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Original research article

Comparison of Clinical Outcome and Toxicity in the Management of Carcinoma Cervix Treated with Conventional Vs Intensity Modulated Radiotherapy with Concurrent Chemotherapy

Dr. Rajeshwar Avancha[1], Dr. Sandhya Rani Nippani[2]

[1]Associate Professor. Dept of Surgical Oncology. MNJ Institute of Oncology and Regional Cancer Centre, Hyderabad, Telangana State, India.

[2]Assistant Professor, Department of Radiation Oncology, MNJ Institute of Oncology and Regional Cancer Centre, Hyderabad, Telangana State, India.

Corresponding Author: Dr. Rajeshwar Avancha
Email: rajeshavancha@gmail.com

Abstract

Background: Carcinoma cervix is now the seventh most frequently diagnosed malignancy worldwide. The incidence is increasing in developing countries. Most cases of carcinoma cervix present at advanced stages. Concurrent Chemo-radiation is the standard of treatment in the case of locally advanced carcinoma cervix. The current study aimed to assess and compare the acute toxicities of Conventional RT with concurrent chemotherapy & IMRT with concurrent chemotherapy.

Methods: The prospective randomized study was conducted at MNJ Institute of Oncology and Regional Cancer Centre Blood Bank. RCC, Hyderabad. Patients included were those with Positive biopsy for squamous cell carcinoma and stage IIA-IIIB Carcinoma cervix patients according to FIGO Guidelines. After patients signed the consent form, they were randomized into either Group A or Group B by computer-generated random numbers. Group A: Concurrent chemo-radiation using IMRT followed by Brachytherapy. Group B: Concurrent chemo-radiation using Conventional RT followed by Brachytherapy.

Results: Moderately Differentiated Squamous Cell Carcinoma was the most common type with n=37 patients (73.3%) in Group A and n=29 patients (48.3%) in Group B. All patients received concurrent weekly Cisplatin at a dose of 40 mg/m^2 of body surface area. The majority of patients in both arms received 4-5 cycles as shown in figure 3 below. 1 patient in Group A and 2 in Group B received 3 cycles. All patients in both groups started ICRT within 1 week of completion of EBRT. Group A, n=34 patients (57.6%) out of n=59 and in Group B, n=43 patients (75.4%) out of n=57 developed proctitis. No patient in either group had Grade 3 or 4 toxicity. The p-value for proctitis, when compared in both groups, was 0.0403, statistically significant.

Conclusion: toxicity between the two modalities of treatment was comparable with the advantage of IMRT in reducing the acute lower gastrointestinal toxicity. The loco-regional

control was comparative in both groups. However, the limitation of this study was the short duration of follow-up. As a result, the late toxicity could be assessed only for a short period. So, there is a need for long-term follow-up.
Keywords: Carcinoma Cervix, Intensity Modulated Radio Therapy (IMRT), Conventional Radiotherapy, Chemotherapy

Introduction

According to estimates, 528,000 new instances of cervical cancer occurred in women in 2012, making it the seventh most frequent malignancy worldwide. [1] The majority of patients appear in late or advanced stages in developing nations like India. [2] Based on the five randomized control trials, concurrent radiation with chemotherapy based on cisplatin has been regarded as the standard of care for patients presenting in stages IB to IVA. [3-7] However, patients receiving chemoradiation as opposed to patients receiving radiation alone experience significantly more grade 3 and 4 gastrointestinal and hematological effects. [8-10] Conventional radiation has produced effective tumor control with tolerable normal tissue harm when using bone features to define treatment volume. However, these methods have led to greater doses to normal tissues like the small bowel, bladder, rectum, and bone marrow as well as insufficient coverage of regional lymph nodes in the clinical target volume (CTV). [11, 12] These issues can be resolved with conformal radiotherapies, such as 3DCRT or intensity-modulated radiotherapy, and 3D treatment planning systems. A series of fixed radiation beams that are shaped using the target volume projection and typically have a uniform intensity across the field are used to perform conventional 3DCRT. When necessary, basic tools like compensating filters or wedges can be used to alter conventional fields. In computer treatment software and linear accelerator collimation capabilities, IMRT represents a new radiotherapy delivery method that combines high-resolution imaging, advanced inverse planning, and radiation beam flux modulation to produce highly conformal dose distributions that are not possible with traditional methods. When pelvic cancers are treated with IMRT, radiation exposure to the nearby intestine and bladder is minimized while tumor coverage is maintained. [13-15] In comparison to conventional whole pelvis radiation, modern approaches like IMRT provide superior planned treatment volume (PTV) coverage with less acute gastrointestinal and hematological sequelae. [16] Some groups have investigated IMRT in the gynecologic setting as a method to reduce the gastrointestinal, genitourinary, and bone marrow toxicity that occurs in conventional RT. Under similar target coverage, IMRT is superior to conventional techniques in normal tissue sparing for the treatment of cervical cancer. [17] Before our investigation, it was hypothesized that patients getting 3DCRT and IMRT would spare more normal tissues than those receiving traditional radiation therapy, leading to a lower incidence of acute toxicities [16, 17] and a higher quality of life overall. To examine the amount of normal tissue irradiated by 3DCRT and IMRT, two conformal radiation methods, as well as their acute toxicity profiles, we did this study.

