http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v7i7.115

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

A Comparative Study between two different HDR Fractionation schedules of Intracavitary Brachytherapy in Carcinoma Cervix Stage-III

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Abstract
Aim: *To compare and analysis two high-dose-rate intracavitary brachytherapy schedule of 7.5Gy per fraction per for 3 fractions over 6Gy per fraction for 4 fractions in the treatment of carcinoma of uterine cervix.*
Materials and Methods: *Total 50 patients with carcinoma of the uterine cervix (Stages III) were treated with External Beam Radiotherapy (EBRT) and High Dose Rate Intracavitary Brachytherapy (HDR-ICBT). These were randomized to arm A- 6 Gy per fraction for 4 fractions and arm B – 7.5Gy per fraction for 3 fractions. In both Arms 25 patients were included, out of those 1 patient from Arm Blost during follow up. Then follow up was done after 1yr, 2yr & 3yr to evaluate the Local control rate, disease-free survival and overall survival.*
Results: *The median follow-up period in the study was 22 months for Arm A and 21 months for Arm B. In the Control Arm A, Local control rate, disease-free survival and overall survival were 84%, 84%and 92 %, respectively, while in the Study Arm B, were 87.50%, 87.50% and 91.66%, respectively (p value >0.05).*
Conclusion: *In Indian context taking into account of increased hospital burden of locally advanced cancer cervix patients, HDR intracavitary brachytherapy schedule of 7.5 Gy per fraction 3 fractions is the preferable option over 6 Gy per fraction 4 fractions with regard to comparable, acute and late toxicity, loco-regional control, disease free survival and better patients compliance to lesser fractionation schedule.*
Keywords: *External beam radiotherapy, Gynecological malignancy, latetoxicity, ICBT _ 6Gy per fraction _ 7.5Gy per fraction.*

Introduction

Cervical cancer is the fourth most common malignancy in females worldwide and the second most common malignancy in India and most of the patients presents in locally advanced stage such as Federation of Gynecology and Obstetrics (FIGO) stage II and III[1]. Radiotherapy plays an important role in treatment of carcinoma of uterine cervix and combination of External Beam Radiotherapy (EBRT) and Intracavitary Brachytherapy (ICBT) is accepted as definitive mode of treatment. ICBT has been considered as an essential and integral component to maximize the curative potential of radiotherapy in uterine

cervix cancer management[2]. The traditional practice of Low Dose Rate (LDR) ICBT was replaced by High Dose Rate (HDR) ICBT in most of the countries of the world[3]. Though, some practical gains such as shorter treatment time, less radiation hazard to health care givers, by HDR ICBT, still there are concerns about late toxicity of large dose per fraction[4]. In treatment of cancer cervix ICBT with HDR brachytherapy is being performed since many decades, but there is no consensus about an optimal fractionation schedule available in English literature. American Brachytherapy Society (ABS) recommends that individual fraction size should be less than 7.5 Gy per fraction and number of fractions should range from four to eight depending on fraction size[2]. The current study was undertaken to compare the two regimes of brachytherapy in cervical cancer in terms of local control, disease-free survival, overall survival and toxicity—6Gy per fraction in four fractions (Control ArmA) and 7.5Gy per fraction in three fractions (Study Arm B).

Materials and Methods

This is a prospective randomized control study conducted in Department of Radiotherapy, Acharya Tulsi Regional cancer Treatment center, Bikaner. From 2014 to 2016, 50 patients of histologically biopsy proven squamous cell carcinoma of uterine cervix FIGO stage III with ECOG 2-3 were included in this study. All patients underwent complete evaluation by history taking, gynecological examination and systemic examination. Histological proof of malignancy was attained through biopsy in all patients. All patients were evaluated by complete blood count, liver function tests, renal function tests, chest radiograph and, ultrasound abdomen and pelvis. CECT abdomen and pelvis or MRI pelvis was done as appropriate. FIGO Staging system[5] was used to stage the patients. This study was started after getting approval from institutional ethical committee. Written informed consent was taken from the patients before start of treatment.All enrolled patients in this study received EBRT to pelvis with a dose of 50Gy in 25 fractions at the rate of 2 Gy per fraction with concurrent weekly cisplatin chemotherapy at a dose of 40 mg/m2 as per institutional protocol followed by HDR-ICBT. After the completion of EBRT, HDR brachytherapy was started after an interval of one week. Before starting the brachytherapy patient was investigated for Renal, Hematological and viral markers. PS/PV done for HDR fitness. The patients were allocated into two Arms by randomization done by the computerized random number tables. Patients in Arm A received the dose fractionation of 6 Gy per fraction, for 4 fractions, and patients in study Arm B received the dose of 7.5Gy per fraction for 3 fractions. EBRT was delivered to whole pelvis, the target volume included was primary tumor, lymph nodes and sub clinical disease. Patients were planned in either two parallel opposed Antero Posterior-Postero Anterior (AP-PA) field or four-field box techniques or 3D conformal radiotherapy planning as indicated. All patients were planned in supine position. Portals were marked based on bony anatomy. 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 vagina to cover the tumor with a margin of 2 to 3 cm. The lateral border was kept 1.5 to 2 cm away from the lateral pelvic brim to include the pelvic nodes. 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 posterior border was set to cover the entire sacral hollow. Dose was delivered to center of field with iso-centric technique.

