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Original Research Article

Comparative Study on Symptomatic Response and Toxicity of Concurrent Chemo-Radiotherapy and Radiotherapy Alone in the Treatment of Cervical Cancer

Dr. Barun Kumar Das[1*], Dr. Supriti Rani Ghosh[2], Dr. Arif Hosen[3], Dr. Muhammad Adnan Arifeen[4], Dr. Tasnim Mahmud[5]

[1]MBBS, M Phil (Radiotherapy) Department of Oncology, Khwaja Yunus Ali Medical College and Hospital, Sirajganj, Bangladesh
[2]MBBS, DGO, FCPS - Gynecology and Obs, BIHS General Hospital, Dhaka, Bangladesh
[3]MBBS, MD (Oncology) Rajshahi Medical College and Hospital, Rajshahi, Bangladesh
[4]MBBS, MD (Oncology) Khwaja Yunus Ali Medical College and Hospital, Sirajganj, Bangladesh
[5]MBBS, MPH, Department of Epidemiology, North South University, Dhaka

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Abstract: This prospective observational study was carried out to compare the symptomatic response and acceptable toxicity in concurrent chemo-radiotherapy and radiotherapy alone in the treatment of cervical cancer. A total of 60 patients (30 patients in arm A & 30 patients in arm B) who have biopsy proven cervical carcinoma with no history of previous treatment were selected from the Department of radiotherapy Rajshahi Medical College Hospital, Rajshahi & in the department of Radiation & Oncology, National Institute of Cancer Research & Hospital. All patients in both arms received external beam radiation with 50Gy in 25 daily fractions over five weeks. Followed by three insertions (one insertion per week) of Intracavitary brachytherapy each 700 cGy. Patients in arm-A received Inj. Cisplatin 40mg/m^2 in IV infusion on the first day of each treatment per week in addition to radiotherapy. In this study it was observed that a significant symptomatic improvement was found in arm-A after treatment than arm-B and no severe unwanted reaction was noted in most of the patients. Systematic toxicity developed in both groups and comparatively more in arm-A (chemo radiation) but that was not statistically significant and well managed with conservative treatment. Regarding performance status patients treated with concurrent chemo radiation showed better performance status than the patient treated with radiotherapy alone. In this study it was observed that patients of carcinoma cervix treated with concurrent chemo radiotherapy was effective for symptomatic improvement and feasible with acceptable toxicity for advanced cancer of the uterine cervix than those with radiation alone.

Keywords: Chemotherapy, cervical cancer, radiotherapy, systemic response, toxicity.

INTRODUCTION

Cervical cancer is both the fourth-most common cause of cancer and deaths from cancer in women worldwide. In 2012, 528,000 cases of cervical cancer were estimated to have occurred, with 266,000 deaths [1]. It is the second-most common cause of female-specific cancer after breast cancer, accounting for around 8% of both total cancer cases and total cancer deaths in women. About 80% of cervical cancers occur in developing countries [2].

In developing and undeveloped countries, a much more severe prevalence of this malignancy is associated with a generally worse economical and sanitary condition, lack of effective screening, as well as under implemented prevention strategy, where a lot of women were exposed to the risk of, or already affected by, high-risk CC, which remains a major health problem for women in these countries, though important advancement and progress has been witnessed in the last few years [3]. Most women present with locally advanced stage in developing countries compared with developed countries where most people present with early-stage cancer [4].

Carcinoma of cervix is most common in Bangladeshi women comprising of about 25% of all female cancer. A total number of 3251 patients from July 2012 to June 2013 were treated at the department of Radiotherapy, Rajshahi Medical College Hospital,

***Corresponding Author:** Dr. Barun Kumar Das
M.Phil (Radiotherapy) Department of Radiotherapy, Khwaja Yunus Ali Medical College and Hospital, Bangladesh

among them 145 patients that means 4.46% of the patients were suffered from carcinoma cervix [5].

In the HPV vaccination era, we expect that the cervical cancer incidence had reduced, especially in those developed countries where large-scale immunization has been introduced. Most developed countries have introduced HPV vaccines into routine vaccination programs and more than 60 million doses have already been distributed in 2010, which could guarantee a protection rate of ~70%. However, cervical cancer still represents a major public health problem even in developed countries [6].

