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ORIGINAL ARTICLE

Comparison Between Concurrent EBRT and ICA with Conventional EBRT Followed by ICA in Cervical Cancer

Pandu Ranga Kumari M. · Nagarjun Reddy B. · Sanjeeva Kumari C. · Rama Krishna M.

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About the Author

Motepalli Pandu Ranga Kumari has graduated from the Osmania Medical College of NTR University of Health Sciences, Andhra Pradesh. She obtained her MBBS degree from the VMMC of Pondicherry University and is presently working as an Assistant Professor in the Department of Radiotherapy, the Government General Hospital, Kurnool, Andhra Pradesh.

Abstract

Introduction In carcinoma of cervix, if overall treatment time (OTT) is prolonged beyond 6 weeks, then the total dose required to achieve a given probability of tumor control is to be increased by 0.6 Gy for each day of prolongation, to control the accelerative repopulation of the cells, i.e., 1 % loss of tumor control, and to avoid increased treatment delays and drop outs due to the prolonged gap between EBRT and intracavitary brachytherapy (ICBT).

Objectives To evaluate local disease control and early complications of concomitant HDR-ICBT with EBRT and thereby decrease the OTT in I B–III B stage carcinoma cervix.

Methods 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), EBRT and weekly cisplatin were not given on the day of HDR-ICBT; and the control group treated with EBRT followed by HDR-ICBT and weekly cisplatin. Acute reactions and local disease response were compared after treatment and at 6-month follow-up.

Results Medians of OTTs were 42 and 63 days in the study and the control groups, respectively. Dysuria and diarrhoea incidences were more in the study but manageable. At the completion of the treatment, there were 92 and 80 % complete responses; 4 and 4 % partial responses; and 4 and 16 % stable diseases in the study group and the

Pandu Ranga Kumari M., Assistant Professor · Nagarjun Reddy B., Head of Department of Radiotherapy · Sanjeeva Kumari C., Professor · Rama Krishna M., Professor
NTR University of Health Sciences, Vijayawada, Andhra Pradesh, India

Pandu Ranga Kumari M. (✉), Assistant Professor
Mnjio & Regional Cancer Center, Room No-9, Paying Rooms, Bazar Ghat, Red Hills, Hyderabad, India
e-mail: drmprkumari@gmail.com

control group, respectively. DFSs (disease free survivals) at 6-month follow-up were, respectively, 96 and 84 %, and most of the stable diseases were observed in stage III B.
Conclusions Response was better in the study group but statistically insignificant, acute reactions were manageable, and there was decrease in drop outs due to completion of treatment at a stretch, but larger number of patients and longer follow-up are required to arrive at concrete conclusions.

Keywords Cervical cancer · Concurrent EBRT and HDR · Decreasing OTT · Local response · Early reactions · Preventing drop outs

Introduction

Cervical cancer is the third most common malignancy in women worldwide, and it remains the leading cause of cancer-related deaths in women in developing countries, with an estimated 5.3 million new cases and 2.7 million deaths in 2009. About 86 % of the cases occur in developing countries, with 13 % of them accounting for the female cancers. Worldwide mortality rates of cervical cancers are substantially lower than the incidence. The projected incidence-to-mortality ratio is about 52 % (IARC, GLOBOCON 2008).

More than 80 % of cervical cancers are found to occur in developing countries. The cervical cancer risk is 1 % during the life of a woman living in a developed country, whereas the corresponding value for a woman living in a country without preventive programs is 5 %, and around 20 % of the global burden of cervical cancer risk falls within India

Latest estimates indicate that every year 134, 420 women are diagnosed with cervical cancer, and 72,825 die from the disease. Cervical cancer ranks to be the top most frequently occurring cancer among women in India and the top most frequently occurring cancer among women between 15 and 44 years of age. Around 7.5 % of the women in general population are estimated to harbor cervical HPV infection at a given time, and 82.5 % of invasive cervical cancers are attributed to HPV 16 or 18 (IARC, GLOBOCON 2008).

At our institute (MNJIO & RCC), about 30–55 % of female out-patients constitute those with carcinoma cervix.

Before the introduction of radiotherapy, surgery was the only available method for the treatment of cervical cancer. Soon after of the discovery of radium by Madam Curie in 1998, Margaret Cleaves first inserted radium into a malignant uterus. Since then advances in radiotherapy have resulted in achieving the preferred loco-regional control and increased rates of disease free survival (DFS).

The radiotherapy of cervical cancer involves a judicious use of teletherapy and brachytherapy. Teletherapy has evolved from conventional to more conformal, and Intracavitary therapy has evolved from manual insertions of radioactive sources—techniques of manual after-loading—to remotely controlled after-loading techniques, to minimize radiation exposure to health personnel. Interest in the applications of high dose rate intracavitary (HDR) brachytherapy compared with low dose rate (LDR) brachytherapy , has increased considerably over the last 20 years because of advantages such as

a. A short treatment time,
b. Treatment given on out-patient basis, which minimizes the cost,
c. Excellent treatment reproducibility, and
d. Patient comfort with avoidance of long-lasting urinary catheters and vaginal packing

HDR brachytherapy is advantageous as it maintains spatial relationships between the treatment applicator and the dose-limiting normal structure over the short treatment time of ,say, minutes as opposed to hours or days.