HDR-ICBT

After the completion of EBRT, HDR brachytherapy was started after an interval of one week. Before starting the brachytherapy patient was investigated for Renal Hematological and viral markers. PS/PV done for HDR fitness. The patients were allocated into two Arms by randomization done by the computerized random

number tables. Patients in Arm A received the dose fractionation of 6 Gy per fraction per week, for 4 fractions and patients in study Arm B received the dose of 7.5Gy per fraction per week for 3 fractions. Modified Fletcher Suit applicators–intrauterine tandem and paired ovoids of different sizes were used according to individual patient's anatomy. Procedure was done under strict aseptic conditions under conscious sedation. Patients were placed in lithotomy position. Before intracavitory application, bladder and bowel were emptied by catheterization and pc enema. A Foley's catheter was inserted and the balloon was inflated with 7 cc of fluid (2ml normal saline and 5ml iohexol contrast) for identification of the bladder point. Cervical Os was located, dilated with Hegar's dilator. Then, length of uterine canal was measured with sound and appropriate intrauterine tandem was inserted. Two ovoids were selected based on individual anatomy were applied. Adequate posterior and anterior vaginal packing was done by regular betadine soaked gauze packs to push the bladder and rectum away and to stabilize the applicator. For rectal dosimetry a lead wire fix with an ice cream stick by micro-pore was placed along the posterior vaginal wall, rectal point situated 5mm behind the posterior vaginal wall. Treatment planning was done by using C-arm X-ray machine, X-ray pelvis both AP and Lateral view was taken for planning of intracavitary brachytherapy. Total Radiotherapy (EBRT+ HDR Brachytherapy) duration was kept 55-60 days. Brachytherapy was started 7 days interval after completion of EBRT. Each fraction of Brachytherapy was given an interval of 3 days.

Table: Patient Characteristics

PATIENTS CHARACTERSTICS	Arm A (6 GY)	Arm B (7.5 GY)
AGE		
MEDIAN AGE RANGE	48 yr 31 – 70 yr	46 yr 32 - 68 yr
HISTOPATHOLOGY SQUAMOUS CELL CARCINOM	25 (100%)	25 (100%)
ECOG		
0 1 2	3 (12%) 15 (60%) 7 (28%)	4 (16%) 14 (56%) 7 (28%)
FIGO STAGE		
STAGE III a STAGE III b	17 (68%) 8 (32)	19 (76%) 6 (24%)
STATUS		
RURAL URBAN	16 (64%) 9 (36%)	17 (68%) 8 (32%)

*****One patient in 7.5 Gy arm lost follow up at first month.

Table: Treatment response

RESPONSE	Arm A (6 GY)					Arm B (7.5 GY)				
	END OF EBRT	END OF BRACHYTHERAPY	1ST MONTH	3RD MONTH	6TH MONTH	END OF EBRT	END OF BRACHYTHERAPY	1ST MONTH	3RD MONTH	6TH MONTH
COMPLETE RESPONSE	5	10	21	21	21	6	8	20	20	20
PARTIAL RESPONSE	20	15	4	4	4	19	17	4	4	3
PROGRESSIVE DISEASE	0	0	0	0	0	0	0	1	1	1
STABLE DISEASE	0	0	0	0	0	0	0	0	0	0

Table: Late Toxicities

		ARM A (6 GY)	ARM B (7.5 GY)
BLADDER TOXICITY	GRADE 1	3 (12%)	3 (12.5%)
	GRADE 2	1 (4%)	2 (8.33%)
	GRADE 3	0	0
	GRADE 4	0	0
RECTAL TOXICITY	GRADE 1	4 (16%)	4 (16.66%)
	GRADE 2	2 (8%)	3 (12.5%)
	GRADE 3	0	1 (4.16%)
	GRADE 4	0	0

