumor response was assessed by using the clinical examination.
- Final response assessment was done 2 months after completion of Brachytherapy.

Follow Up

All the patient will be followed up regularly on OPD basis monthly for at least six months, 6

monthly thereafter by clinical examination.

- At every visit, each patient will be clinically evaluated for local control of disease and treatment related complications.
- To evaluate the local disease control, local examination using inspection, palpation will be done at each follow up and response will be assessed. On the suspicion of any local recurrence, biopsy will be taken for histopathology and correlated clinically.
- Late toxicities will be assessed after 6 months of completion of Radiotherapy.
- The patients will be assessed for any evidence of distant metastasis during each follow up. In case of suspicion, relevant investigations will be done to rule out the presence of distant metastasis.
- Radiological assessment for response by CT scan at 2 month & 6 months after completion of RT.

Statistical Analysis

- The data thus obtained was compiled in MS Excel 2016 and was analysed using XLSTAT add-in.
- Categorical variables were analysed using percentages and Chi square test.
- P value <0.05 was considered significant.

Results

Total 40 patients taken in both arms for trial based on inclusion and exclusion criteria were randomized to arm A & arm B.

Observation and Results

Table – 1: Shows Patients Characteristics (No. of Patients)

NUMBER OF PATIENTS	ENROLLED	DEFAULTED (EXCLUDED)	NET
ARM A	25	3	22
ARM B	20	2	18
TOTAL	45	5	40

Study was done after excluding defaulters. Total of 5 patients were excluded (3 from Arm A and 2 from Arm B)

Table – 2: Shows Patients Characteristics (Age Wise Distribution)

Age (Years)	Arm A (conventional Radiotherapy) (n=22)		Arm B (concomitant Radiotherapy) (n=18)	
	No.	%	No.	%
20-30	0	0	0	0.00
31-40	5	22.72	3	16.67
41-50	4	18.18	6	33.33
51-60	9	40.90	7	38.89
61-70	4	18.18	2	11.11
Total	22	100	18	100

Maximum no of patients were between 41 and 60 years of age.

Table-3: Shows Patients Characteristics (FIGO Stage Wise Distribution)

STAGES	ARM A (n=22)		ARM B (n=18)	
	No.	%	No.	%
IB	4	18.18	3	16.67
IIA	3	13.63	4	22.22
IIB	4	18.18	3	16.67
IIIA	3	13.63	2	11.11
IIIB	8	36.36	6	33.33
TOTAL	22	100	18	100

P = 0.7028 (non significant)

Majority of patients fell into FIGO STAGE IIIB (45%).

Table – 4: Shows Patients Characteristics (Parity Wise Distribution)

PARITY	ARM A (n=22)		ARM B (n=18)	
	No.	%	No.	%
1-3	14	63.63	9	50.00
4-6	8	36.36	8	44.44
>6	0	0	1	5.55
TOTAL	22	100	18	100

P = 0.592 (non significant)

Majority of patients had parity of 1-3.

Table – 5: Shows Background

PARITY	ARM A (n=22)		ARM B (n=18)	
	No.	%	No.	%
Rural	13	59	11	61.11
Urban	9	41	7	38.89
Total	22	100	18	100

Most of the patients belong to RURAL background.

Table – 6: Shows Patients Characteristics (HB Level Range Wise Distribution)

Hb (gm)%	ARM A (n=22)		ARM B (n=18)	
	No.	%	No.	%
>12	4	18.18	2	11.11
10-12	13	59	10	55.56
<10	5	22.72	6	33.33
Total	22	100	18	100

P = 0.685 (non significant)

Hb more than 12 gm% was seen in 4 patients (18.18%) in Arm A whereas in Arm B in 2 patients (11.11%).

Table – 7: Shows Comparison of Feasibility of ICRT After EBRT Completion

FEASIBILITY OF ICRT	ARM A (n=22)		ARM B (n=18)	
	No.	%	No.	%
YES	21	95.45	16	88.89
NO	01	4.54	02	11.11
TOTAL	22	100	18	100

P = 0.432 (non significant)

Feasibility of ICRT was seen in 21 patients (95.45%) in Arm A whereas in Arm B 16 patients (88.89%).

Table – 8: Shows Clinical Response 2 Months after treatment completion.

TUMOR RESPONSE 2 MONTH AFTER TREATMENT COMPLETION	ARM A (n=22)		ARM B (n=18)	
	No.	%	No.	%
CR	18	81.81	15	83.33
PR	4	18.18	03	16.67
DEATH	0	0	0	0
TOTAL	22	100	18	100

P = 0.9028 (non significant)

More than 80% patients achieved COMPLETE RESPONSE after 2 months of treatment completion. The result showed benefit towards ARM B that was statistically insignificant.