Concurrent administration of the chemotherapy could increase the chance of the local control and survival. Local control is necessary for long-term DFS. It is in this context, various methods of combination of single, multiple chemotherapeutic agents have been integrated with radiotherapy as neo-adjuvant or adjuvant therapy. Recent studies by (GOG-85, 120, 123, SWOG-8797, RTOG-9001) have shown that this method is particularly appropriate for bulky and locally advanced cervical cancers.

The risk of death from cervical cancer has decreased by 30–50 % with the use of concurrent chemoradiation therapy. Based on these results, strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer.

In carcinoma cervix, if overall treatment time (OTT) is prolonged beyond 6 weeks, total dose required to produce a given probability of tumor control is to be increased by 0.6 Gy for each day of prolongation. This is to control the accelerative repopulation of the cells. Increasing dose to control accelerated repopulation is not possible due to dose-limiting structures around cervix.

If HDR is given after EBRT as in conventional method, the total treatment time will be around 10 weeks, and moreover, giving HDR 1 week after EBRT with three continuos weekly visits to hospital results in lot of drop outs either due to sociofinancial problems or due to perceived phobia about HDR procedure.

In this study, the authors have analyzed the results in terms of local control and DFS by reducing the OTT by simultaneously administering external radiotherapy and intracavitary radiation and there by preventing drop outs in treatable cancer like cervix.

Methodology

Target Population

In this prospective two-arm study, the study has been conducted on a total of 50 patients with 25 patients in each arm registered at MNJIO & RCC, with confirmed diagnosis of squamous cell carcinoma of cervix. The objectives were to integrate HDR-ICA with external RT in the treatment of locally advanced carcinoma of cervix, and thereby study the effect of reduction of OTT on survival, and to evaluate local control rates and radiation toxicity to the surrounding structures especially bladder and rectum.

Study period From November 2011 to April 2013. Follow-up till November 2013.

Patient Selection

Inclusion Criteria

1. Age <70 years.
2. Histological confirmation by biopsy: Squamous Cell carcinoma.
3. ECOG performance status ≤2.
4. Stage I B–III B.
5. Hb > 10 gm %.
6. Complete blood picture, renal function test, and liver function test results within normal limits.

All the patients having less than 10 gm% of Hb were given transfusion to raise Hb to more than 10 gm% prior to radiation therapy.

Exclusion Criteria

1. Age >70 years.
2. Other histological variants.
3. ECOG performance status >2.
4. Stage IV.
5. Previously treated case.
6. Other co-morbid conditions.

All patients were given a course of antibiotics before starting the therapy.

Pretreatment Evaluation

1. A complete detailed history which includes presenting complaints, past history, family history, personal history, and socioeconomic history with emphasis on sexually transmitted infections.
2. General physical examination.
3. Local examination: Includes Abdomen, pelvic, rectal examination.
4. Systemic examination.
5. Hematological investigations:
   - Complete Blood picture.
   - Renal function tests.
   - Liver function tests.
6. Screening for HIV/HBs Ag.
7. Biopsy from the primary tumor (edge of gross tumor or four quadrants).
8. X-ray Chest (PA view).
9. Ultrasound abdomen and pelvis.
10. CT perfusion scan: Abdomen and Pelvis (optional).
11. MRI/PET CT (optional).

Informed Written Consent of the Patient

When all the investigations were within normal limits, patient's written consent was taken after explaining the nature of disease, its treatment, and side effects in his/her own vernacular language.

Protocol Design

– Stage I B to III B
– Squamous Cell Carcinoma

Arm A—A total number of 25 cases

Radiation: Pelvic RT 50–50.4 Gy 1.8–2 Gy/Fr. 5 Fr/week over 5 weeks HDR-ICA in between EBRT on the 3rd, 4th, 5th, or 6th week (depending on local assessment) 3 Fr. × 700 cGy

Chemotherapy: Cisplatin weekly (40 mg/m^2/week) (Chemotherapy and EBRT are not given on the day of ICA)

Arm—B: A total of 25 cases

Radiation: Pelvic RT 50–50.4 Gy 1.8–2 Gy/Fr. 5 Fr/week over 5 weeks followed by HDR-ICR 3Fr. × 700 cGy/Fr.(weekly)

Chemotherapy: Cisplatin weekly (40 mg/m^2/week) D_1, D_8, D_{15}, D_{22}

EBRT

Using Linac unit external beam radiation was delivered at 100 cm SAD. Parallel opposed anterior and posterior portal (or) Box techniques were used.

