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A Comparative Study on the Treatment of Cervical Carcinoma by Radiotherapy Alone vs. Radiotherapy with Concurrent Chemotherapy

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Abstract: ***Cervical cancer happens due to cell changes in women's cervix connecting with the uterus and vagina which can also affect the deeper tissues of the cervix and may spread to other parts of the body. In most cases, cervical cancer is caused by a sexually transmitted infection hosted by human papillomavirus (HPV). In this article, we stated about one of our prospective studies on the treatment of cervical carcinoma by radiotherapy and chemotherapy. The study consists of 60 patients of carcinoma cervix in stages II A to III B. Cases were divided into two groups and each group consists of 30 patients. One group was treated with concurrent Radiotherapy and Chemotherapy as radiotherapy- 6000 cGy for 6 weeks, 5 days in a week, and chemotherapy- Inj. Cisplatin 30 mg/m2 on day 1, repeated every week for 6 weeks. Another group was treated with radiotherapy as 6000 cGy in 30 fractions for 6 weeks, 5 days in a week for 6 weeks. A comparison between concurrent chemo-radiotherapy and radiotherapy alone was studied. The mean age of the studied sample taken was 45.50 years. The objectives of the study are to compare the effect of treatment between the aforesaid two groups and observe the side effects on both arms during treatment. Arm having radiotherapy with concurrent chemotherapy a complete response (CR) was found in 20 cases (66.67%) and partial response (PR) was found in 10 cases (33.33%). In the radiotherapy arm, complete response (CR) was found in 12 cases (40%) and partial response (PR) was found in 18 cases (60%). It was found that complete and partial response was 100%. There was no death during treatment or no major complications throughout the study period. Calculated x^2 value was 4.28 & significant. It corresponds to the probability of 0.05 in the x^2 table (P <0.05) mentioned in supplementary data. Hence treatment with concurrent chemo-radiotherapy was statistically significant.***

Keywords: Cervical Cancer; Radiotherapy; Chemotherapy; Cisplatin; Chemo-radiotherapy

I. INTRODUCTION

Since cancer is one of the leading demises in the world. According to the WHO health report 2006, the number of women suffering from cervical cancer increasing surprisingly in the developing countries. Cervical cancer is the second most common type of cancer among women occurs approximately 80% of death in developing countries. The major reasons behind this scenario hide in the poor accessibility of health services and limited screening for cervical cancer [1-4]. Nearly half a million women are developing the disease each year worldwide [5]. Being a developing country, Bangladesh is also experiencing a high ascent number of non-communicable disease patients. Due to social insecurities, most of the female patients feel hesitant to visit a medical specialist with their gynecological problems in the initial stage [6-9].

The exact reasons for cancer remain undetermined. Some vital reasons including smoking, alcohol, ultraviolet radiation, occupational exposure to the industrial process, toxic chemicals, pesticides, laboratory chemicals, drugs, food toxicants, and related stimulants. Other risk factors are related to diet, ionizing radiation and environmental pollution play a major role to develop cancer in the body [10, 11]. The primary reason for cervical cancer development is human papillomavirus (HPV). More than 90% of squamous cervical cancers contain HPV DNA. In most cases, the virus is acquired via sexual activity. HPV infection forms into cancer at the cervical transformation zone e.g. cervix, anus and oropharynx. The position of the cancer-susceptible transformation zone is dynamic and gradually shifts over years towards the endocervical canal as stratified squamous epithelium replaces the mucus-producing glandular epithelium [2, 12-15]. Cervical cancer is the most common cancer in Bangladesh. Though there is no specific screening program that isn't established available yet, the initial treatment is provided by the local doctors with conventional medicines before they refer to any oncologist. As the treatment is quite expensive that's also a major reason behind remissness observed in the patients. In our study, we tried to find out a better treatment pathway to improve loco-regional control with fewer side effects as well as long-term survival achievement.

The study was undertaken to observe the effect of radiotherapy and a combination therapy along with radiotherapy and concurrent chemotherapy in loco-regional control of cervical cancer stage IIa to stage IIIb and also observed the immediate adverse effects in both treatments. Cisplatin, a chemotherapy medication used in our study. Cisplatin interferes with HPV DNA replication which kills the fastest proliferating cancer cells. [16] In cervical cancer treatment radiotherapy usually applied for six weeks. The Cisplatin was added once in a week with radiotherapy for six weeks throughout the treatment session. Cisplatin was used due to its affordability and fewer side effects [17-20].

The study observed that the patients treated with combination therapy along with chemotherapy and radiotherapy achieved better response than radiotherapy alone with considerable side effects. The results are considerably better for locoregional control. The study found its potentiality in treating cervical cancer.