Material and Methods

The prospective randomized study was conducted at MNJ Institute of Oncology and Regional Cancer Centre Blood Bank. RCC, Hyderabad. Institutional Ethical approval was obtained for the study. Written consent was obtained from all the participants of the study after explaining the nature of the study in the local language.

Inclusion Criteria:

1. Positive biopsy for squamous cell carcinoma.
2. Stage IIA-IIIB Carcinoma cervix patient according to FIGO Guidelines.
3. Age 30-80 yrs.
4. Informed consent.
5. Karnofsky performance score 80-90%.
6. No evidence of Metastatic disease.

Exclusion Criteria

1. Post Hysterectomy patients (carcinoma vault) will be excluded.
2. Patients with Metastatic disease outside the pelvis.
3. Immuno-compromised patients and HIV-positive patients will be excluded.
4. Patients who refuse informed consent will be excluded.
5. Pregnancy.
6. Presence of synchronous double primary.

A total of n=120 patients were taken for the study from OPD based on the inclusion and exclusion criteria

Pre-treatment evaluation

- Complete history and physical examination including punch biopsy from the cervical lesion.
- Complete blood picture, renal function tests, and liver function tests.
- Chest x-ray PA view
- Ultrasound of the abdomen and pelvis.
- Cystoscopy on suspicion of a vesicovaginal fistula, colonoscopy on suspicion of a rectovaginal fistula, and MRI pelvis if parametrium cannot be assessed adequately on clinical examination.
- Any other investigation as and when needed.

Randomization to Groups: After patients signed the consent form, they were randomized into either Group A or Group B by computer-generated random number. Group A: Concurrent chemo-radiation using IMRT followed by Brachytherapy. Group B: Concurrent chemo-radiation using Conventional RT followed by Brachytherapy.

Conventional Radiotherapy: DRR (Digitally reconstructed radiograph) is generated and then radiation treatment portals were placed using beams eye view. *Plan evaluation:* After prescribing RT dose, the plan was evaluated for dose homogeneity, cold and hotspots in the target area, and dose constraints of OARs. Dose distribution was maintained between 95% and 107%. *Implementation:* Simulated position was reproduced using a thermoplastic mask, and fiducials. Planning was implemented on the treatment machine using EPID (Electronic Portal Imaging Device). Images taken from EPID were matched with DRR in 3 dimensions to reproduce the simulated position.
Radiotherapy Pelvic Dose: Patients in both groups were treated with a total dose of 50 Gy in 25 fractions, 2 Gy per fraction for 5 days a week along with concurrent chemotherapy, injection cisplatin I.V. 40 mg per m^2 followed by brachytherapy, 3 fraction 7Gy per week.

Intensity-Modulated Radiation Therapy (IMRT) Plan

- The primary planning target volume (PTV) and nodal PTV receive 50 Gy in 25 fractions
- Treatment is delivered once daily, 5 fractions per week, over 5 weeks

- All targets are treated simultaneously
- The dose prescription and reported to target volumes was done as per ICRU-83
- Target and nodal volume delineation was done as per institutional protocols per internationally accepted guidelines

Treatment Delivery: Treatment planning was done on the Varian treatment planning system version 8.3. Treatment was delivered on DHX Linear Accelerator with Intensity Modulated Radiation Therapy Technique.

Chemotherapy: Chemotherapy with cisplatin of a uniform dose of 50mg was given to patients intravenously immediately the next day after the 1st fraction of cisplatin and was ensured that the patient had taken radiotherapy on the day of infusion 4 hours after cisplatin therapy and even the next day after that. The patient was given tablet Zofer 8 mg thrice a day for 3 days as routine anti-emetic therapy after cisplatin. Thereafter it was repeated weekly for the entire duration of EBRT.