Table – 9: Shows Clinical Response 6 Months after treatment completion

TUMOR RESPONSE 6 MONTH AFTER TREATMENT COMPLETION	ARM A (n=10)		ARM B (n=8)	
	No.	%	No.	%
CR	7	70.00	6	75
PR	01	10.00	01	12.50
PD	2	20.00	01	12.50
EXPIRED	0	0	0	0
TOTAL	10	100	8	100

P = 0.909 (non significant)

- 3 & 2 patients lost to follow up in each arm
- 7 & 6 patients in each arm lost to follow up after 6 months

Table – 10: Shows Overall Treatment Time (OTT) Comparison.

OTT (WEEKS)	ARM A (n=22)		ARM B (n=18)	
	No.	%	No.	%
< 7 WK	0	0	17	94.44
7-9 WK	20	90.90	01	5.55
> 9 WK	02	9.09	0	0
TOTAL	22	100	18	100

P = 0.354 (non significant)

More patients completed treatment well within 7 weeks in arm B when compared with ARM A. **Treatment delays** were increasingly seen with ARM A patients. **Results were statistically insignificant.**

Table – 11 Shows Mean Overall Treatment Time (OTT)

	ARM A	ARM B
MEAN OTT (DAYS)	62 days	40 days

Mean Overall Treatment Time (OTT) in Arm A was 62 days and in Arm B was 40 days.

Discussion

Brachytherapy employs techniques of intracavitary insertions as well as interstitial applications for boosting parametrial disease. In our study, most of the patients presented with FIGO STAGE IIIB (45.283%).

In our study, we employed the available resources in the form of Cisplatin as concurrent chemotherapeutic agent, EBRT using Linear

Accelerator (6 & 15MV photon) and Cobalt 60 installations, and Brachytherapy using HDR Intracavitary applicators.

In our study, most of the patients were in the age group of 41 to 60 years in accordance with the literature showing peak incidence between 55-59 years. (GLOBOCAN 2012, Awasthy Sreedevi, Reshma Javed, and Avani Dinesh 2015).

As has been reported in literature, in our study most of the patients were multiparous having parity from 1 to 3 (56.5%). (Rao and Showalkar, 2000).

Metanalysis (107) showed a 3% survival benefit after studying 3452 patients of FIGO Stages IB to IVA that compared chemoradiation versus RT alone. The median follow up duration was 62 months.

Arm A had a mean overall treatment time of 62 days (8.85 weeks) and Arm B had that of 40 days (5.71weeks). The corresponding impact of locoregional response rates has been elucidated by a minor statistically insignificant reduction in complete response rates in Arm A patients when compared with Arm B (81% CR in Arm A VS 84% in Arm B at the end of 2 months of treatment completion.). This is in accordance with literature evidence (Chen SW1, Liang JA et al. 2003; Wang N, Arch et al 2010): analysis of the data demonstrates that the adverse effect of treatment prolongation was observed later in the treatment course for the high-dose rate (HDR) series compared to the LDR analog, however, treatment-time prolongation still negatively influenced the cause-specific survival and pelvic control rate. Schedules with shortened overall treatment time have the potential of minimising the impact of accelerated repopulation.

Wong FC et al. (2003) studied 220 patients with carcinoma of the cervix. They were treated with whole pelvic irradiation giving 40 Gy to the midplane in 20 fractions over 4 weeks. This was followed by parametrial irradiation, giving 16-20 Gy in 8-10 fractions. HDR intracavitary brachytherapy was given weekly, with a dose of 7

Gy to point A for three fractions and, starting from 1996, 6 Gy weekly for four fractions. The median overall treatment time was 50 days (range 42-73 days). The complete remission rate after radiotherapy was 93.4% (211/226). The complete remission rate after radiotherapy was 93.4% (211/226); treatment results and complication rates were compatible with those of the LDR series.

Conclusion

After completing the study following conclusions have been drawn.

- 1) Carcinoma cervix was more common in multiparous women.
- 2) Most of the women presented in fourth to sixth decades of life.
- 3) Vaginal discharge and bleeding were the most common symptoms at initial presentation.
- 4) Most of the patients presented in advanced stages, mainly IIIB.
- 5) Concomitant HDR ICRT brachytherapy sessions along with EBRT and concurrent cisplatin administration resulted in better complete response rates, toxicity profile, shortened overall treatment time, decreased hospital stay and can be considered as a reasonable alternative to sequential HDR ICRT or LDR ICRT.
- 6) Shortened overall treatment time seems to be beneficial for a country with high disease burden such as India.

