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Original Research Article

Toxicity outcome of concurrent teletherapy and brachytherapy compared with teletherapy followed by brachytherapy in locally advanced carcinoma cervix

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ABSTRACT

Background: Teletherapy and intracavitary brachytherapy are definitive treatment modalities for stages IIB to IVA cervical carcinoma. Globally, it is the second most common cancer among female. Majority of patients attend the hospital with locally advanced stage due to less screening facility and social stigma.
Methods: This quasi-experimental study was conducted from January 2019 to June 2020 with a total of 76 patients. The patients were equally divided into two groups: A and B after obtaining their informed written consent.
Results: Final follow up was given after completion of treatment at 24 weeks. Patients in both groups developed grade 1 gastrointestinal and genitourinary toxicities (10.5% versus 13.1%, 13.1% versus 15.7% in group A and B respectively). Two patients in group A and three patients in group B developed grade 2 gastrointestinal toxicities. In genitourinary toxicities, grade 2 toxicities were observed in two patients of group A and four patients of group B, ($p>0.05$). None developed grade 3 and 4 gastrointestinal and genitourinary toxicities. There were no statistically significant variations in treatment related toxicities between the two groups.
Conclusions: Both gastrointestinal, genitourinary toxicities were comparable between two groups. The toxicities were acceptable and well tolerated.

Keywords: Carcinoma cervix, Teletherapy, Brachytherapy, Cisplatin

INTRODUCTION

Cervical cancer is the most common gynecological malignancy and it is a major world health problem for women. It is the 8th most common cancer with an estimated 604127 (3.1%) cases and 341831 (3.4%) deaths in 2020 worldwide. In 2020, new cases of cervical cancer in Bangladesh were 8268 (5.3%) it ranked 5th (5.3%) among the whole cancer patients and the 2nd (12%) most common cancer among female.[1] Teletherapy and intracavitary brachytherapy has been identified as an optimal modality for the treatment of locally advanced carcinoma cervix.[2] The entire radiation treatment time should be as short as possible (within 8 weeks) and completed without any interruptions or delay. The prolongation of overall treatment time significantly affects treatment outcome in cervical cancer.[3] The timely integration of teletherapy and intracavitary brachytherapy is an important factor for improving local control of pelvic tumor in carcinoma of uterine cervix.[4] Any interruption between treatments increased the accelerated repopulation of tumor cells. It starts early in a fractionated radiotherapy and occurs preferentially at the 4th week of radiotherapy. To prevent this accelerated repopulation of tumor cells it is essential to give radiation within shortest possible overall time.[5] In addition, the optimal insertion of high dose rate intracavitary

brachytherapy, dose per insertion and adjustments of the total dose are also the important factors in lowering the frequency of complications without compromising the treatment results. The high dose rate intracavitary brachytherapy in a higher number of insertions with smaller doses per insertion is associated with higher radiobiological effects and reduced toxicity.[6] The aim of this study was to compare the toxicity outcome of concurrent teletherapy and brachytherapy with teletherapy followed by brachytherapy using two different fractionation schedules in locally advanced cervical carcinoma (stage IIB-IVA).