Treatment Monitoring: Hydration, protein and caloric intake, and hygiene were adequately maintained for all the patients during the entire treatment course. Hemogram and a biochemical investigation were done and noted before giving chemotherapy. All patients were examined once weekly during the treatment. The clinical appearance of the primary tumor and at the initiation of treatment was noted. The regression of primary tumor during the treatment was assessed and noted weekly. Any delay causing treatment interruption was noted and necessary gap correction for radiotherapy was done. Patients completing the complete schedule of radiotherapy irrespective of the delay and receiving chemotherapy were evaluated for response and assessed for intracavitary brachytherapy (ICBT) feasibility. 1st fraction of High dose rate (HDR) intracavitary brachytherapy was given immediately after completing external beam radiation 7Gy per fraction in total 3 fractions with a week gap between each fraction. Patients who were not fit for HDR-ICBT due to the central residue were boosted by lateral portals up to 66Gy and those of them with parametrial residue were boosted to 60Gy with midline block.

Assessment of toxicity: The acute toxicity was assessed using RTOG acute toxicity criteria weekly during treatment and at 6 weeks and 3 months after completion of the treatment chemotherapy-induced toxicity like nausea, vomiting, hematological and other toxicities were assessed as per the Common Terminology Criteria for Adverse Events

Assessment of Response: The Response is assessed as per the RECIST 1.1 Criteria after the last fraction of HDR-ICBT and after 6 weeks and 3 months.

Statistical Analysis: The p-value was calculated by chi-square test at a 95 % confidence interval p-value was considered significant when p is less than or equal to 0.05.

Results

A total of n=120 patients, who satisfied the eligibility criteria, were included in the study with 60 patients in each group, A and B. N=1 patient in Group A and n=3 patients in Group B defaulted during External Beam Radiotherapy. N=116 patients were evaluated at the end of the study, N=59 in the IMRT arm (Group A) and N=57 in the Conventional RT arm (Group B). The age range in Group A was 30-65 years with the mean age was 50.25 ± 5.5 years age of 50 years. The age range in Group B was 32-63 years and the mean age was 51.36 ± 6.25 years the details have been depicted in table 1.

Table 1: Age-wise and group-wise distribution of the cases in the study

Age group	Group A	Group B	Total (%)
30 – 39	6	5	11 (9.16)
40 – 49	21	24	45 (37.5)
50 – 59	19	27	46 (38.33)
60 - 69	14	4	18 (15.0)
Total	60	60	120 (100.0)

Pathological Grade: Moderately Differentiated Squamous Cell Carcinoma was the most common type with n=37 patients (73.3%) in Group A and n=29 patients (48.3%) in Group B shown in Figure 1.

