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Original Article

A Prospective Randomized Comparison of Concurrent Chemoradiation with Neoadjuvant and Adjuvant Chemotherapy with Concurrent Chemoradiation Alone for Locally Advanced Carcinoma Cervix

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Abstract

Aims: The aim of this study was to compare concurrent chemoradiation along with neoadjuvant and adjuvant chemotherapy versus concurrent chemoradiation alone in locally advanced cervical cancer regarding treatment response and toxicities. **Subjects and Methods:** A randomized control study was done on 116 patients with locally advanced carcinoma cervix (Stage IIB to IIIB) registered between January 2014 and February 2015. Patients were randomly divided to receive either one cycle of cisplatin/5-fluorouracil neoadjuvant chemotherapy and two cycles of the same adjuvant chemotherapy with concurrent chemoradiation with weekly cisplatin (Arm A) or only concurrent chemoradiation (Arm B). All patients received three fractions of high-dose-rate intracavitary brachytherapy after completion of the external radiation. **Results:** A higher proportion of the patients of chemotherapy arm achieved complete response (94%) as compared to the nonchemotherapy arm (56%), and this was statistically significant. There was a trend toward more treatment-related acute toxicity with chemotherapy. **Conclusions:** These results have corroborated the view that if neoadjuvant and adjuvant chemotherapies are added to concurrent chemoradiation, it could further the effects of concurrent chemoradiation for patients with locally advanced cancer of the uterine cervix.

Keywords: *Acute toxicity, adjuvant chemotherapy, complete response, concurrent chemoradiation, locally advanced cervical cancer, neoadjuvant chemotherapy*

Introduction

The present survival rates achieved with concurrent chemoradiation therapy (CCRT), the current standard treatment for locally advanced cervical cancer (LACC), are only 58%–66%.[1] Adding chemotherapy upfront in the form of neoadjuvant therapy along with CCRT may decrease the disease burden that has to be addressed by CCRT. Continuing with chemotherapy in the adjuvant setting could further augment the local radiation tumor kill by taking care of any disease residua systemically.

Since evidence regarding the benefit of additional chemotherapy along with CCRT for LACC is inconsistent, further Phase III studies are warranted. Here, we seek to explore the potential advantages of both neoadjuvant and adjuvant chemotherapies along with the standard of care CCRT in a prospective randomized controlled trial in patients of LACC with Stages IIB–IIIB.

Subjects and Methods

Patient selection

The patients with histologically proven squamous cell carcinoma cervix; International Federation of Gynecology and Obstetrics (FIGO) Stage IIB–IIIB; age <70 years; and normal hematological, renal, and liver parameters were included in the study after taking their informed consent. The patients having prior treatment, comorbid illnesses, another malignancy, distant metastasis, enlargement of para-aortic lymph node more than 1 cm on contrast-enhanced computed tomography (CT) scan, and vesicovaginal fistula or rectovaginal fistula were excluded from the study. The present study was approved by the Ethics Committee of the Institute.

Treatment

All patients were randomized into two arms, A and B, using computer-generated

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random numbers. Arm A comprised neoadjuvant chemotherapy followed by CCRT and adjuvant therapy and is the experimental arm whereas Arm B comprised CCRT and constituted the control arm.

Treatment approach in Arm A was one cycle of cisplatin (70 mg/m^2) and 5-fluorouracil (5-FU) (2 g/m^2)-based neoadjuvant chemotherapy, followed by external beam radiation therapy with concurrent cisplatin 40 mg/m^2/week, and high-dose-rate (HDR) intracavitary brachytherapy (ICRT) comprising three fractions with a dose of 7 Gy per fraction. All the fractions of brachytherapy had an interval of 1 week between them. This was followed by two cycles of 3-weekly cisplatin and 5-FU-based adjuvant chemotherapy with doses the same as given in neoadjuvant therapy. The treatment approach in Arm B was concurrent chemoradiation similar to that used in Arm A without any neoadjuvant or adjuvant chemotherapy.

During chemotherapy, intravenous normal saline was administered to ensure proper hydration. Antiemetics were used in the usual doses to ameliorate chemotherapy-induced nausea and vomiting.

All patients received external beam radiotherapy (EBRT) by Co^{60} as 46 Gy in 23 fractions, single fraction of 200 cGy daily, 5 days a week by four-field box technique to the whole pelvis. EBRT was followed by HDR-ICRT using Fletcher–Suit after loading applicators. Orthogonal films were taken to verify the placement of applicators and to perform the dosimetric plan. No other imaging was done during brachytherapy.

