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ORIGINAL ARTICLE

Evaluation of the Response of Concurrent High Dose Rate Intracavitary Brachytherapy with External Beam Radiotherapy in Management of Early Stage Carcinoma Cervix

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Abstract

Objectives To evaluate local disease control and early complications of concomitant brachytherapy with external beam-radiotherapy in early stage carcinoma cervix.

Methods Fifty patients of early stage carcinoma cervix (FIGO-IB/IIA) were randomly divided into study group concomitant external beam irradiation (EBRT) and HDR-ICBT (intra-cavitary brachytherapy, *xrt* = 50 Gy/25 Fr, HDR 5.2 Gy*5 Fr) and the control group EBRT followed by HDR-ICBT (*xrt* = 50 Gy/25 Fr, HDR 7.5 Gy*3 Fr). Acute reactions and local disease response were compared between treatment and at 6-month follow up.

Results Median overall treatment times were 38 and 61 days in the study and the control groups, respectively. Acute skin reactions and diarrhea were more in the study but manageable. At the completion of the study, there were 80 and 68 % complete responses, 16 and 20 % partial responses, 0 and 8 % stable diseases in the study group and the control group, respectively.

Conclusions Response was better in the study group but statistically insignificant. Larger number of patients and longer follow up are required to arrive at concrete conclusion.

Keywords Concurrent · High dose rate intracavitary brachytherapy · Carcinoma cervix · External beam radiotherapy

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Introduction

Carcinoma of the uterine cervix is the most common malignancy to affect females in developing countries. In developing countries, it accounts for about 3.4 lakh new cases and 1.6 lakh deaths every year [1]. In India about 1.25 lakh new cases and 80,000 deaths are reported every year from this disease. At present, the age-adjusted incidence rates for cervical cancer range from 19 to 44 per lakh women in various cancer registries of India. The life-time risk of cancer cervix would be estimated at 3.7 % in the absence of screening. At our center, carcinoma cervix is the second-most common cancer among females, after Cancer Breast. In the year 2009, total cases of carcinoma cervix were 537, which is 8.74 % of the total cancer cases and 19.66 % of all female malignancies.

Either surgery or radiotherapy alone can be used to treat early stages of cervix cancer. The main objective of radiotherapy is to deliver lethal dose to tumor cells without

inducing irreparable or unacceptable damage to the surrounding normal tissues. At our center, we employ high dose rate brachytherapy GAMMAMED-12i Remote after loading the unit with a radioactive iridium-192 source.

Several studies have described lower pelvic tumor control and survival rates in invasive carcinoma of the uterine cervix when the overall treatment time (OTT) in a course of irradiation is prolonged [2, 3]. American Brachytherapy Society recommends restricting the total treatment duration including external beam irradiation (EBRT) and intra-cavitary brachytherapy (ICBT) to less than 8 weeks [2]. Some studies have suggested that there may be as much as 1 % decrease in survival and local control for each extra day of treatment beyond a total treatment time of 55–60 days [2, 3]. The OTT would be unduly prolonged if ICBT was begun after completion of EBRT. ICBT can be inter-digitated during the course of EBRT if vaginal geometry is suitable for brachytherapy application, and early-stage (IB–IIA) non-bulky disease is usually optimal for the same. Therefore, ICBT is started at end of the 1st week of EBRT, and administered once a week along with EBRT.

Methods

From September 2009 to June 2010, 50 patients histopathologically confirmed, newly diagnosed cases of squamous cell carcinoma cervix stages IB and IIA were registered for treatment in our department. The patients were randomly divided into concomitant (study) and conventional (control) groups, each comprising 25 patients.

EBRT was delivered at cobalt-60 or 6 MV LINAC teletherapy units. Two AP-PA or four field box techniques were used. Upper border of pelvic field was at L4–L5 junction; lower border was at the lowest part of the obturator foramen, which was modified according to the extent of the vaginal disease. Lateral borders were kept at 1.5 cm beyond the widest part of the pelvic brim. For the four field box technique, anterior and posterior borders of the lateral portals were kept at the anterior part of pubic symphysis and the S2–S3 junction, respectively. Patients were treated to the mid plane dose on AP-PA and at isocenter on four field box technique.