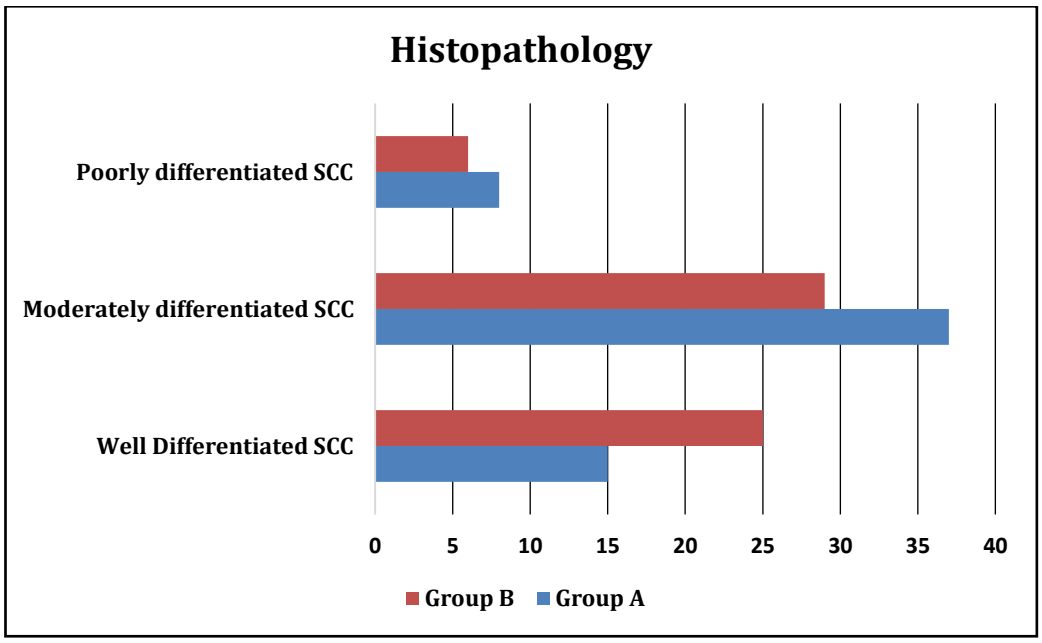

Figure 1: Showing the Histopathology of the carcinoma in the cases of study

Tumor Morphology: Exophytic growth was the most common type with n=51 patients (85%) in Group A and n=43 patients (71.7%) in Group B. The distribution of tumor morphology

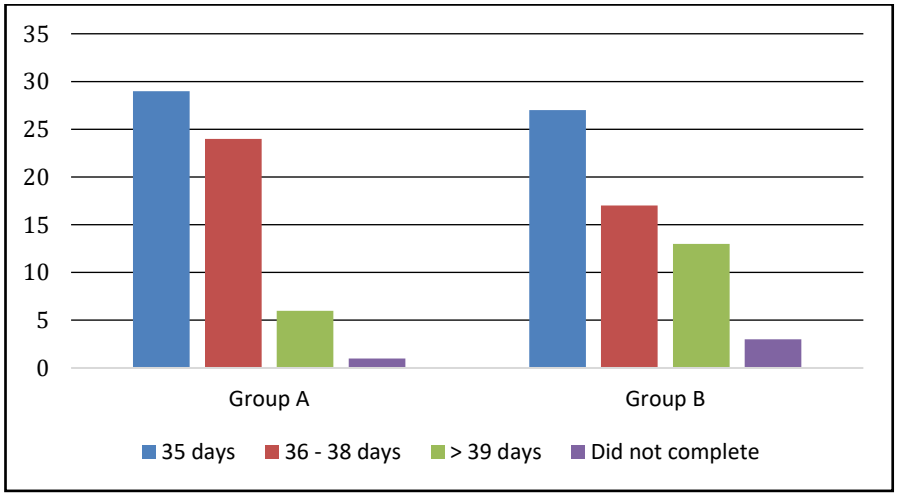

Figure 2: External Beam Radiation Therapy (EBRT) duration

All patients received concurrent weekly Cisplatin at a dose of 40 mg/m^2 of body surface area. The majority of patients in both arms received 4-5 cycles as shown in figure 3 below. 1 patient in Group A and 2 in Group B received 3 cycles. All patients in both groups started ICRT within 1 week of completion of EBRT.

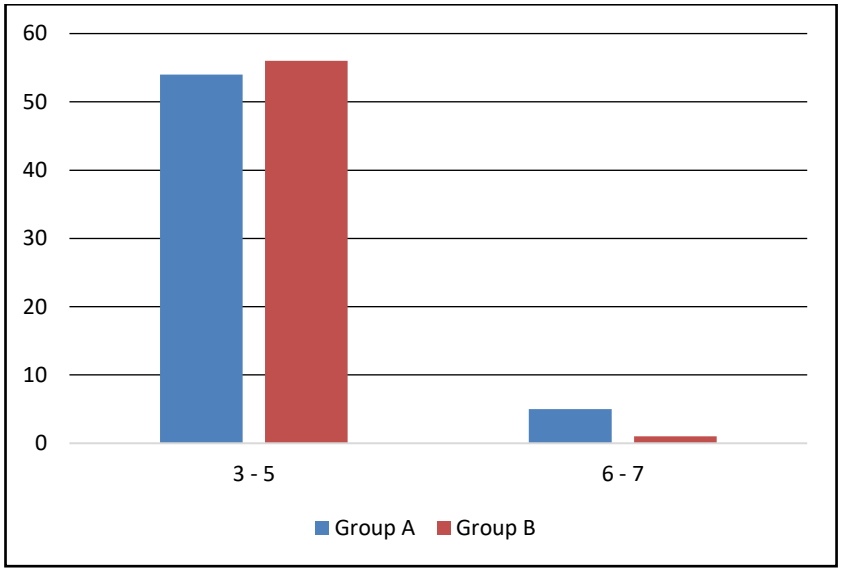

Figure 3: Cycle of chemotherapy given in the two groups

The Overall Treatment Time (in days): Overall treatment Time was ≤8 weeks (56 days) in n=43 patients (72.9%) in Group A & n=42 patients (73.7%) in Group B. Treatment has delayed in n=16 patients in group A and n=15 patients in group B. The delay included a gap during EBRT as well as the gap between EBRT and ICRT depicted in Figure 4.