Evaluation of treatment

During the study, the patients were reviewed weekly along with weekly hemogram and kidney function test for acute reactions such as hematological, gastrointestinal, genitourinary, and skin reactions. Toxicity was graded according to the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria. All patients, who developed Grade III–IV reactions, were given supportive intravenous fluid in the form of 5%–10% dextrose, normal saline with multivitamin infusions, and hematinic drip along with protein supplementation if required.

On completion of treatment, the patients were assessed every month for a period of 3 months. After that they were planned for follow-up once every 3 months for a duration of 2 years, and once every 6 months thereafter. The patients were assessed for symptomatic and clinical improvements, and symptom-guided investigations and ultrasound or CT scans were done as and when required. Positron-emission tomography scans were not employed in this study. Regular follow-up was done to assess the disease status, and it was classified into disease free, residual disease, metastasis, and recurrence.

The response was assessed after 4 weeks on completion of radiotherapy according to WHO criteria.

Statistical analyses

All the statistical analyses were done in SPSS software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). $P < 0.05$ was considered statistically significant. Values were represented in mean ± standard deviation and *n* (%).

Results

Patients and treatment

Between January 2014 and February 2015, of 116 patients enrolled in the study, 54 patients were randomized to Arm A and 62 patients to Arm B. The mean age was 50 years (range, 35–68 years) in Arm A and 49 years (range, 30–68 years) in Arm B. In Arm A, 72% and 26% of patients had Karnofsky Performance Score (KPS) of 70 and 80, respectively, whereas in Arm B, it was 53% and 32%, respectively. A majority of patients in Arm A (61%) had FIGO Stage IIB disease, and 35% had Stage IIIB. In Arm B, 53% of patients had Stage IIIB, and 47% patients had Stage IIB.

As four patients from Arm A and six patients from Arm B did not complete EBRT, they were not given ICRT. Although a higher proportion of ICRT defaulters were found in Arm B (21%) as compared to Arm A (12%), the difference between the two groups was not statistically significant ($P = 0.254$). The mean overall treatment

Table 1: Patient demographics and other treatment parameters

	Arm A (54), *n* (%)	Arm B (62), *n* (%)
FIGO stage		
IIB	33 (61.1)	29 (46.8)
IIIA	2 (3.7)	0 (0)
IIIB	19 (35.2)	33 (53.2)
Histopathological differentiation		
MD	21 (38.9)	37 (59.7)
PD	3 (5.6)	8 (12.9)
WD	30 (55.5)	17 (27.4)
Mean duration of follow-up (months)	9.907	7.226
Mean OTT (days)	67.94	67
Mean age (years)	50	49
Performance status (KPS)		
70	39 (72.2)	33 (53.2)
80	14 (25.9)	20 (32.3)
90	11 (1.9)	9 (14.5)

KPS – Karnofsky Performance Score; OTT – Overall treatment time; FIGO – International Federation of Gynecology and Obstetrics; MD – Moderately differentiated; PD – Poorly differentiated; WD – Well differentiated

time (OTT) of Arm A patients (67.94 days) was no different than the mean OTT (67 days) of Arm B patients (P = 0.738). The mean duration of follow-up of Arm A patients was 9 months, and it was 7 months for the patients in Arm B [Table 1].

Toxicity

In general, chemotherapy with CCRT was well tolerated. The acute systemic toxicities in both arms are detailed in Table 2, scored according to the RTOG Acute Radiation Morbidity Scoring Criteria. None of the patients died during treatment or within 1 month thereof. The most common Grade 2 or higher toxicity was gastrointestinal (30% in Arm A and 7% in Arm B, P = 0.052). The most common hematological toxicity of Grade 2 or higher was anemia seen in 6% in Arm A and 5% in Arm B (P = 0.321). There was no incidence of nephrotoxicity or neuropathy of Grade 2 or higher.

Owing to the short duration of follow-up available in this study, late toxicities could not be assessed.

Response and failure

At 6 months of follow-up, 33 patients (94%) had a complete response (CR), and two (6%) had a partial response (PR) in the experimental arm (A). In the control arm (B), 27 patients (56%) achieved CR and 21 (44%) got PR (P = 0.01) [Table 3].

Arm A had two (10%) patients with a local residual disease with no distant metastases. Two patients with residual disease expired 4 months after the last cycle of chemotherapy, and 17 patients were lost to follow-up. In Arm B, 21 (57%) patients had a PR. One patient developed bone metastasis and one suffered liver metastasis along with the residual disease. Two patients expired 3 months after ICRT, and 12 patients were lost to follow-up. There was a statistical difference between the two arms regarding failure (P = 0.004) [Table 4]. There were no recurrences seen in the limited follow-up duration in both arms.