RT Technique

- Simulation
  - Position: Supine (comfortable and easily reproducible) Prone (reduces bowel toxicity) or with belly board
- Bladder should be full to reduce dose to the small intestine
- CTV: Gross disease (if present), Uterus, Cervix, Vagina with sufficient margin, parametrial tissue, utero-sacral ligament, pelvic lymph nodes including internal, external and common iliac lymph nodes, para aortic lymph nodes (selected cases) ,presacral nodes, tumor bed (post op)
- Beam energy—15 MV photons
- Conventional
  - Vaginal tube or barium to delineate extent of tumor
  - Portals: Two portals AP/PA or four fields box technique by AP, PA, and two laterals.
  - Superior: L4–L5 interspace
  - Inferior: Inferior border of obturator foramen or if there is a vaginal extension, 3-cm clear margin below the lower extent of the lesion (if lower vagina is involved, inguinal nodes should be treated.
  - Lateral: 1.5 cm lateral to the bony pelvis
  - Anterior: 1 cm anterior to pubic symphysis
  - Posterior: Designed to cover at least 50 % of the rectum in stage I B or extend up to sacral hollow in patients with advanced tumors.
  - All portals were treated at each session, and dose was calculated at mid plane.

Brachytherapy

ICA Procedure

1. Bowel preparation.
2. GA/sedation.
3. Perineum cleaned.
4. Foleys catheterisation with 7 ml of 1:2 diluted urografin inflated in balloon.
5. Cervical canal found by gentle probing and dilated; Gold seed marker is placed into healthy tissue in cervix or upper vagina, for checking radiographically at subsequent treatment.
6. Uterine canal length measured with sound, and appropriate intrauterine tube inserted.
7. Ovoids inserted.
8. Anterior and posterior packing done.
9. Rectal tube inserted.

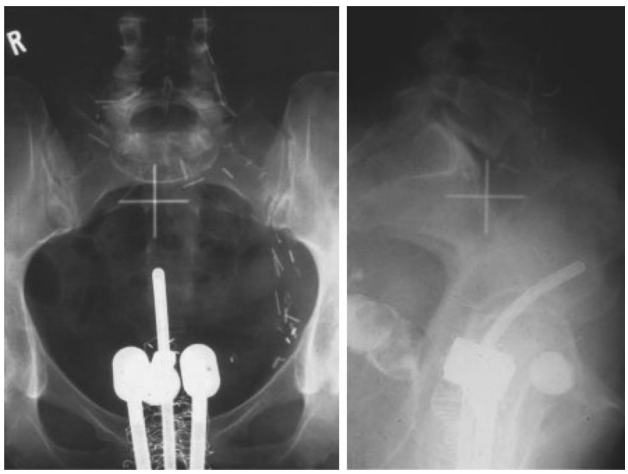

Fig. 1 ICA Orthogonal films

10. Patients were treated with HDR brachytherapy.
11. Dose fractionation: 700 cGy/Fr./3 Fr (Fig. 1).

Pelvic Dosimetry

The dose was calculated using 3D computerized treatment planning system and two orthogonal radiographs of the pelvis with the applicators containing dummy sources in situ. The isodose distribution was plotted, and the dose calculated at point A. Dose calculations were also made for rectum and bladder according to the ICRU—38 recommendations

Plan Evaluation

- Point A: 100 % dose
- Bladder dose:
  - Bladder dose to 90 % of point A. Total bladder dose below 80 Gy (LDR equivalent at 50 cGy/hr).
  - 65–75 % of point A for HDR.
- Rectal dose:
  - Total rectal dose below 75 Gy
  - 55–65 % of point A for HDR.

Cisplatin Regimen

- Injection Ranitidine 50 mg IV 8 hourly.
- Injection Dexamethasone 16 mg IV stat.
- Injection Granisetron 3 mg IV stat.
- IV fluid 1 pint DNS with 1 ampoule of KCL.
- IV fluid 1 pint DNS with 1 ampoule of MgSO4.
- IV 20 % Mannitol 100 ml IV stat.

- IV normal saline 1 pint with Cisplatin 40 mg/m2 over 1-h infusion.
- IV fluid 1 pint DNS

Follow-Up

Every week during treatment, patients were reviewed for assessing early radiation morbidity and also for remarking the radiation portals, if necessary.

On completion of the treatment: First 2 years—Every 3 months; Third and fourth years—Every 6 months; From the fifth year onward—Annually. *Response assessment* is done according to GOG criteria (Annexure II), and *Toxicity grading* is done according to RTOG toxicity grading scale (Annexure III).

Results

In this prospective comparative study of total 50 patients with 25 patients in each arm, with squamous cell carcinoma of cervix following strict selection criteria as outlined previously and treatment protocol as mentioned before, the following observations were made (Tables 1, 2, 3, 4, 5, 6, 7).

In this prospective study, HDR was concurrently given with EBRT to reduce the overall treatment to 6 weeks with an intention to observe the local control and toxicity profile. With a mean follow-up of 15 months (min. 6 months and max. 24 months), about 21 patients (84 %) of arm A and 19 patients (76 %) of arm B developed Gr. I and Gr. II acute rectal toxicities with a *P* value of 0.49—insignificant, and six patients (24 %) in arm A and 3 patients (12 %) in arm B developed Gr. III rectal toxicity with a *P* value of 0.279—insignificant. There were no Gr. IV acute rectal toxicities (Figs. 2, 3, 4, 5, 6, 7).