References

1. International Journal of women`s health. 2015; 7:405-414. Published online 2015 Apr 16. Aswathy Sreedevi, Reshma Javed, and Avani Dinesh. PMCID: PMC4404964.
2. Cervical cancer treatment; National Cancer Institute at the National Institutes of health, U.S. Department of Health and Human Services: June 12, 2015.
3. NCCN Guidelines version 2.2015 (and

- 1.2017 updates): Cervical cancer; NCCN Framework: Enhanced level.
4. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. Subir Nag, M.D., Beth Erickson, M.D., Bruce Thomadsen, M.D., Colin Orton, Ph.D., Jeffrey D Demanes, M.D., Daniel Petereit, M.D., American Brachytherapy Society. *Int J Radiat Oncol Biol Phys.* 2000 Aug 1;48(1):201-11.
5. High-dose-rate versus low-dose-rate brachytherapy in the treatment of cervical cancer: analysis of tumor recurrence—the University of Wisconsin experience. Daniel G. Petereit, M.D.1, Jann N. Sarkaria, M.D.2, David M. Potter, Ph.D.3, Julian C. Schink, M.D. *Int J Radiat Oncol Biol Phys.* 1999 Dec 1;45(5):1267-74.
6. High dose rate brachytherapy for carcinoma of the uterine cervix: comparison of two different fractionation regimens. Le Pechoux C1, Akine Y, Sumi M, Tokuuye K, Ikeda H, Yajima M, Yamada T, Tanemura K, Tsunematsu R, Ohmi K, et al. *Int J Radiat Oncol Biol Phys.* 1995 Feb 15;31(4):735-41.
7. Carcinoma of the uterine cervix: twice-versus once-weekly high-dose-rate brachytherapy. Hama Y1, Uematsu M, Nagata I, Shioda A, Suda A, Sakurai Y, Kono M, Tamura T, Kusano S. *Radiology.* 2001 Apr;219(1):207-12
8. Combination external beam radiotherapy and high-dose-rate intracavitary brachytherapy for uterine cervical cancer: Analysis of dose and fractionation schedule. kafumi Toita, M.D., Yasumasa Kakinohana, Ph.D., Kazuhiko Ogawa, M.D., Genki Adachi, M.D., Hidehiko Moromizato, M.D., Yutaka Nagai, M.D., Toshiyuki Maehama, M.D., Kaoru Sakumoto, M.D., Koji Kanazawa, M.D., Sadayuki Murayama, M.D. *Int J Radiat Oncol Biol Phys.* 2003 Aug 1;56(5):1344-53.
9. Effects of Treatment Duration During Concomitant Chemoradiation Therapy for Cervical Cancer. Narek Shaverdian, Vinai Gondi, MD, Kathryn L. Sklenar, Emily F. Dunn, MD, Daniel G. Petereit, MD, Margaret R. Straub, PA- C, Kristin A. Bradley, MD. *Int J Radiat Oncol Biol Phys.* 2013 Jul 1;86(3):562-8. doi: 10.1016/j.ijrobp.2013.01.037. Epub 2013 Apr 2.
10. The adverse effect of treatment prolongation in cervical cancer by high-dose-rate intracavitary brachytherapy. Chen SW1, Liang JA, Yang SN, Ko HL, Lin FJ. *Radiother Oncol.* 2003 Apr;67(1):69-76.
11. "Long-term follow-up of potentiation of radiotherapy by cis- platinum in advanced cervical cancer." (Wong LC, *Gynecol Oncol.* 1989 Nov;35(2):159-63.).
12. Efficacy of Concomitant Cisplatin Plus Radiotherapy and High Dose Rate Brachytherapy versus Radiotherapy Alone. For Stage IIIB Epidermoid Cervical Cancer: A Ten-Year Randomized Controlled Trial. A.C. Zuliani, L.O. Sarian,
13. S.C. Esteves, G.A. Souza, M.O. Cunha, J.C. Teixeira, L.C. Teixeira. Campinas University, Brazil. *J Clin Oncol.* 2014 Feb 20;32(6):542-7. doi: 10.1200/JCO.2013.50.1205. Epub 2014 Jan 21.
14. Radiochemotherapy versus radiotherapy in locally advanced cervical cancer: a meta-analysis." Wang N, Arch et al. *Arch Gynecol Obstet.* 2011 Jan;283(1):103-8. doi: 10.1007/s00404-010-1385-5. Epub 2010 Feb 16.