Discussion

We performed a prospective study to compare neoadjuvant and adjuvant chemotherapies with concurrent chemoradiation versus concurrent chemoradiation alone in the treatment of locally advanced carcinoma cervix regarding the treatment response and toxicities. After taking into consideration the inclusion and exclusion criteria, 116 patients were taken into the study. The patients were randomized into two arms, study (n = 54, Arm A) and control (n = 62, Arm B). Of 116 patients, 83 received full treatment as planned.

Age of the patients in our study ranged from 30 to 68 years with a mean age of presentation being 50 years in Arm A and 49 years in Arm B. Majority of the patients in both arms was between 40 and 49 years. In this study, there was no impact of the age on outcome between the groups, as in the studies by Wong *et al.* and Vrdoljak *et al.*[2,3] Statistically, no significant difference was observed in the distribution of patients between the two arms according to KPS scores (P = 0.05). Thus, there was no impact of KPS on outcome between the two groups in our study. Choi *et al.* reported that the performance status of a majority of the patients is relatively poor in developing countries including India.[4]

We included only histologically proven squamous cell carcinoma cases in our study, as the most common histology variant in cervical cancer is squamous cell carcinoma (about 90%). Regarding tumor differentiation, the most common type observed was well differentiated in Arm A (56%) and moderately differentiated in Arm B (60%). In this study, there was no impact of tumor differentiation on outcome in both arms. Choi *et al.*, Wong *et al.*, and Vrdoljak *et al.* have shown no significant correlation between survival and tumor behavior with the degree of differentiation of squamous cell carcinoma or adenocarcinoma of the cervix. Although Reagan and Fu revealed the prognostic value of histologic differentiation in patients treated with irradiation, Crissman *et al.* failed to observe a correlation between histologic parameters and patient survival.[5,6]

A higher number of patients (21 of 48) had PR in Arm B as compared to Arm A of this study, perhaps explained by the greater number having Stage IIIB (53%); however, there was no significant difference between the distribution of patients among various stages between the two arms (P = 0.064). This is in agreement with Choi *et al.* Most of the studies show a decrease in pelvic control rate and survival rate with increase in the stage.[7,8] The patterns of care study stated a 5-year survival rate of 74% for Stage I, 56% for Stage II, and 33% for Stage III patients

Table 2: Comparison of patients in the two arms according to the grade of adverse reaction during treatment

RTOG grade	Arm A (n=54), n (%)				Arm B (n=62), n (%)			
	1	2	3	4	1	2	3	4
Hematological	2 (3.7)	2 (3.7)	1 (1.9)	0 (0)	2 (3.2)	0 (0)	3 (4.8)	0 (0)
GIT	20 (37)	8 (14.8)	5 (9.3)	3 (5.6)	28 (45.2)	2 (3.2)	1 (1.6)	1 (1.6)
GU	5 (9.3)	0 (0)	0 (0)	3 (5.6)	13 (21)	2 (3.2)	0 (0)	1 (1.6)
Skin	0 (0)	0 (0)	0 (0)	0 (0)	2 (3.2)	2 (3.2)	0 (0)	0 (0)

RTOG –Radiation Therapy Oncology Group; GIT – Gastrointestinal, GU – Genitourinary

Table 3: Treatment response at 6 months

	Arm A (*n*=54), *n* (%)	Arm B (*n*=62), *n* (%)
CR	33 (94.28)	27 (56.25)
PR	2 (3.7)	21 (33.9)
PD	0 (0)	0 (0)
Default	19 (35.2)	14 (22.6)

CR – Complete response; PR – Partial response; PD – Progressive disease

Table 4: Pattern of failure

	Arm A (*n*=54), *n* (%)	Arm B (*n*=62), *n* (%)
Residual (local)	2 (9.52)	21 (56.76)
Residual + bone mets (local + systemic)	0 (0.00)	1 (2.70)
Residual + liver mets (local + systemic)	0 (0.00)	1 (2.70)
Res dis, expired	2 (9.52)	2 (5.41)

of cervical cancer after radiotherapy.[9] Another report of 1988 found 89% of patient survival in Stage IB, 85% in IIA, 76% in IIB, 62% in IIIA, 50% in IIIB, and 20% in Stage IV.[10]

In the course of treatment in our study, 19 patients defaulted in Arm A. During EBRT, three patients defaulted due to adverse reactions, and two patients defaulted in the initial 10 days due to reasons not known. Two patients left the treatment in between EBRT and ICRT, and three patients absconded after two fractions of ICRT. Nine patients defaulted after the first cycle of adjuvant chemotherapy due to adverse gastrointestinal reactions. In Arm B, 14 patients defaulted. During EBRT, five patients defaulted due to adverse reactions and three patients defaulted in the initial 12 days due to personal reasons. Three patients left treatment in between EBRT and ICRT, and three patients defaulted after taking one fraction ICRT for reasons not known. The number of defaulters in Arm A was more as compared to Arm B, possibly owing to the increased duration of assigned treatment.