The acute bladder Gr.I and Gr.II toxicities were found in18 patients (72 %) of arm A and eight patients (32 %) of arm B with a *P* value of 0.04—significant. There were no Gr. III and Gr. IV acute bladder toxicities in both the arms.

On further analysis of bladder toxicities between two arms, it was observed that, 15 patients (60 %) in arm A and three patients (12 %) in arm B developed Gr. I and Gr. II acute bladder toxicities before 5 weeks of OTT when HDR was given concurrently with EBRT with a *P* value of 0.000—significant; and three patients (12 %) in arm A and five patients (20 %) in arm B developed acute bladder toxicity with a *P* value of 0.451—insignificant.

Most of the significant bladder toxicities occur before 5 weeks in arm A, when the HDR is given concurrently with EBRT. This was not observed in arm B, when HDR was given after EBRT.

All the acute rectal and bladder toxicities were managed medically, and there were no treatment interruptions due to

Table 1 Age distribution

Age Group	ARM—A		ARM—B	
	No. of patients	%	No. of patients	%
31–40	6	24	4	16
41–50	10	40	9	36
51–60	8	32	10	40
61–70	1	4	2	12

Table 2 Stage distribution

Stage	ARM—A		ARM—B	
	No. of patients	%	No. of patients	%
II B	22	88	18	72
III B	3	12	7	28

Table 3 Acute rectal toxicity

Rectal toxicity	ARM—A		ARM—B	
	No. of patients	%	No. of patients	%
Gr. II, Gr. III	21	84	19	76
Gr. III	6	24	3	72

Table 4 Acute bladder toxicity

Bladder toxicity	ARM—A		ARM—B	
	No. of patients	%	No. of patients	%
Gr. I, Gr. II	18	72	8	32
Gr. III, Gr. IV	–	–	–	–

Table 5 Bladder toxicity (duration)

Duration	ARM—A		ARM—B	
	No. of patients	%	No. of patients	%
<5 weeks	15	60	3	12
>5 weeks	3	12	5	20

Table 6 Local–regional control

Loco-regional control	ARM—A		ARM—B	
	No. of patients	%	No. of patients	%
Initial local control after treatment	23	92	20	80
Disease free survival during follow-up	24	96	21	84

Table 7 Statistical evaluation

	Sum of squares	df	Mean square	F	Sig.
Rectal toxicity. Gr. I, II					
Between groups	0.080	1	0.080	0.485	0.490
Within groups	7.920	48	0.165		
Total	8.000	49			
Rectal toxicity. Gr. III					
Between groups	0.180	1	0.180	1.200	0.279
Within groups	7.200	48	0.150		
Total	7.380	49			
Bladder toxicity Gr. I, II					
Between groups	2.000	1	2.000	9.160	0.004
Within groups	10.480	48	0.218		
Total	12.480	49			
Bladder Toxicity Gr.III, IV					
Between groups	0.000	1	0.000		
Within groups	0.000	48	0.000		
Total	0.000	49			
Bladder toxicity <5 weeks					
Between groups	2.880	1	2.880	16.000	0.000
Within groups	8.640	48	0.180		
Total	11.520	49			
Bladder toxicity >5 weeks					
Between groups	0.080	1	0.080	0.578	0.451
Within groups	6.640	48	0.138		
Total	6.720	49			
Local control after completion of treatment					
Between groups	0.180	1	0.180	1.479	0.230
Within groups	5.840	48	0.122		
Total	6.020	49			
Disease free survival during follow-up					
Between groups	0.180	1	0.180	2.000	0.164
Within groups	4.320	48	0.090		
Total	4.500	49			

acute toxicities. The patients tolerated the treatment well. There were no Gr. IV or chronic rectal and bladder toxicities observed during the current study.

Twenty three patients (92 %) of arm A and 20 patients (80 %) of arm B had no local disease after completion of treatment with *P* value of local control in terms of complete response being 0.230—insignificant, but the local–regional control was high in the study arm (92 %) when compared with control arm.

Disease free survival (DFS) at follow-up accounted for 24 patients of arm A (96 %) and 21 patients (84 %) of arm B, with a *P* value of 0.164—insignificant. Most of the decreased local–regional controls and stable diseases were observed in stage III B patients in both arms.