HDR brachytherapy was delivered by a Micro Selectron device attached with an iridium-192 source (Ir-192) having nominal activity of 10 Ci. Applicator system consisted of an intrauterine tandem with three different angles and paired colpostat. Applicator insertion was done under strong sedation. Vagina was packed with regular betadine-soaked gauze packs to push bladder and rectum away and stabilize applicator. A Foley's catheter was inserted and balloon was inflated with 7 cm^3 of diluted urograffine to allow for the identification of bladder neck region. A rectal catheter with lead wire inside was inserted into the rectum to visualize rectal mucosa for rectal points. After applicator's insertion, AP and lateral semi orthogonal marker X-ray films were taken for pelvic dosimetry. The programming was done by means of Abacus treatment planning system. Dose was prescribed to the point "A". Point "A" is described as a point 2 cm above the distal end of the lowest source in tandem and 2 cm lateral to tandem. With bladder as reference point (ICRU-38), a straight line is marked in the anterior–posterior plane from the center of balloon in a lateral graph. The reference point is the posterior point crossing the back of the balloon on this line. This is the center of the balloon in the anterior–posterior film. An anterior–posterior straight line is marked from the bottom tip of the intrauterine tandem or the middle of the intra-vaginal ovoids. The point 5 mm behind from the posterior vaginal wall is the rectum reference point (ICRU-38).

In the study group, EBRT was administered with 2 Gy/Fr, from day 1 to 5 along with HDR-ICBT, 5.2 Gy/Fr on the 6th day of every week, and the treatment was continued for 5 weeks, with the total amount of dose being equal to 82.9 Gy, i.e., equivalent to 2 Gy fractionation.

In the control group, the irradiation schedule was as follows: EBRT—50 Gy (200 cGy/Fr, total 25 Fr), 5 Fr/week followed by a rest of 2 weeks, and then 3 Fr HDR-ICBT (7.5 Gy/Fr) on every third day, with the total dose amount being equal to 81 Gy, i.e., dose equivalent to 2 Gy fractionation, after applying gap correction factor.

Patients were accessed during treatment for local disease response and development of any acute skin reactions and diarrhea and followed up at the 1st, 3rd, and 6th months after treatment. Response will be evaluated in terms of no change, partial response (PR), progressive disease, or complete response (CR) according to WHO Clinical Response Criteria [4]. Grading of normal tissue reactions will be done by Radiation Therapy Oncology Group toxicity criteria.

Statistical analysis was performed using the χ^2 test. Statistical significance was considered with p values of less than 0.05.

Results

Mean ages were 49.9 and 48.6 years, and hemoglobins were 10.9 and 10.5 g/dl in the study and the control groups, respectively. The median OTTs in the two groups were 38 and 61 days in the study and the control groups, respectively. At the 3rd month of follow up, 18 (72 %) patients of the study and 16 (64 %) patients of the control group had CR; 7 (28 %) patients of the study and 6 (24 %) patients of the control group had PR; and nil patients of the study and

Table 1 Acute complications observed during treatment

Acute reactions	Treatment duration	Study group					Control group					Statistics	
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	χ^2	p
Diarrhea	4th week	13	8	4	0	0	16	7	2	0	0	1.04	0.59
	5th week	14	8	2	1	0	16	6	2	1	0	0.41	0.93
	End of treatment	14	8	2	1	0	20	3	2	0	0	4.33	0.22
Acute skin reactions	4th week	0	13	11	1	0	0	15	9	1	0	0.43	0.84
	5th week	0	9	13	3	0	0	10	12	3	0	0.09	0.95
	End of treatment	0	9	13	3	0	15	10	0	0	0	31.0	0.00

2 (8 %) patients of the control group had stable disease ($\chi^2 = 3.19$, $p = 0.363$). At the 6th month of follow up, 20 (80 %) patients of the study and 17 (68 %) patients of the control group had CR, 4 (16 %) patients of the study and 5 (20 %) of the control group had PR and nil patients of the study and 2 (8 %) patients of the control group had stable disease ($\chi^2 = 2.35$, $p = 0.502$). One patient in each group was lost to follow up at 6th month in the study while at 3rd month in control arm. Pap smear examination of the study and the control group at 6th month of follow up, 5 (20 %) patients of the study group and 9 (36 %) patients of the control group had Pap smear positive for malignant cells ($\chi^2 = 1.613$, $p = 0.446$). As shown in Table 1, acute gastrointestinal and skin reactions began to appear from 2nd and 3rd week, respectively. Acute toxicities were continuously observed with higher proportion and greater severity in the study group as compared to those in the control group but not found to be statistically significant. None of the patients recruited in this study developed grade 4 acute gastrointestinal and skin reactions. At the end of treatment, skin reaction was significant, but it was due to EBRT just completed in the study group, while in the control group, there was an elapse of approximately 22 days.