METHODS

This was a quasi-experimental study conducted in the department of clinical oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), radiation oncology department of National Institute of Cancer Research and Hospital (NICRH) and Ahsania Mission Cancer and General Hospital (AMCGH) from January 2019 to June 2020. A total of 76 patients were selected for the purpose of this study following the inclusion and exclusion criteria. The inclusion criteria were biopsy proven squamous cell carcinoma of cervix (FIGO stage IIB to IVA). Only patients who had given informed consent were admitted into the study. Those who did not consent to the study or were outside the FIGO staging of IIB-IVA were excluded from the study. The selected patients were equally divided in two groups, group A and group B. Ethical approval for this study was obtained from the respective institutional ethical review committees. Selected patients of each group were treated by teletherapy 50 Gray in 25 fractions, 2 Gray per fractions over 5 weeks along with injection cisplatin 40 mg/m^2 every week 1-2 hours before radiotherapy. Three-dimensional conformal radiotherapy technique was used in both groups during teletherapy and brachytherapy. In group A, 1st insertion of intracavitary brachytherapy started concurrently from 4th week of teletherapy treatment. Second, 3rd and 4th insertions were given on 5th, 6th and 7th week respectively. Each brachytherapy insertion composed of 6 Gray (high dose rate) and the total duration of the treatment was within 7 weeks. In group B, 1st insertion of intracavitary brachytherapy started after completion of teletherapy on 6th week. 2nd and 3rd insertions were given on 7th and 8th weeks consequently. Brachytherapy completed on day 55 counting from the 1st day of treatment. In this group of patients, each brachytherapy insertion composed of 7 Gray (high dose rate) and the total duration of the treatment time was 8 weeks. Patients were assessed for acute gastrointestinal and genitourinary toxicities weekly during teletherapy and intracavitary brachytherapy period. Late toxicities were assessed at 6 months after completion of treatment. Toxicities were assessed as per toxicity criteria of the Radiation Therapy Oncology Group (RTOG).[7] All the relevant data were compiled on a master chart and then statistical analysis was done by using the SPSS (Statistical Package for Social Science) software program for Windows, version 24.0. Differences between two means were assessed by t test. The toxicity outcomes were compared by Chi square test. A $p<0.05$ in two tailed test was considered as statistically significant.

RESULTS

From July 2019 to June 2020, a total number of 76 patients with locally advanced squamous cell carcinoma of uterine cervix (FIGO stage IIB to IVA) were included in this study. Among the 76 patients, 38 were taken in each group. The patients of group A were treated with concurrent teletherapy and brachytherapy and group B were treated by teletherapy followed by brachytherapy. The mean age of patients in group A was 49.47±7.0 years and for group B it was 48.55±7.5 years. Most of the patients were in stage IIB in both groups (65.6% and 60.6% for the group A and group B respectively). One patient of group A and two patients of group B had stage IVA disease. Histologic differentiation of tumour observed in this study has been shown in Table 1. Most of the patients in both groups had moderately differentiated tumour (76.3% and 65.7% patients of group A and B respectively. Regarding toxicity profile, during follow up four patients in group A and seven patients in group B developed acute grade 2 lower gastrointestinal toxicities. In terms of genitourinary toxicity, there were five patients in group A and six patients in group B those who developed acute grade 2 toxicities. No statistically significant differences were observed between two groups regarding gastrointestinal (0.533) and genitourinary (0.855) toxicities (Table 2). Regarding late toxicity, two patients in group A and three patients in group B were developed grade 2 lower gastrointestinal toxicities. There were two and four patients in group A and group B, respectively, who developed late grade 2 genitourinary toxicities (Table 3).

Table 1: Patient characteristics.

Characteristics	Group A (n=38)	Group B (n=38)
	N (%)	N (%)
Age (mean ± SD)	49.47±7.0	48.55±7.5
Clinical stage (%)		
IIB	25 (65.7)	23 (60.6)
IIIA	3 (7.8)	3 (7.8)
IIIB	9 (23.6)	10 (26.3)
IVA	1 (3)	2 (5.2)

Continued.

Characteristics	Group A (n=38)	Group B (n=38)
Histological differentiation (%)		
Well differentiated	6 (15.7)	8 (21)
Moderately differentiated	29 (76.3)	25 (65.7)
Poorly differentiated	3 (7.8)	5 (13.1)

Table 2: Acute gastrointestinal and genitourinary toxicities.

Acute toxicity	Group A (n=38)	Group B (n=38)	Chi square test	P value
	N (%)	N (%)		
Lower gastrointestinal toxicities				
No toxicity	12 (31.5)	13 (34.2)	1.258	0.533
Grade 1	22 (57.8)	18 (47.3)		
Grade 2	4 (10.5)	7 (18.4)		
Genitourinary toxicities				
No toxicity	11 (28.9)	9 (23.6)	0.313	0.855
Grade 1	22 (57.8)	23 (60.5)		
Grade 2	5 (13.1)	6 (15.7)		

Table 3: Late gastrointestinal and genitourinary toxicities.