Follow Up

Patients were assessed for tumor response at the end of EBRT, end of brachytherapy, first month, Patients were examined once in a month for first 3 months, then 3 monthly thereafter for one year and four monthly in second year after of completion of radiotherapy. Response assessment was done based on RECIST (Response Evaluation Criteria In Solid Tumors) criteria[7]. Acute reactions occur within first 3 months after the start of radiotherapy. They were in the form of vaginal, mucositis, tenesmus, abdominal cramps and diarrhea. Late reactions occur after 3 months and they are in the form of proctitis, cystitis, RVF, VVF and vaginal fibrosis. During follow up patients were evaluated for late reactions, local recurrence and distant failure. All patients underwent thorough clinical examination and necessary investigations were done as per indications. Bladder and rectal morbidity was documented during follow up period and grading of late rectal and bladder morbidity done according to the Radiation Therapy Oncology Group/ criteria[8].

Statistical Analysis

Local pelvic control rate and disease-free survival were calculated from the date of start of treatment to the date of local or distant recurrence. Treatment failures were categorized as local pelvic recurrence (cervix, vagina or pelvic nodes) or distant recurrence (metastases to lymph nodes outside pelvis, bones, or viscera). The association between two categorical variables was evaluated by Chi-Square ($\chi 2$) test. Student's t-test was used to compare continuous variables between the groups. A p-value of less than 0.05 was considered as statistical significance for -square ($\chi 2$) test and student's t-test. Local control, survival, and late complication rates were calculated by the Kaplan Meier method, and differences between groups were compared by the log-rank test. A p-value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was done using the Statistical Package for Social Sciences, version 20.

Results

In this study 50 patients of cervical cancer histologically proven were included. Patient only with squamous cell carcinoma were included. The median follow-up time for Control Arm A was 22 months (range, 11.5–32.4 months) and that of Study Arm B was 21 months (range, 10.6–31.2 months). Treatment Parameters All patients in both arms received pelvic EBRT dose of 50 Gy in 25 fractions at the rate of 2 Gy per fraction. Arm A received 6 Gy per fraction per week x 4 fractions and Arm B received 7.5Gy per fraction per week x 3 fractions. All patient received concurrent weekly cisplatin chemotherapy. Total rectum BED was 110 Gy (97.4-137) in arm A and 111Gy (94.4 -142). Total bladder BED3 was 110Gy (92.8-143) in arm A and 125Gy (93.8-145) in arm B. The median overall treatment time was 53 days (48-81) in Arm A and 48 days (40- 58) in Arm B. The median follow-up for the whole group at the time of analysis was 30 months (22 to 35).

Patterns of failure: Two patients (6.6%) in Arm A and three patients (10%) in Arm B developed loco regional recurrence. One patient (3.3%) in

Arm A and three patients (10%) in Arm B developed distant failure.

Acute toxicity: During course of radiation, acute toxicities were evaluated according to the National Cancer Institute; Common Terminology Criteria of Adverse Event (CTCAE) version 4. Acute toxicities related to hematologic profiles, gastro intestinal and genitourinary toxicity were evaluated. No patient showed grade 3 or 4 toxicity in terms of the hematologic, gastrointestinal, or genitourinary systems. All acute toxicities were relieved spontaneously or controlled with minor medications.

Late toxicity: Late toxicity was graded according to the Radiation Therapy Oncology Group Criteria[8]. The six patient's in Arm A and eight patients in Arm B developed late rectal toxicity. Four patients in Arm A and five patients in Arm B developed late bladder toxicity. Late bladder toxicity: Three patients developed Grade-I, only one patient developed grade II toxicity in arm A. Three patients developed Grade-I toxicity and only two patient developed grade II toxicity in arm B. Mean time to develop bladder toxicities: 12 months (11-12 months) in Arm A and 14 months (13-18 months) in Arm B. The median total bladder BED received by patients in Arm A from EBRT and three brachytherapy sessions was 110Gy (92.8-143), and in Arm B, it was 125G (93.8145) from EBRT and all four brachytherapy sessions. Range of BED3 in patients developing bladder toxicity was 125 -142Gy3. All patients had BED 3 more than 125 Gy3.

Late rectal toxicity: Four patients developed Grade-I toxicity and two patients developed grade II toxicity in Arm A. No grade 3 or 4 late toxicities seen in Arm A. In Arm B Four patients developed Grade-1 toxicity and three patients had grade –II, toxicity and only one patient developed grade III toxicity. No grade 4 toxicity seen in Arm B. The median total rectal BED received by patients in Arm A from EBRT and three brachytherapy sessions was 110 Gy3 (97.4-137) and in Arm B, it was 108.51 Gy3 from EBRT and all four brachytherapy sessions was 111Gy3 (94.4 -142). Range of BED3 in patients developing rectal toxicity 92-142Gy3. Only two patient in Arm A and two patients in Arm B more than BED3 125Gy3. Rectal and bladder toxicity were documented according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) criteria.