The disease is extremely rare in virgins. The incidence is higher in married women than single women and increases with the number of pregnancies. There is a fivefold higher incidence among prostitutes. It is commoner in women of lower socioeconomic groups. This is thought to be due to the early age of first intercourse [7].

The cervix is easily accessible to examination and the epithelial shed from it can give reliable evidence of early cancer of precancerous changes. The test is universally known as the "Pap's Smear" test. Vaginal cytology can reveal cervical cancer in its preclinical stage when it is completely curable with 5 years survival rates of 97-100%. The Pap`s Smear provides a strong suspicion of malignance, which requires confirmation by cervical biopsy. More than 97% of uterine cervix tumours are squamous cell carcinoma. Approximately 7% to 10% are classified as adenocarcinoma and 1% to 2% is clear cell mesonephric type [8]. VIA test is very cost effective and is usually done in every Medical College Hospital in Bangladesh by which cervical cancer may be diagnosed easily and early. VIA or Visual Inspection with Ace-tic acid sounds like a scary way to test for cervical cancer, but in reality, it is quite simple [9].

In CC patients without distant metastasis, several factors have been demonstrated as directly associated with a worse prognosis, including locally advanced disease, bulky tumor, deeply invasive disease, and pelvic lymph node or parametrial involvement. Patients with the aforementioned characteristics are at higher risk of recurrence and generally have a shorter survival period.4–8 Primarily applied conventional treatment modality for high-risk CC is radiotherapy (RT) with or without hysterectomy; however, inefficient local control and lymph node metastasis remain the major causes of treatment failure [10]. Therefore, treatment strategy combining RT with chemotherapy has been evaluated in a lot of clinical trials, initially in several pilot studies published ~15 years ago, most of which were randomized controlled trials (RCTs) [11].

In these trials, concurrent chemoradiotherapy (CCRT) was the experimental treatment mode most widely assessed. Chemotherapy, at first, was applied exclusively as palliative care for patients with unfavorable prognosis. Among the drugs used for chemotherapy in advanced CC, cisplatin was one of the most effective agents [12]. Thus, cisplatin was primarily selected as one of the drugs tested in trials investigating CCRT. Among early researches comparing cisplatin-based concurrent chemoradiotherapy (DDP-CCRT) with RT, results with apparent discrepancies were reported. Four studies reported positive results, with a maximum risk reduction of 49% for estimated 4-year overall survival (OS), which supported the superiority of DDP-CCRT [7,11].

However, no significant benefits in favor of DDP-CCRT concerning survival outcomes and toxicity profile were revealed in two other studies [12]. These differences might be attributed to different study designs, subjects enrolled, control settings, regimens used, and duration of follow-up.

Although more than 2 decades have passed since the initial application of DDP-CCRT in treating high-risk CC patients, during which time new agents and modalities have been developed, tested, and utilized, DDP remains in the first-line drug list for this specific population. Most recently, an RCT conducted in Brazil again evaluated the difference in treatment effects between DDP-CCRT and exclusive RT in advanced CC, using patients with International Federation of Gynecology and Obstetrics (FIGO) Stage III disease as the targeted population (Zuliani AC *et al.*, 2014). With accumulated and updated data from relevant studies available for a new pooled analysis, we performed this study with refined design and analytical methods to provide more definitive evidence for clinical guidance.

METHODS

This Cross-sectional comparative study had conducted from January 2015 to June 2015 in the department of radiotherapy, Rajshahi Medical College Hospital & in the department of Radiation & Oncology, National Institute of Cancer Research & Hospital. A total of 60 patients with histologically proved cervical carcinoma had selected randomly according to pre-defined inclusion and exclusion criteria and divided into two arms. Every alternate patient had enrolled for each arm. 30patients had treated with concurrent chemo-radiation by Cisplatin 40 mg/m2 weekly for 5 weeks on day 1,8,15,22 & 29 with a radiation dose- 50Gy in 25 fractions, 2 Gy per day/ fraction, 5 days in a week for 5weeks by Telecobalt machine (Co-60) & Linac & ICRT 21Gy in 3weekly insertion.