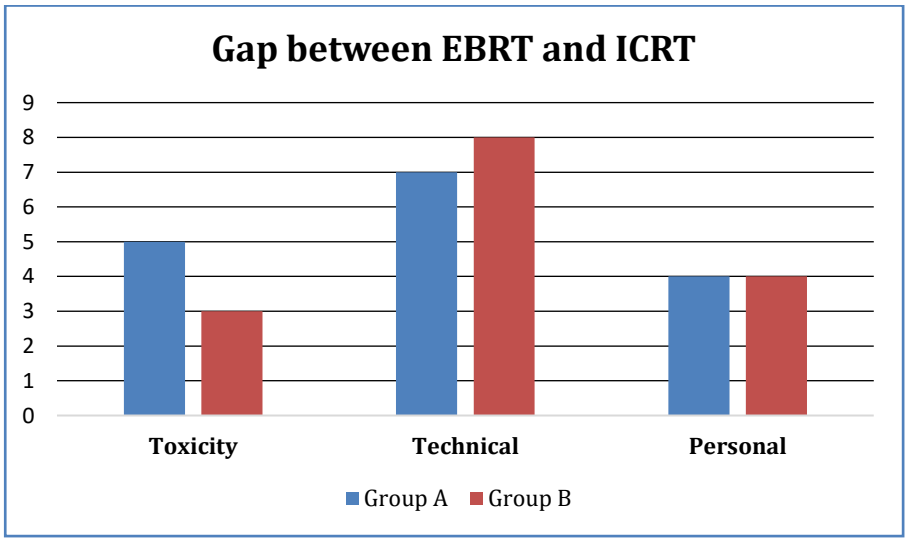

Figure 4: Gap between EBRT and ICRT in the cases of the study

In Group A, n=50 patients (84.7%) out of n=59 patients had anemia during EBRT while in Group B the number of patients who had anemia was n=45 out of n=57 (79%). No patient in either group had Grade 4 toxicity. The p-value for anemia, when compared in both the groups, was (0.7355) statistically insignificant. The number of patients with different grades of Acute Hemoglobin Toxicity.

Leucopenia: In Group A, n=32 patients (54.2%) out of n=59 and in Group B, n=34 patients (59.6%) out of n=57 developed Acute Leucocyte Toxicity. No patient in either group had Grade 3 or 4 toxicity. The p-value for acute leucocyte toxicity, when compared in both groups, was 0.8342, statistically insignificant.

Platelets: Only n=1 patients in each group developed Grade 1 toxicity. N=58 patients (98.3%) in Group A and n=56 patients (98.2%) in Group B had no toxicity. No patient had Grade 2, 3, or 4 toxicities.

Nausea: In Group A, n=54 patients (91.5%) out of n=59 and in Group B, n=51 patients (89.5%) out of n=57 developed nausea. No patient in either group had Grade 4 toxicity. The p-value for nausea, when compared in both groups, was 0.9052, statistically insignificant.
Vomiting: In Group A, 54 patients (91.5%) out of 59, and in Group B, 51 patients (89.5%) out of 57 developed vomiting. No patient in either group had Grade 3 or 4 toxicity. The p-value for vomiting, when compared in both groups, was 0.8408, statistically insignificant.
Diarrhea: In Group A, n=39 patients (66.1%) out of n=59 and in Group B, n=49 patients (86%) out of n=57 developed diarrhea. No patient in either group had Grade 4 toxicity. The p-value for diarrhea, when compared in both groups, was 0.0966, statistically insignificant.
Proctitis: In Group A, n=34 patients (57.6%) out of n=59 and in Group B, n=43 patients (75.4%) out of n=57 developed proctitis. No patient in either group had Grade 3 or 4 toxicity. The p-value for proctitis, when compared in both groups, was 0.0403, statistically significant.
Serum Creatinine: Only 1 patient in each group developed Grade 1 toxicity. 58 patients (98.3%) in Group A and 56 patients (98.2%) in Group B had no toxicity. No patient had Grade 2, 3, or 4 toxicities.
Cystitis: In Group A, n=23 patients (39%) out of n=59 and in Group B, n=27 patients (47.4%) out of n=57 developed cystitis. No patient in either group had Grade 3 or 4 toxicity. The p-value for cystitis, when compared in both groups, was 0.5383, statistically insignificant.
Dermatitis: N=2 patients in Group A and 4 patients in Group B developed Grade n=1 toxicity. N=57 patients (96.6%) in Group A and n=53 patients (92.9%) in Group B had no toxicity. No patient had grade 2,3,4 toxicity.
In Group A, 48 patients (81.4%) out of 59, and in Group B, 43 patients (75.4%) out of n=57 showed complete response on the First follow up as shown in figure 5.