Discussion

In management of early stage carcinoma cervix with radiotherapy, importance of OTT on pelvic tumor control and survival rates has been well documented [5]. Response in the study group was better than that in the control group due to treatment with radiation triggers surviving cells in a tumor to divide faster than before, known as accelerated repopulation. Withers et al. [6] analyzed to conclude that clonogen repopulation in human cancer accelerates at about 28 days after the initiation of radiotherapy in fractionated regimen, so that after 4 weeks of irradiation, first 0.61 Gy of each day's dose fraction is required to overcome proliferation from previous day. In carcinoma cervix, a mean of 0.5 % (range 0.3–1.1 %) local control is lost for each prolonged day. Firuza Patel et al. [7] reported that the actuarial local control rates at 5 years were 100 % for stage IB, and 80 % for stage IIA. Local control was better in their study than that of the present control group. The probable reason could be that they used 9 Gy/Fr ICBT in the case of their patients [7]. Chen SW et al. (2003) [8] observed that treatment times less than 63 days and equal to or greater than 63 days had pelvic control rates of 83 and 72 %, respectively. These findings were significant for stages IB/IIA [97 and 79 % ($p = 0.01$), and 100 and 87 % ($p = 0.02$), respectively)]. Results in their study were better than in the present study, which may be due to the small number of patients and the short duration of follow up [8]. Takafumi Toita et al. [9] reported the 3-year actuarial pelvic control rate as 96 % for those with early disease, with median OTT being 49 days. The result of their study is better than that of the present study. There is no obvious cause of this difference. The number of cases in this study is too small for drawing any firm inference [9]. Frank Wong et al. [10] reported that the 5-year actuarial failure-free survival rates and the cancer-specific survival rates for stages IB and IIA were 87.7 and 86.6 %, 85 and 85 %, respectively. The difference may be due to the shorter follow-up (6 month) period in the present study [10]. Robson Ferrigno et al. [11] found 62 % of local control at 5 yearswith OTT up to 50 days as the only statistically significant adverse variable for the overall survival and actuarial local control. In our study, local control at the end of study is better than that of the above mentioned study which may be due to early stage, OTT being less than 40 days, and higher cumulative dose given to point A [11]. Lanciano et al. [12] described that the 4-year actuarial in-field recurrence increased from 6 to 20 %, when total treatment time increased from 6 weeks or less to 10 weeks.

The American Brachytherapy Society recommends limiting the total treatment duration to less than 8 weeks,

because prolongation of the total treatment duration can adversely affect local control and survival.

Acute skin reactions were the most common sequelae of radiotherapy in both groups. They were not statistically significant during the treatment period. None of the patients recruited in the study developed grade 4 skin reactions. At the end of the treatment, grades 2 and 3 reactions were more in the study group. Statistically significant grades 2 and 3 reactions are seen in the study group because the end of treatment corresponded to completion of both EBRT and ICBT in the study group, while in the control group it corresponded to completion of ICBT, with EBRT completed about 25 days back and thus skin reactions got time to recover (Table 1).

Acute diarrhea was observed in both groups. Grade 4 reactions were seen in none of the patients recruited in the study. Grades 1 and 2 reactions were significantly more in the study group at end of 3rd week of treatment ($p = 0.51$) because the study group was receiving concomitant ICBT with EBRT, while the control group was receiving only EBRT at that time. Similarly, grade 2 reactions were significantly more in the study group at the end of 4th week of treatment ($p = 0.59$). At the end of treatment, grades 1, 2, and 3 reactions were more in the study group, but not statistically significant ($p = 0.228$) (Table 1).

Thus, it was observed that among the two groups, CR was better in the study group but it was found to be statistically insignificant when analyzed by using χ^2 test for co-relation, when carried out for stages IB and IIA disease with 6 month follow up.

The results in the present study with 6 month follow up were quite encouraging but the post-treatment follow up was too short to definitely establish the role of this regimen.

Conclusions

Concurrent ICBT with EBRT was found to be a better treatment regimen for the management of carcinoma cervix stages IB and IIA and achieve better local control with shorter OTT than that with EBRT followed by ICBT. This was not, however, found to be statistically significant in the present study.

However, the results found were encouraging, and it shall require a larger number of patients for study and longer follow up duration to arrive at a concrete conclusion so far as disease-free survival, cancer-specific survival, pelvic control rate, and long-term sequelae, or complications are concerned.

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