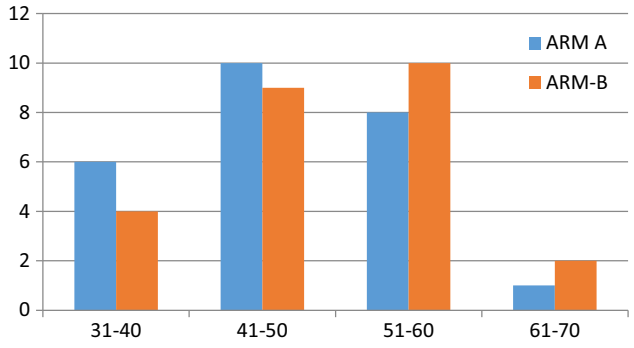

Fig. 2 Age distribution

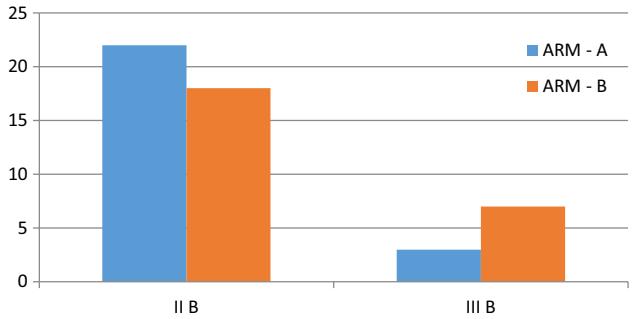

Fig. 3 Stage distribution

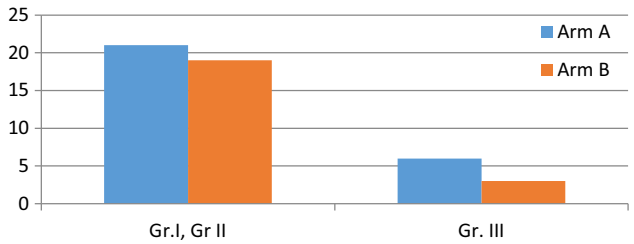

Fig. 4 Acute rectal toxicity

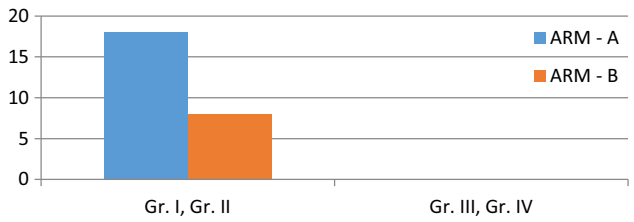

Fig. 5 Acute bladder toxicity

Discussion and Review of Studies

In India, carcinoma of uterine cervix is the most common malignancy among women, and it is the leading cause of cancer-related deaths accounting for 26 % of all cancer deaths in India.

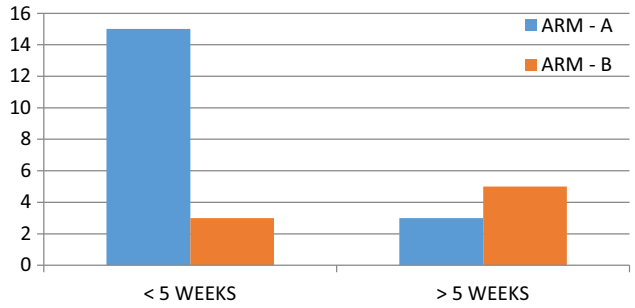

Fig. 6 Bladder toxicity (duration)

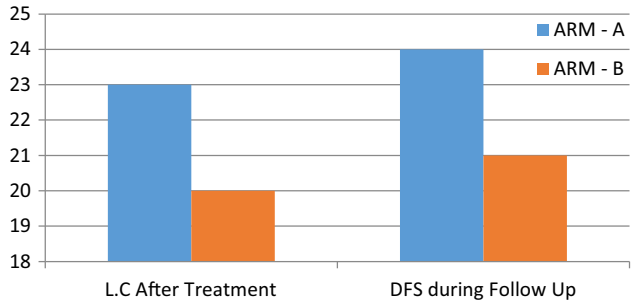

Fig. 7 Loco-regional control statistics

MNJIO and RCC means my institute MNJ institute of oncology and regional cancer center where around 30–40 % of out patients are carcinoma cervix patients. Treating such a large number of patients in proper time without compromising on the treatment schedule needs a judicious planning.

Usually in MNJIO & RCC by conventional method, first EBRT is given for 5-6 weeks, and the patients who are fit for ICA are called after a week according to the vacany list at HDR-ICA machines, and ICA is given on weekly basis for 3 weeks with OTT of around 10 weeks. Due to a time gap of a week between EBRT and ICA and continuous weekly visits to hospital for 3 weeks, there is an increase in drop outs for HDR either due to socioeconomic problems or due to perceived phobia about ICA procedure.

At MNJIO & RCC, we observed around 20 % of drop outs for HDR after EBRT, as these patients had not received the complete tumoricidal dose and they were presenting at later stage with an incurable disease.

This study was mainly done with an intention to decrease the OTT by integrating HDR-ICA with EBRT rather than giving HDR-ICA after completion of EBRT; this decreases the OTT from 10 to 6 weeks—a 50 % reduction in treatment time, given at a stretch which also prevents the drop outs for HDR.

Treating a patient in as short time as radiobiologically possible is beneficial to both the patient and hospital administration in the following ways:

1. Patient benefits
   a) *Tumor related* for fast proliferating tumors like carcinoma cervix, short OTT decreases accelerated repopulation and causes increase in the local control and the overall survival rate, as there is 1 % loss of local control and 0.6 % of loss of survival per day of prolongation of OTT beyond 30 days.
   b) *Financial burden* whole treatment will be completed at a stretch without gaps per HDR, thereby reducing the cost incurred by the patient for traveling every week for HDR.
2. Hospital benefits
   a) Hospital bed occupancy is decreased.
   b) Financial burden will be decreased in terms of food and drugs and by saving a great amount of health care cost.
   c) Drop outs for HDR prevented, and cure rates are increased.