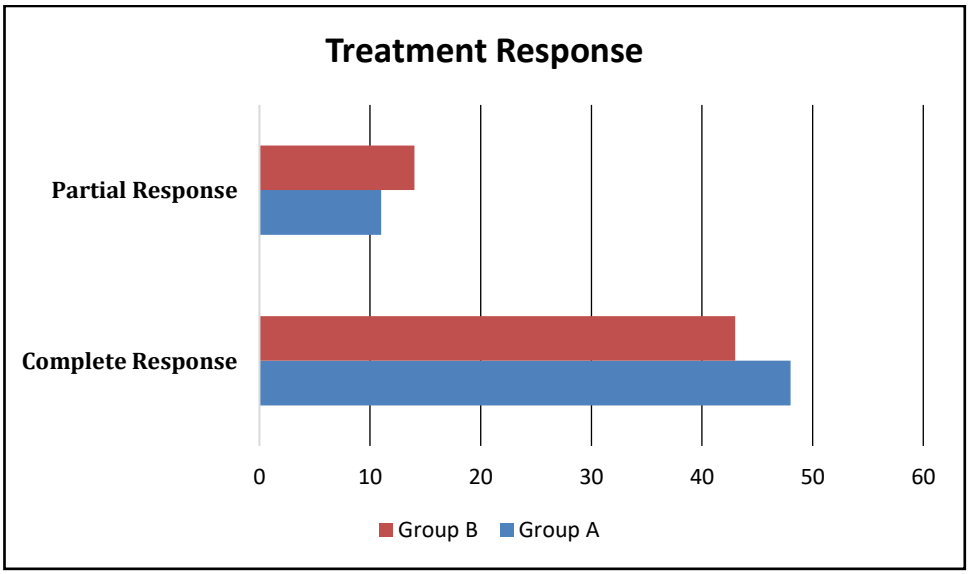

Figure 5: Response to treatment at first follow up

Small Intestine/Large Intestine: In Group A, n=6 patients (10.2%) out of n=59, and in Group B, n=8 patients (14.1%) out of n=57 developed late small or large intestine toxicity. No patient in either group had Grade 3 or 4 toxicity. The p-value, when compared in both groups, was 0.7962, statistically insignificant.
Kidney Toxicity: n= 2 patients each in Group A and Group B developed Grade 1 toxicity. N=57 patients 96.6% in group A & n=55 patients 92.9% in group B had no toxicity. No patient had grade 2,3,4 toxicities.
Bladder: In Group A, n=12 patients (20.3%) out of n=59 and in Group B, n=14 patients (24.6%) out of n=57 developed late bladder toxicity. No patient in either group had Grade 3 or 4 toxicity. The p-value, when compared in both groups, was 0.8499, statistically insignificant.
Response At Median Follow-Up: Loco regional Control was seen in 53 patients (89.8%) in Group A and 50 patients (87.6%) in Group B. 1 patient was lost to follow up in Group B. 2 patients (3.4%) in Group A and 3 patients (5.3%) in Group B developed distant metastasis. Loco regional failure was seen in 4 patients (6.8%) and 3 patients (5.3%) in Group A and B respectively.