30patients had treated by radiotherapy alone with a radiation dose- 50 Gy in 25 fractions, 2 Gy per day/ fraction, 5 days in a week for 5 weeks by Telecobalt machine (Co-60) & Linac & ICRT 21Gy in 3 weekly insertions. All patients had received weekly till the completion of the treatment, all findings of the local and

systemic examination had recorded and to compare with previous findings and had documented.

Data analysis was done according to the objectives of the study by using statistical package for social science software program from version 23. Statistical significance had taken at p≤ 0. 05.

Inclusion Criteria:

1. Patients- Clinically diagnosed and histologically proved squamous cell cervical carcinoma.
2. FIGO stage- Stage IIb to stage IVa (Few cases of bulky Ib and IIa).
3. Age group- Less than 60 years.
4. Performance status-Karnofsky performance status score >60.

Exclusion Criteria:

1. Patients- With prior treatment.
2. FIGO stage- Preinvasive to some case of stage IIa and stage IVb.
3. Age group- More than 60 years.
4. Performance status-Karnofsky performance status score <60.

Figo staging: [13]

Stage I:
The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded) • IA Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm ○IA1 Measured stromal invasion <3 mm in depth ○IA2 Measured stromal invasion ≥3 mm and <5 mm in depth • IB Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri ○IB1 Invasive carcinoma ≥5 mm depth of stromal invasion and <2 cm in greatest dimension ○IB2 Invasive carcinoma ≥2 cm and <4 cm in greatest dimension ○IB3 Invasive carcinoma ≥4 cm in greatest dimension
Stage II:
The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall • IIA Involvement limited to the upper two-thirds of the vagina without parametrial involvement ○IIA1 Invasive carcinoma <4 cm in greatest dimension ○IIA2 Invasive carcinoma ≥4 cm in greatest dimension • IIB With parametrial involvement but not up to the pelvic wall
Stage III:
The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes. • IIIA Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall • IIIB Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause) • IIIC Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (with r and p notations)c ○IIIC1 Pelvic lymph node metastasis only ○IIIC2 Paraaortic lymph node metastasis
Stage IV:
The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV • IVA Spread of the growth to adjacent organs • IVB Spread to distant organs

RESULT

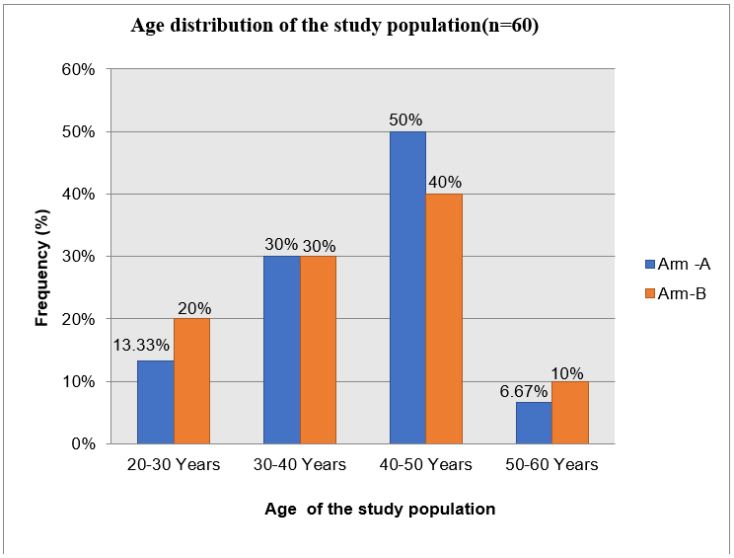

Figure-1: Age distribution of the study population (n=60).

Figure 1 showed the age distribution of the study population. The study populations had divided into 4 age groups. Age ranges from 20-60 years. The pick age incidence of cervical cancer had found in age groups of 40-50 years.