Discussion

Combined radiotherapy approach in the form of external beam radiotherapy and intracavitary brachytherapy has been accepted as the standard of radical treatment in uterine cervical cancer worldwide. The incorporation of brachytherapy enhances the curative potential by dose escalation after EBRT and delivers high dose directly to tumor while sparing surrounding normal structure. Although, HDR brachytherapy has practical advantage of shorter treatment time, low radiation hazard to staff, dose optimization, but there is a large concern about late toxicity due to large dose per fraction. A study by Orton et al., who done an analysis on the data obtained from a survey of 56 institutions treating a total of over 17,000 cervix cancer patients with HDR-ICBT, found that patient morbidity rates were significantly lower for Point A doses/fraction < 7 Gy compared with > 7 Gy for both severe injuries (1.28% vs. 3.44%) and moderate plus severe (7.58% vs. 10.51%)[10]. they demonstrated that fractionation of the HDR treatments significantly influenced toxicity. But, this study by Ortan et al., is a retrospective analysis, and only physical doses were taken into consideration, not BED values, and toxicity scoring was done by morbidity criteria[10]. In further analysis, Orton et al., stated that 4 to 9 Gy can be acceptable fractionation range, but proper packing/retraction technique in ICBT and midline blocking in EBRT technique are important to decrease dose to central normal structures there by late complications[11]. Petereit et al., reviewed 24 articles on HDR brachytherapy for cervical cancer using different regimens tried to correlate BED10 and BED3 to pelvic control and complications,

respectively[12]. But, no dose-response relationship for tumor control (median BED10- 96 Gy3) or late tissue complications was noted. They observed that the technique and experience of individual centers might have played a more important role than attempts to optimize fractionation. The ABS recommends individual fraction size of less than 7.5 Gy per fraction using 4 to 8 fractions. However, ABS also includes a caution that these guidelines are no substitute for clinical experience and need to be tested in clinical setting. In the literature, various[13-18] studies compared different fractionation schedules in HDR ICRT, but the doses of EBRT to the whole pelvis differ widely in their studies. So, simple comparison of fraction size and total physical dose, may lead to incorrect interpretation of results. Since, the concept of BED was accepted in the clinical field, some have reported upon the results of various combinations of EBRT and ICBT fractionations in terms of BED10 or BED3. Ferrigno et al., noticed that the 5-yr late bladder complication rate was higher among patients treated with BED of larger than 125 Gy3 at bladder reference point, although the difference was not statistically significant (17% vs. 9%, p 0.27)[19]. Toita et al., recommended that the rectal BED3 should be kept below 100-120 Gy[20]. Clark et al., found a dose response relationship and a threshold for late rectal complications above 125 Gy3 at rectal reference point, in a study involving concurrent chemo radiotherapy[21]. Ogino et al., not showed any grade IV rectal complications even with dose to rectum was equivalent or less than 147Gy[22]. In our study, the range of rectal BED3 to point A, in patients developed rectal toxicity was 96 to 145Gy Gy. The range of bladder BED3 to point A for patients developed bladder toxicity was 125-145Gy in our study. Total 12 patients in our study developed rectal toxicity, but out of 12 patients 9 patients having BED3 less than 120 Gy. No correlation was found between BED3 to rectal and bladder complications. Patel et al., done a prospective randomized study in 104 cervical cancer patients treated with external beam and HDR[23], either 9 Gy for two fractions (Arm A) or 6.8 Gy for three fractions (Arm B) each fraction 1 week apart. 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 Gy (p = 0.3). They further states that despite using high dose per fractions (9 Gy per fraction in arm A), incidence of major late toxicity were low, because of doing application under general anesthesia and effective vaginal packing. They concluded that fewer fractions are more economical by reducing number of hospital admissions.

Limitation

Small sample size and short follow-up.

Conclusion

In our study, two fractionation schedules showed comparable treatment outcomes and toxicity. So, both schedules seem to be safe and effective. With supporting literature, we can say, fraction size may not influence the local control and late toxicity. Taking into account of increased hospital burden of locally advanced cancer cervix patients in Indian context, high dose rate intracavitary brachytherapy schedule of 8 Gy per fraction per week x 3 fractions is the preferable option over 6 Gy per fraction per week x 4 fractions with regard to comparable loco-regional control, acute and late toxicity, disease free survival and better patients compliance to lesser fractionation schedule.

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