Optimal OTT for any tumor depends on [1]

1 doubling time of tumor cells.
2 intrinsic radio sensitivity (α/β).

Short OTTs are required for tumor with low α/β or fast proliferating tumors and long OTTs for slow proliferating tumors.

Cervical cancer especially squamous histology is a fast proliferating tumor and needs short OTT. If OTT is prolonged beyond 6 weeks, the total dose required to produce a given probability of tumor control needs to be increased to combat accelerated repopulation, but the dose-limiting structures around cervix limit dose enhancement.

Several analysis suggested that accelerated repopulation occurs preferentially after the 4th week of startup radiotherapy, and this repopulation starts early in a fractionated radiotherapy. The molecular basis for accelerated repopulation is mediated through radiation-induced receptor activation and cellular growth, especially the cancer stem cells (clonogens). This occurs even after a single radiation exposure of 2 Gy and even with chemotherapy [2].

Supportive Trials

Fyles et al. [3] studied 830 patients of cervical cancer, they studied the effect of prolongation of OTT beyond 30 days, on local control and survival. They have reported 1 % loss of tumor control per day prolongation of OTT. Stage subgroup analysis showed that the effect is predominantly observed in stage III/IV relative to that in stage I/II.

Lanciano et al.'s [4] study of cervical cancer on 837 patients treated with radiation therapy showed that local recurrence within 4 years of completion of treatment increased from 6 to 20 % when the OTT was increased to 6–10 weeks ($P = 0.0001$). This translated into significantly decreased rate of survival.

Girinsky et al. [5] studied 386 patients of cervical cancer treated with radiation therapy. They reported relative risk of local recurrence has increased by a factor of 2.4 when OTT was increased up to 62 days. 1.1 % of loss of pelvic tumor control per day prolongation of treatment time is observed. 10 year-recurrence-free survival rate also decreased.

Perez et al. [6] studied 1,227 patients of cervical cancer treated with radiation therapy. They showed a strong correlation between OTT and clinical tumor stage except for patients with stage I A tumor size being <3 cm (Tables 8, 9).

OTT has a strong correlation with pelvic tumor control and survival in stages I B, II A , and II B.

Performance of all ICR insertions within 4–5 weeks from the initiation of the irradiation yielded lower pelvic failure rate.

Local failure rate was 8.8 % versus 18 % in stage I B disease $P \leq 0.1$ (Figs. 8, 9)

Delaloye et al. [7] studied 360 patients of cervical cancer stages I B to III B treated with external RT and Brachytherapy. They observed 5-year survival rate of 61 % when OTT was <60 days compared with 53 % when OTT was more than 60 days ($P = 0.03$) and 50 % increase in death rates for longer therapy group.

It is finally concluded that the shorter treatment duration is a factor associated with the longer survival in cervical cancer.

AU Mayer et al. [8] studied 210 patients cervical cancer stages II A to III B treated with EBRT and HDR-ICA. Two regimens were compared.

Table 8 Cause-specific survival

	<7 weeks (%)	7–9 weeks (%)	>9 weeks (%)	*P* value
I B	86	78	55	0.01
II A	73	41	43	0.01
II B	72	60	65	0.01
III B	42	40	38	0.01

Table 9 Pelvic failure rate

OTT	<7 weeks (%)	7–9 weeks (%)	>9 weeks (%)	*P* value
I B	5	22	36	0.01
II A	14	27	36	0.08
II B	20	28	34	0.09

Sequential Radiation Therapy with 4 × 8 Gy. HDR BT to point A was followed by EBRT.

Continuous Radiation Therapy was given as 5 × 6 Gy. HDR BT to point A. One session per week was integrated into EBRT. No EBRT was given on the day of HDR BT. Total dose given was 68–70 Gy. to point A

Median follow-up was 3.4 years (Table 10).

Preterit et al. [9] retrospectively studied the relation of OTT with pelvic control and overall survival. They studied 209 patients of cervical cancer stages I B–III B disease.

5-year survival rate—65 % when OTT < 55 days

54 % when OTT > 55 days

For stages I B and II A, the effect of OTT was significant.

Survival rate has decreased by 0.6 % per day.

Pelvic control decreased by 0.7 % per day for each additional day beyond 55 days.

There was no significant difference in late complications.

Aravind Kumar Patidar et al. [10] studied 55 patients of early-stage carcinoma by integrating HDR with EBRT and found that response rates were better with the increased acute skin reaction and diarrhea in the study group.

All the trials shown above proved that prolonged treatment time had an adverse affect on outcome because of accelerated repopulation of tumor cells. In patients treated with radiation therapy, OTT should be as short as possible, and any planned or unplanned interruptions or delays should be avoided. Timely integration of EBRT and ICA in patients with carcinoma of uterine cervix and thereby decrease of OTT is an important factor in improving pelvic tumor control and to prevent drop outs for HDR-ICA.