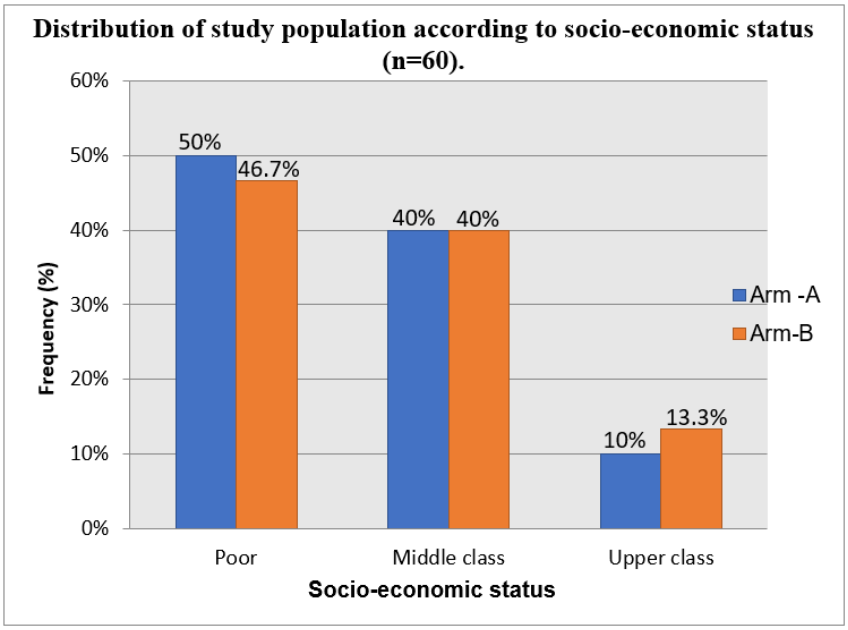

Figure-2: Distribution of study population according to socio-economic status (on the basis of monthly income) (n=60)

Figure 2 showed socio-economic status of the study population. The socio-economic status of the study population was categorized according to poor, middle class and upper class. Most of the populations in both arms were in poor group followed by middle class.

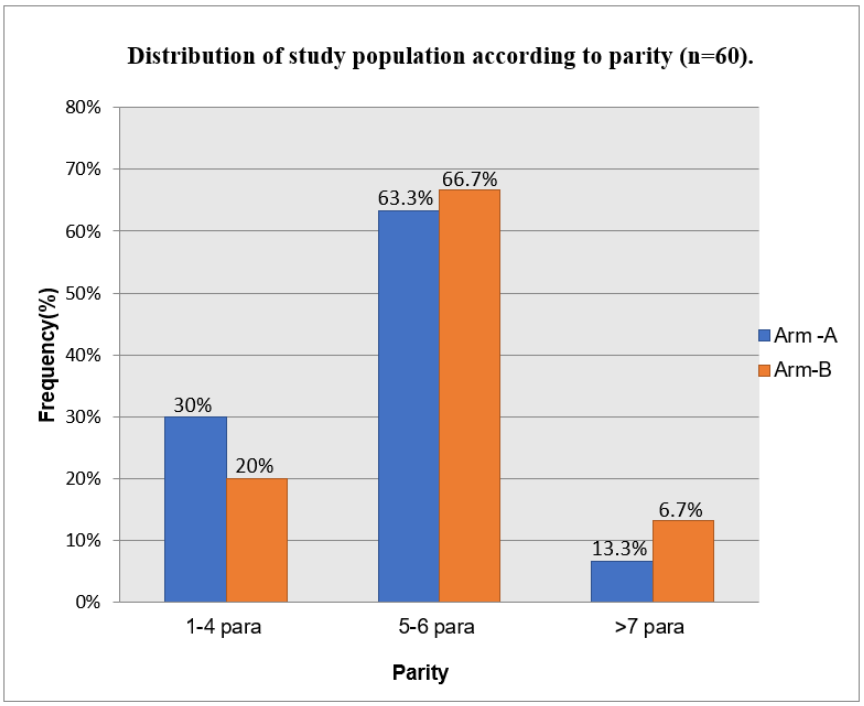

Figure-4: Distribution of study population according to parity (n=60)

Figure 3 resembles distribution of study population according to parity. majority of the patient was multiparous. 19(63.3%) of the study population had given birth to 5-6 children in arm-A and 20(66.7%) in arm-B.