Late toxicity	Group A (n=38)	Group B (n=38)	Chi square test	P value
	N (%)	N (%)		
Lower gastrointestinal toxicities				
No toxicity	32 (84.2)	30 (90.9)	0.376	0.829
Grade 1	4 (10.5)	5 (13.1.)		
Grade 2	2 (5.2)	3 (7.89)		
Genitourinary toxicities				
No toxicity	31 (81.5)	28 (73.6)	0.910	0.634
Grade 1	5 (13.1)	6 (15.7)		
Grade 2	2 (5.2)	4 (10.5)		

DISCUSSION

Concurrent chemoradiation followed by intracavitary brachytherapy is an important modality of treatment for the patients of locally advanced cervical carcinoma (Stage IIB to IVA). The aim of this study was to compare toxicities between concurrent teletherapy and brachytherapy (4 insertions, 6 Gray each) with teletherapy followed by brachytherapy (3 insertions, 7 Gray each) in locally advanced carcinoma cervix. This study was conducted from July 2019 to June 2020. After meeting the inclusion and exclusion criteria, a total number of 76 patients were allocated in this study and were divided into two groups, A and B respectively. The mean age of patients at diagnosis was 49.47 (±7.0) years in group A and in group B 48.55 (±7.5) years. The mean age of the participants from both groups were similar to the findings of multiple other studies.[8,9] In this study, patients were distributed according to the FIGO stage. Out of 76 patients, most of the patients had stage IIB disease, 25 (65.6%) and 23 (60.6%) patients were in group A and B respectively. This was similar to the findings of another study, where majority of patients were from FIGO stage IIB.[10] However, globally majority of cancer cases present at more advanced stages, ranging from stage III to stage IV of FIGO staging.[11-13] The patients of both the groups completed their treatment as per protocol without any treatment delay or any interruption. The patients in group A tolerated the integration of brachytherapy with teletherapy well. There was no interruption of treatment due to toxicity. All the observed toxicities were managed accordingly. The most prevalent toxicities in both the groups were lower gastrointestinal and genitourinary toxicities. During follow up, grade 2 acute lower gastrointestinal toxicities were observed in group A 10.5% and 18.4% in group B respectively. Grade 2 genitourinary toxicities were seen in 13.1% and 15.7% patients of group A and B respectively. No patients developed acute grade 3 and 4 lower gastrointestinal and genitourinary toxicities. After the completion of treatment, patients were appointed to visit in a follow-up program. There was no treatment related deaths and no patients were lost to follow up in this study. During follow up at 6 months after completion of treatment, 2 patients in group A and 3 patients in group B developed late grade 2 lower gastrointestinal toxicities. Regarding genitourinary toxicity, there were two patients in group A and 4 patients in group B who developed grade 2 genitourinary toxicities. Statistically, there were no statically significant difference between the two

treatment groups which was consistent with the findings of study conducted by Tharavichitkul et al 2012.[14] All the acute grade 1 toxicities were well tolerated by the patient and grade 2 toxicities were managed accordingly.

Limitations

The study was conducted with a very small sample size, the results may not represent the whole demography. As this was a quasi-experimental study, further research with larger sample size and duration of follow up was necessary.

CONCLUSION

In conclusion, treatment related acute and late lower gastrointestinal as well as genitourinary toxicities were acceptable. The value was statistically insignificant between two groups. Additionally, total treatment duration was less in group A than the group B. In Bangladesh, with high disease burden of carcinoma cervix and inadequate number of radiotherapy centers, concurrent teletherapy and brachytherapy is beneficial for the patients in terms of better toxicity outcome and reduction of the patients load in our radiotherapy centers.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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