In this study, patients were examined at the first visit, and the patients with proliferative tumours and squamous histology were taken into consideration.

External RT was planned on simulator with 1.8–2 Gy per fraction. After completion of treatment with 3,000 cGy, patients were assessed for suitability of intracavitary application, and two fractions of HDR were given, while the patient was on external RT, and the last fraction was given 1 week after completion of external RT. Thus, the total treatment time was completed within 5–6 weeks, and the entire treatment from initiation to completion of radiation was completed during single stay of the patient in the hospital,

In this study, HDR brachytherapy was used which has two distinct features:

a) Because of high dose rate, no sublethal damage repair can occur during treatment.
b) HDR fractionation requires relatively large fraction size.

From LQ model, the larger the fraction size, the greater the potential for late tissue damage compared with tumor

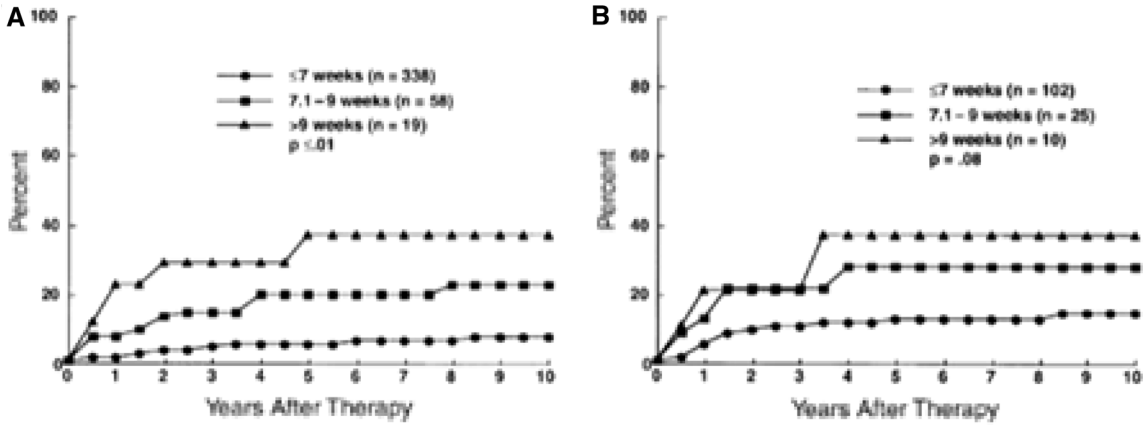

Fig. 8 Pelvic failure rates in Perez et al. [6] study

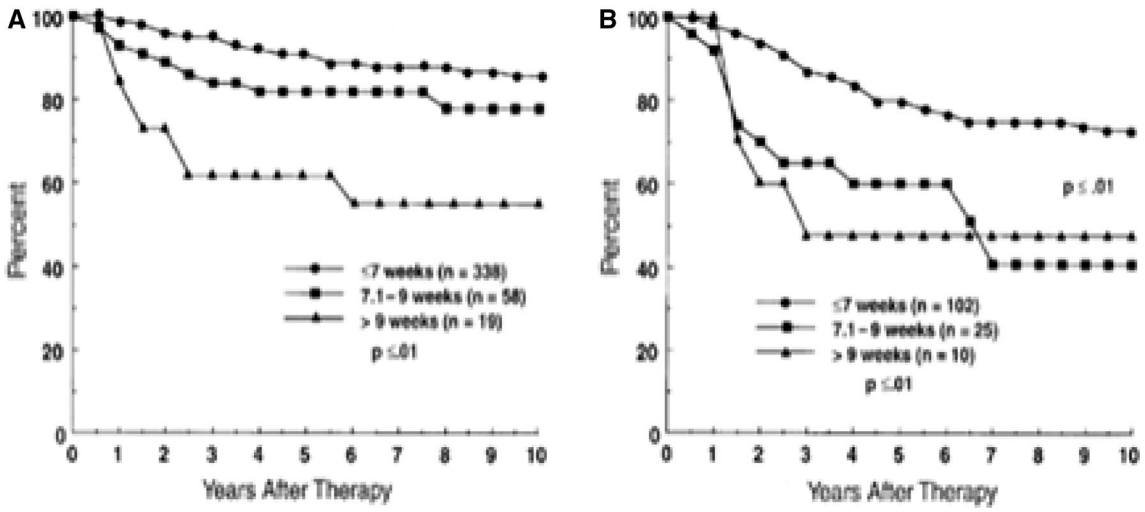

Fig. 9 Cause-specific survival in Perez et al. [6] study

Table 10 PFS IN A. U Mayer et al.'s study

	SRT	CRT
OTT	56 days	35 days
PFS	56 %	71 %

control. The practical advantages of HDR may counterbalance its radiobiological disadvantages. Each application lasts only for 10–15 min and thus eliminates the morbidity arising from prolonged bed rest. Applicator movement during treatment is minimized making dosimetric calculations more representative of actual treatment.