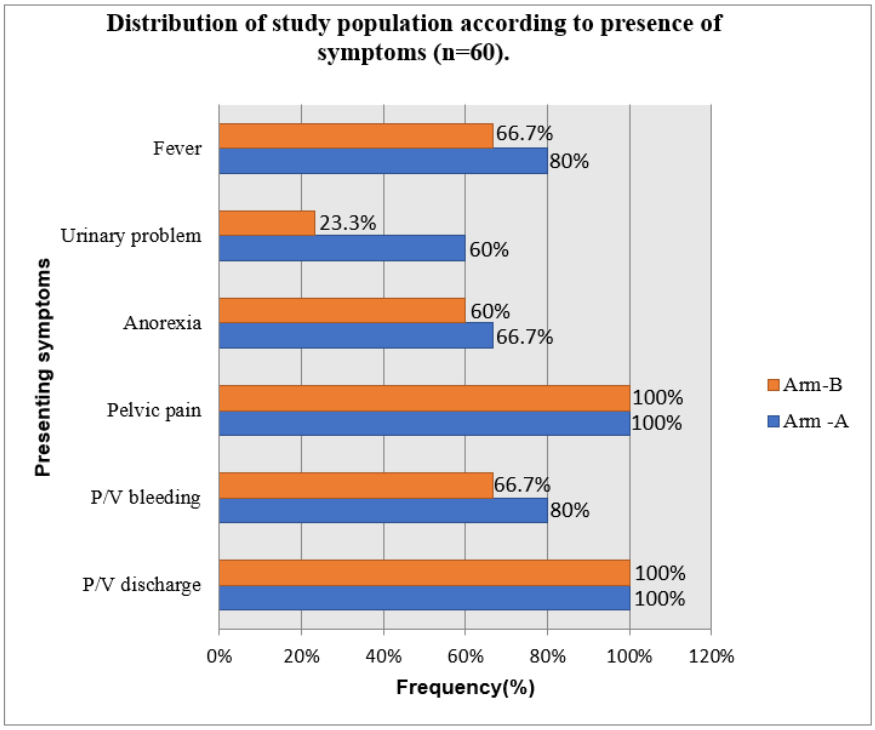

Figure-5: Distribution of study population according to presence of symptoms (n=60)

Figure 4 showed distribution of study population according to presence of symptoms. Almost all the study population had presented with P/V watery discharge with pelvic pain. Majority of the patient presented with P/V bleeding, fever and anorexia.

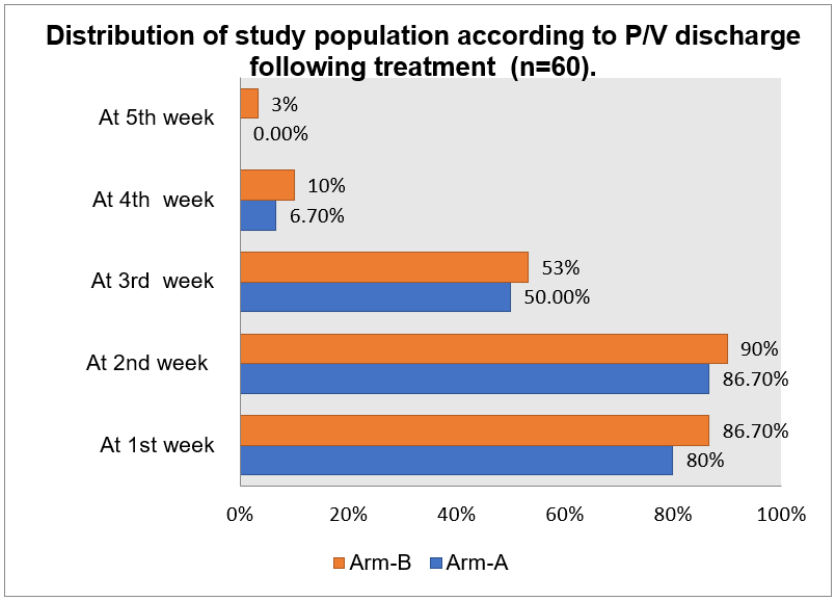

Figure-6: Distribution of study population according to Karnofsky Performance Status Scale (KPS) (n=60)

Figure 5 showed distribution of study population according to Karnofsky Performance Status Scale (KPS). It was observed that Karnofsky Performance Status Scale (KPS) score in both arms was 60-80 in most of the study population.

Table-1 below showed distribution of study population according to treatment related toxicity. Overall- treatment related toxicity was more in arm-Athan arm-B. In Grade-I nausea/vomiting and skin reaction in Grade-II were more in arm-A. Leukopenia and anaemia II also more in arm-A Grade-I and II respectively. Data was analyzed by using chi-square test and result was not significant in nausea/vomiting and skin reaction and significant in leukopenia at $p < 0.05$.