Discussion

A total of N=120 patients who satisfied the eligibility criteria were enrolled in the study. The patients were randomized with n=60 patients in the IMRT arm as Group A and 60 patients in the Conventional RT arm as Group B. Patients in both the groups planned for concomitant chemoradiation with an RT dose of 50 Gy in 25 fractions at a dose of 2 Gy per fraction and cisplatin @ 40 mg/m^2. This was followed by Brachytherapy. This is following data from cancer registries in developing countries which suggest that about 80 to 90 percent of confirmed cervical cancers cases occur among women aged 35 years or older because cervical cancer progresses slowly from a precancerous condition to advanced cancer, and the incidence of cancer is very low in women under the age of 25. Incidence increases at about ages 35 to 40 and reaches a maximum in women in their 50s and 60. [18] In the current study, we found most common cancer type was moderately differentiated squamous cell carcinoma, seen in a total of 66 patients (55%) out of a total of n=120. It was followed by well-differentiated squamous cell carcinoma seen in 40 patients (33.3%). Poorly differentiated squamous cell carcinoma was the least common subtype seen in 14 patients (11.7%). All the patients in both groups received concurrent chemoradiation. This complies with the NCI alert in 1999. The alert was issued following the five landmark trials: Keys et al., [19] Morris et al., [20] Rose et al., [21] Whitney et al., [22] Peters et al., [23]. All patients received chemotherapy in the form of Inj. Cisplatin at a dose of 40 mg/m before EBRT every week.

Rose PG et al., [24] reported the results of the GOG-120 trial in which a course of standard pelvic radiotherapy was combined with one of the three concurrent chemotherapy regimens – (i) cisplatin alone (40 mg / m^2 weekly), (ii) cisplatin (50 mg/m^2 on days 1 and 29) plus 5-FU (4 g /m^2 as 96 hours infusion on days 1 and 29) plus hydroxyurea (2 g/m^2 orally twice weekly), or (iii) hydroxyurea alone (3 g/m^2 orally twice weekly) in patients with FIGO II B to IVA cervical carcinoma. At a median follow-up of 35 months, survival curves for the two cisplatin groups were almost identical and both were statistically superior to the survival curve of the hydroxyurea alone group. However, toxicities were much more in the combined drug arms than in the cisplatin alone arm.

In 1999 Keys et al., [19] reported the results of the GOG-123 study in which 369 patients with bulky stage IB disease and without any evidence of paraaortic lymph node metastasis were randomized between weekly cisplatin (40 mg/m^2) and radiation versus radiation only. Patients

underwent hysterectomy 3 - 6 weeks after completion of radiation. At a median follow-up of 36 months, local recurrence and distal metastasis rates were 9% and 21% and 12% and 16% respectively, both in favor of the concomitant arm. At a median follow-up of 36 months, local recurrence and distal metastasis rates were 9% and 21% and 12% and 16% respectively, both in favor of the concomitant arm. These trials proved that single agent Cisplatin is as efficacious as a triple-drug combination therapy with reduced toxicity.

There have been controversies about the optimum timing of Cisplatin administration concerning radiation treatment. Pre-clinical data suggests enhanced tumor response by a factor of 1.7 when Cisplatin was administered at least thirty minutes before radiation treatment. Pearcey et al., [25] have extrapolated that in terms of tumor cell kill, Cisplatin appropriately synchronized with radiation would be equivalent to a ten percent increase in radiation dose, which would theoretically improve local control.

Cisplatin is one of the most active cytotoxic agents in squamous cell carcinoma of the uterine cervix. When cisplatin and irradiation are used concomitantly, substantial enhancement of cell killing is observed. Green et al., [26] did a Cochrane review including twenty-four trials (21 published, 3 unpublished) and 4921 patients. The review strongly suggested that chemoradiation improves overall survival and progression-free survival, with absolute benefits of 10% and 13% respectively. There was some evidence that the effect was greater in trials including a high proportion of stage I and II patients. Chemoradiation also showed significant benefit for local recurrence and a suggestion of a benefit for distant recurrence. Acute hematological and gastrointestinal toxicity was significantly greater in the concomitant chemoradiation group. Late effects of treatment were not well reported and so the impact of chemoradiation on these effects could not be determined adequately.