The dose distribution can be optimized using computer controlled variable dwell times. Finally, out-patient HDR brachytherapy may be well tolerated if given along with external RT. Chemotherapy is not given on the day of integrated HDR-ICA

Out of 25 patients treated with integrated ICA therapy in this study with OTT less than 6 weeks, 24 patients, i.e., 96 %, had local control and DFS at the end of follow-up compared with 21 patients: 84 % treated with standard protocol of EBRT followed by HDR of total OTT of more than 9 weeks with a loss of 12 % LC and PFS when OTT is increased from 6 to 9 weeks which is in comparison to A.U. Mayer et al.'s study which showed a PFS of 56 % for OTT of 5 weeks and 71 % for OTT of 8 weeks with a loss of PFS 15 % when OTT is increased

In this study LC and PFS decreased by 0.57 % per day prolongation of treatment which is in comparison with Preterit et al.; study which showed a decrease in survival by 0.6 % when OTT is increased.

In this study, there was an increase in acute rectal and bladder toxicities of Gr-I, II during integration HDR with EBRT which were easily managed medically and there were no treatment interruptions or delays. There were no Gr III,IV acute toxicities or chronic toxicities

MNJ Institute of Oncology is the only tertiary cancer center and referral hospital in A.P with an annual registry

of 9,000–9,500 new cancer cases among which cervical cancer constitutes 30–40 % of cases. The majority of the patients coming to the hospital are below poverty line, who cannot afford 4–5 times of hospital visit for treatment, which resulted in high rate of drop outs after EBRT for ICA. By integrating HDR with EBRT, the treatment time will be reduced, and whole treatment will be given in one visit itself, thereby reducing the financial burden to the patient and hospital.

The long-term survival and late rectal and bladder toxicities cannot be assessed because of short follow-up period.

However, a randomized study with a large number of patients and longer follow-up period has to be done to show consistent and long-term results in terms of the benefits of concurrent EBRT and HDR brachytherapy

Conclusions

In this prospective randomized trial by decreasing the OTT, the observations of the following results were made.

1. Increase in local control
2. Drop outs for HDR-ICA are prevented and cure rates increased
3. Increase in disease free survival during the current study
4. Increased acute bladder and rectal toxicities with acceptable toxicity profile
5. No local or distant relapse during the current study
6. No significant chronic rectal or bladder morbidity during the current study

From the above observations, it may be concluded that local control is better in the study group but statistically insignificant. Much larger number of patients and longer follow-up are required for arriving at concrete conclusions.

Summary

A prospective randomized comparative study with a total of 50 patients, 25 in arm A and 25 in arm B, with biopsy-proven squamous cell carcinoma of cervix was done with the mean ages being 48.28 years and 52.40 years in arm A and in arm B respectively, while the overall pooled mean age for the entire study was 50.16 years. The patients in both arms had good performance status (ECOG 0–1). Stage distribution of patients in arm A: 22 in II B and 3 in III B, and in arm B; 18 in II B and 7 in III B.

The treatment protocol design was to treat arm A patients with concurrent EBRT of 50–50.4 Gy. (1.8–2 Gy. per fraction) for 25–28 fractions with weekly cisplatin (40 mg/m^2) and integrating HDR of three fractions: 700 cGy per fraction in the 3rd, 4th and 5th weeks to a total dose of >85 Gy. EBRT and weekly cisplatin were not given on the day of HDR.

Arm B patients were treated with concurrent EBRT of 50–50.4 Gy (1.8–2 Gy per fraction) for 25–28 fractions with weekly cisplatin (40 mg/m^2) followed by HDR of three fractions 700 cGy per fraction to a total dose of >85 Gy.

During concurrent chemoradiation, patients were evaluated for tumor response and acute normal tissue toxicity at the right time and treated accordingly. On completion of the treatment, the final response was noted by assessing tumor response according to GOG criteria. All the patients completed treatment as per protocol without any treatment delays or interruptions

In the study group, 21 patients developed Gr. I and Gr. II rectal toxicities, 6 Gr. III rectal toxicity, and 18 Gr. I, Gr. II bladder toxicities in arm A; the respective numbers of patients were 19, 3, and 8 in arm B. Acute treatment-related toxicities were managed medically in both arms. None of the patients developed Gr. IV or chronic toxicity during the current study.

The patients in the study group tolerated integration of HDR well. Local controls in terms of complete response were 23 and 20 in arm A and arm B, and the progression-free survivals (PFCs)were 24 and 21 in arm A and arm B. In one patient in arm A, there was stable disease without any local or distant relapse compared with four patients in arm B. Most of the stable diseases were seen in stage III B patients. There were no treatment-related deaths.

Based on the above data, it was concluded that integrating HDR with EBRT results in high control rate, but not statistically significant, defaulters for ICA are prevented, and treatment-related toxicities were within acceptable limits.

A much larger number of patients and longer follow-up periods are required to arrive at concrete conclusions.

Conflict of interest None.

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