Comparison of disease status after completion of EBRT in this study revealed no residual disease in 82% of patients in Arm A as compared to 48% in Arm B. It was statistically significant (P = 0.01). The actual difference in treatment response was evident after completion of treatment. After completion of radiotherapy, response assessment was done 1 month later; and then, the patients were assessed monthly for 3 months followed by 3-monthly assessments. In the chemotherapy arm, adjuvant chemotherapy was started 3 weeks after ICRT completion, and response checked a month after the last chemotherapy cycle. The patients with no response or progressive disease on regular follow-up were subjected to salvage chemotherapy as found appropriate by the treating radiation oncologists. The response assessment could be done for 35 patients of Arm A and 48 patients of Arm B. The majority of the patients in Arm A (n = 33, 94%) achieved CR, PR in two patients (6%), with no patient having no response or progressive disease at 6 months after completion of treatment. In Arm B, 27 patients (56%) achieved CR, PR in 21 patients (44%), with no patient having no response or progressive disease. The CR was higher in study arm (Arm A) as compared to control arm (Arm B), and the difference was statistically significant (P = 0.01).

Wong *et al.* compared the treatment effects of epirubicin-based CCRT plus adjuvant epirubicin for five cycles (110 patients) versus radiotherapy alone (110 patients). Their results showed that CCRT and adjuvant chemotherapy produced better local control and higher survival. In Vrdoljak *et al.*, the CR rate for adjuvant chemotherapy group was 100%. The duration of treatment did not influence local control. The main reason why this study differs from others may be a small number of patients and very short follow-up period.

We analyzed treatment toxicities regarding hematological, gastrointestinal, genitourinary, and skin reactions. The most common adverse reaction was gastrointestinal and genitourinary in both arms. Frequencies of Grade 2 and Grade 3 gastrointestinal and genitourinary reactions were high in the study arm (Arm A). The frequency of hematological toxicity was equal in both groups. However, these were statistically not significant (P = 0.052). Most of the gastrointestinal reactions were vomiting and diarrhea. In Wong *et al.*, median follow-up for the whole group at the time of the analysis was 96 months. Leukopenia and thrombocytopenia were significantly more common in patients who received CCRT plus adjuvant chemotherapy, whereas the frequency of other toxicities had no difference in the two groups. There was no occurrence of Grade 3 or higher vomiting, diarrhea, proctitis, and/or hematuria in our study. In the study by Vrdoljak *et al.* on CCRT plus consolidation chemotherapy, two cases of rectovaginal fistula, one of the vesicovaginal fistulas, and two of ureteral obstruction were observed. The major shortcoming of the present study is lack of adequate follow-up to see the late toxicity and response.

The mean duration of follow-up for Arm A was 9 months whereas it was 7 months for Arm B. The longer follow-up duration of Arm A could not be attributed to any specific reason. The difference was statistically significant. In the study arm, no patient developed metastasis, but two patients expired. One died of lower respiratory tract infection; however, the second mortality's cause could not be ascertained. In the control arm, two patients developed metastasis and two expired. It was statistically significant. We need further longer follow-up period to assess the disease-free survival and overall survival. In Wong *et al.*, as the median follow-up duration was 96 months, the response was assessed regarding local control, 3-year actuarial

disease-free survival, and pattern of failure. The results of our study show that the local control and complication rates are comparable with those reported by Wong *et al.*, Vrdoljak *et al.*, and Choi *et al.*

Conclusion

In summary, if neoadjuvant and adjuvant chemotherapies are added to concurrent chemoradiation, it could further the effects of concurrent chemoradiation for patients with carcinoma of the uterine cervix. However, these findings are not conclusive due to the small sample size and the relatively short follow-up period. Further larger, multicentric, and randomized controlled trials with longer follow-up will be needed to prove the benefit of the addition of neoadjuvant and adjuvant chemotherapies to concurrent chemoradiation.

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Conflicts of interest

There are no conflicts of interest.

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