In our study, n=49 patients out of 120 (40.8%) received four cycles of cisplatin instead of the planned five cycles. The 5^{th} cycle was omitted either due to toxicity or financial reason. About three-fourths of patients in both groups completed treatment (EBRT and ICRT) in eight weeks ($\leq$ 56 days). In groups A and B, the numbers were 43 (72.9%) and n=42 (73.7%) respectively. The patients who completed EBRT without any treatment gaps were 29 (48.3%) in Group A and n=27 (45%) in Group B. The delay in EBRT was made up by only a small delay, 3-5 days, in ICRT for most of the patients (91.5% and 98.2% in Groups A and B respectively). The gap between EBRT & ICRT was seven days or less in all the patients who completed the treatment. This was achieved by reserving the tentative dates for ICRT at the initiation of EBRT. The treatment delay was seen in a total of 16 patients in Group A and 15 patients in Group B. It was caused due to toxicity in 5 patients (31.3%) and 3 patients (20%) in Group A and B respectively. The rest of the delays were either due to personal or technical reasons or it was due to a holiday. ICRT was given at a dose of 7 Gy per fraction for 3 fractions, once every week, specified at point A, dose varying depending upon the bladder and rectum doses. The American Brachytherapy Society recommendation for HDR brachytherapy is a schedule of 5-6 Gy for five fractions, specified at point A. [27] In comparison to developed countries, developing countries have a higher incidence of cervical cancer. So, using more fractions for treatment increases the burden on the health care system. It increases the duration of treatment and adversely affects the local control of the tumor while adding to cost.

The most common toxicity seen was nausea and vomiting seen in about 90%patients in both groups. In Group A and B, grade 1, 2, 3 nausea was 28.8%,57.6%, 5.1% and 24.6%, 61.4% and 3.5% respectively. There were no significant differences between both the groups but

overall, the number of patients having acute upper gastrointestinal toxicity in the form of nausea and vomiting was very high. Also, grade 2 toxicity was seen from the first week of treatment in some patients in both groups. Concurrent chemotherapy in the form of cisplatin may have been responsible for the same. Though all the patients were counseled about chemotherapy, the anti-emetic medication compliance was not good. Few patients were not taking anti-emetics properly. Either they missed their dose or took only half of what was prescribed. This led to a decrease in oral intake which decreased the overall performance status of the patient. Three patients in Group A and two patients in Group B were hospitalized for supportive care.

The second most common toxicity was hematological toxicity in the form of anemia, 84.7% in Group A and 79% in Group B. There were no statistically significant differences between both the groups as bone marrow was not contoured as an Organ at Risk (OAR) during treatment planning. One patient in Group A and two patients in Group B developed grade 3 anemia for which a treatment break was given. Grade 2 toxicity was seen in 61% of patients in Group A and 52.7% of patients in Group B. The anemia was corrected using nutritional supplements and blood transfusion when required.

When compared with the study done by Chen et al., [28] the grade 3 hematologic toxicity was less, 1.7% in our study vs. 23.9% in their study. It may be because, as per institutional protocol, patients were advised of blood transfusion when the hemoglobin decreased to 9.0 g/dl. Acute leukocyte toxicity was seen in 54.2% and 59.6% of the patients in Group A and B respectively. Out of these most of the patients had Grade 1 toxicity, 78.1% in Group A and 79.4% in Group B. The leukocyte toxicity was corrected using growth factors when required. No patient had Grade 2 or more platelet toxicity. Only one patient in each group had Grade 1 platelet toxicity. Chen et al., [28] bone marrow sparing IMRT was compared with conventional box RT. They found that in the IMRT arm, Grade 0, 1, 2, and 3 or more acute hematological toxicities were seen in 14, 8, 9, and 2 patients respectively. The above comparison shows the advantage of contouring bone marrow as an OAR. It resulted in lesser hematologic toxicity. In another study done by Beriwal et al., [29] n=36 patients were treated with Extended Field IMRT. Out of these, 1 patient had Grade 3 GI toxicity. N=22 patients out of n=36 (61%) had grade 2 toxicity while n=4(11.1%) had grade 1 toxicity. It was observed that IMRT has less acute gastrointestinal toxicity than Conventional RT. Though IMRT showed a slightly better response than Conventional RT, it may be due to a short follow-up. The late toxicities could not be compared very well due to the short duration of follow-up, less than 12 months for many patients. Randomized control trials with larger sample sizes and longer follow-up periods are required to have a better comparison between the two modalities of treatment.

Conclusion

Concurrent chemoradiation using IMRT is routinely practiced, in addition to conventional treatment, at our institute. We randomized the patients into two groups to compare the toxicities and assess the response to the two modalities. All patients in both groups received concurrent chemotherapy. From our study, we conclude that toxicity between the two modalities was comparable with the advantage of IMRT in reducing acute lower gastrointestinal toxicity. The loco-regional control was comparative in both groups. However, the limitation of this study was the short duration of follow-up. As a result, the late toxicity could be assessed only for a short period. So, there is a need for long-term follow-up.

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