Table-1: Distribution of study population according to treatment related toxicity (n=60)

Toxicity	Arm-A		Arm-B		p-value
	No. of patient (n=30)	Percentage (%)	No. of patient (n=30)	Percentage (%)	
Nausea/Vomiting					
Grade-0	04	13.3	12	40	0.06^{NS}
Grade-I	24	80	16	53.3	
Grade-II	02	6.7	02	6.7	
Skin reaction					
Grade-0	00	00	02	6.7	26^{NS}
Grade-I	05	16.7	07	23.3	
Grade-II	25	83.3	21	70	
Leukopenia					
Grade-0	10	33.3	20	66.7	00.01^{S}.
Grade-I	18	60	06	20	
Grade-II	02	6.7	04	13.3	
Anaemia					
Grade-0	00	00	00	00	
Grade-I	10	33.3	18	60	
Grade-II	20	66.7	12	40	

n= no of study population, S = significant, NS= not significant.

Table-2 below showed distribution of study population according to KPS performance status. Categorization had done according to Karnofsky Performance Status Scale (KPS)into 3 groups in both arms at the time of diagnosis and after treatment to see the symptomatic improvement. A significant improvement was found in arm-A after treatment. Data was analyzed by using chi-square test and result was significant in arm-A at $p < 0.05$.

Table-2: Distribution of study population according to Karnofsky Performance Status Scale (KPS) (n=60).

Performance status	Arm-A (n=30)			Arm-B (n=30)		
KPS	**Pre-treatment** (%)	**Post-treatment** (%)	**p-value**	**Pre-treatment** (%)	**Post-treatment** (%)	**p-value**
0	06(20.0%)	16(53.3%)	0.02^{S}	05(16.7%)	12(40.0%)	0.08^{NS}
1	19(63.3%)	12(40.0%)		21(70.0%)	17(56.7%)	
2	05(16.7%)	02(6.7%)		04(13.3%)	01(3.3%)	

n= no of study population, S = significant, NS= not significant

n= no of study population, S = significant, NS= not significant

DISCUSSION

This Cross-sectional comparative study had conducted from January 2015 to June 2015 in the department of radiotherapy, Rajshahi Medical College Hospital & in the department of Radiation & Oncology, National Institute of Cancer Research & Hospital.

Majority of the patients in this study were in age groups of 40-50 years in both arms (50% and 40% respectively). Nine cases were found in between 30- 40 years (30% in both arms). A study occurred in 2008 showed 51.1% cases had got chemoradiation in between 41-50 years. So, these observations were in conformity with that the present study [14].

In agreement with studies conducted in Bangladesh our study also revealed that 19(63.3%) of the population had given birth to 5-6 children in arm-A and 20(66.7%) in arm-B. Almost all the study population had presented with P/V watery discharge with pelvic pain and 80% patient presented with P/V bleeding, 80% fever and 66.7% anorexia. It had been observed that Karnofsky Performance Status Scale (KPS) score in both arms was 60-80 in most of the study population. These clinical findings were almost similar with previous studies [15].

A significant symptomatic improvement was found in arm-A after treatment than arm-B which was similar to observations made in several other studies [16]. Overall treatment related toxicity was more in arm-Athan arm-B. In Grade-I nausea/vomiting and skin reaction in Grade-II were more in arm-A. Leukopenia and anaemia II also more in arm-A Grade-I and II respectively. Studies abroad have also demonstrated increased cytotoxicity when cisplatin was combined with radiation therapy [16]. One GOG (Gynecologic Oncology Group) trial with weekly cisplatin combination radiation in IIB-IIIB cervical cancer showed 5 years survival rate [17].

A significant improvement was found in arm-A after treatment according to Karnofsky Performance Status Scale (KPS). Almost similar types of results were

found in previous study. From the result of present findings as well as the findings obtained by a number of studies, it is conceivable that concurrent chemo-radiotherapy is more effective than radiotherapy alone in advanced cervical cancer [18].

CONCLUSION

In conclusion, use of concurrent chemotherapy with radiotherapy is effective for symptomatic improvement and feasible with acceptable toxicity for advanced cancer of the uterine cervix. It is recommended to conduct more clinical trials with more intensive dose of chemotherapy or combination of two or three agents.

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