II. MATERIALS AND METHODS

The prospective investigational study was carried out with the involvement of the patients of carcinoma in the cervix attending the Department of Radiotherapy, Rajshahi Medical College Hospital, Rajshahi, Bangladesh. All the patients were closely examined and interviewed accordingly with the fulfillment of the inclusion and exclusion criteria included in the study.

A. Selection Criteria of the Patients

1) Inclusion Criteria

a) Patients diagnosed clinically and histologically confirmed for cancer of the cervix.

b) Stage IIA to IIIB according to the International Federation of Gynecological & Obstetrics (FIGO 1995) patients were selected for both groups. [21, 22]

c) The patients did not have any major impairment in Liver, Kidney, Lung, and involvement of Supraclavicular nodes.

d) Patients who did not receive any concerned treatment previously.

e) Patients were required to have the International Union against Cancer (UICC) performance status score between 0 – 2 (grade). [23]

2) Exclusion Criteria

a) Patients with Diabetes Mellitus, hypertension & distant metastasis.

b) Age above 75 years.

c) Impaired renal function.

B. Data Collection Procedure

All the patients of the study group were informed consent willingly before enlisting into the study and proper permission was taken from each patient by the concerned department. An informative collection sheet was used to carrying out the study containing patients name, age, registration number, address, region, occupation, socioeconomic condition, risk factors, gynecological history, obstetric history, symptoms and clinical findings. The clinical, general and local examinations were done properly. Gynecological examinations and clinical stages were recorded carefully. Relevant investigations such as routine blood count, blood chemistry eg. Liver function tests, Kidney function tests, radiological and imaging studies like X-ray chest, ultrasonography of the whole abdomen were done and noted. As already diagnosed cases were taken, the histopathology was documented carefully.

A total number of 60 patients were selected for the study and divided equally into two groups containing 30 patients in each group. One group named Study group (Arm-A) treated with concurrent radiotherapy and chemotherapy (radiotherapy- 6000 cGy for 6 weeks, 5 days in a week, and chemotherapy- Inj. Cisplatin 30 mg/m2 on day 1, repeated every week for 6 weeks). Another group named as Control group (Arm-B) was treated with radiotherapy only, 5 days in a week for 6 weeks with a total dose of 6000 cGy. In both groups, the patients were treated with Cobalt-60. Informed consent was taken from each patient. Each patient was then interviewed and her particulars, history and investigation reports were documented in the prescribed datasheet.

C. Patient Assessment

Patients were assessed based on tumor regression, symptomatic relief, local skin reactions, gastro-intestinal toxicities, blood parameters and renal function tests. After completion of the treatment, the patients were advised to attend the outpatient department after 06 weeks. To assess tumor regression all gynecological examinations, general and systemic examinations were done. Ultrasound study and chest x-ray were also done. Gynecological examinations included per abdominal, per vaginal, per rectal, per speculum and bimanual pelvic examinations.

Finally, comments on treatment were written according to WHO response criteria as complete response / partial response / stable disease / progressive disease. A complete response means the disappearance of all measurable disease for at least one month. This response is clinically the most important indicator of the effectiveness of therapy and is the prerequisite for the cure. Partial response is defined as at least a 50% reduction in measurable tumor mass without the appearance of new lesions for at least two months. Stable disease is characterized as either a decrease or an increase of tumors by less than 25%. Progressive disease means an increase of tumor mass by more than 25% or the appearance of new tumor lesions. [24]

D. Sampling Technique and Data Analysis

The entire study was carried out with 60 patients having cervical cancer attending the Department of Radiotherapy, Rajshahi Medical College Hospital, Rajshahi. All the data were collected from the out-patient department of the concerned hospital authority. The author persuades the purposive sampling technique. All collected data were checked for any omissions, logical inconsistencies and errors. Data were compiled and analyzed manually by preparing a master sheet. Data were processed according to the conventional statistical methods and techniques. Finally, computer technology was used for entry, classification, analysis, & statistical presentation and interpretation of results was furnished. Significance tests are included in the relevant aspect of the study.

III. RESULTS

A total number of 60 diagnosed cases of carcinoma cervix stage IIa to IIIb were enlisted and divided equally into two groups of Study group, Arm-A (e.g. Radiotherapy with concurrent Cisplatin); and Control group, Arm-B (e.g. Radiotherapy only). All 60 patients attended at Rajshahi Medical College Hospital.

The study group (Arm-A) included 30 patients were administered Cisplatin at a dose of 30 mg/m2 on day 1 and the process was repeated every week for a total duration of 6 weeks with concurrent Radiotherapy following a daily tumor dose of 200 cGy, five days in a week for 6 weeks. The total tumor dose received by each patient was 6000 cGy. The control group (Arm-B) included 30 patients and were given Radiotherapy alone.

The treatment-related death or major complications throughout the study period were not observed. The results are shown below in the following figures and tables.

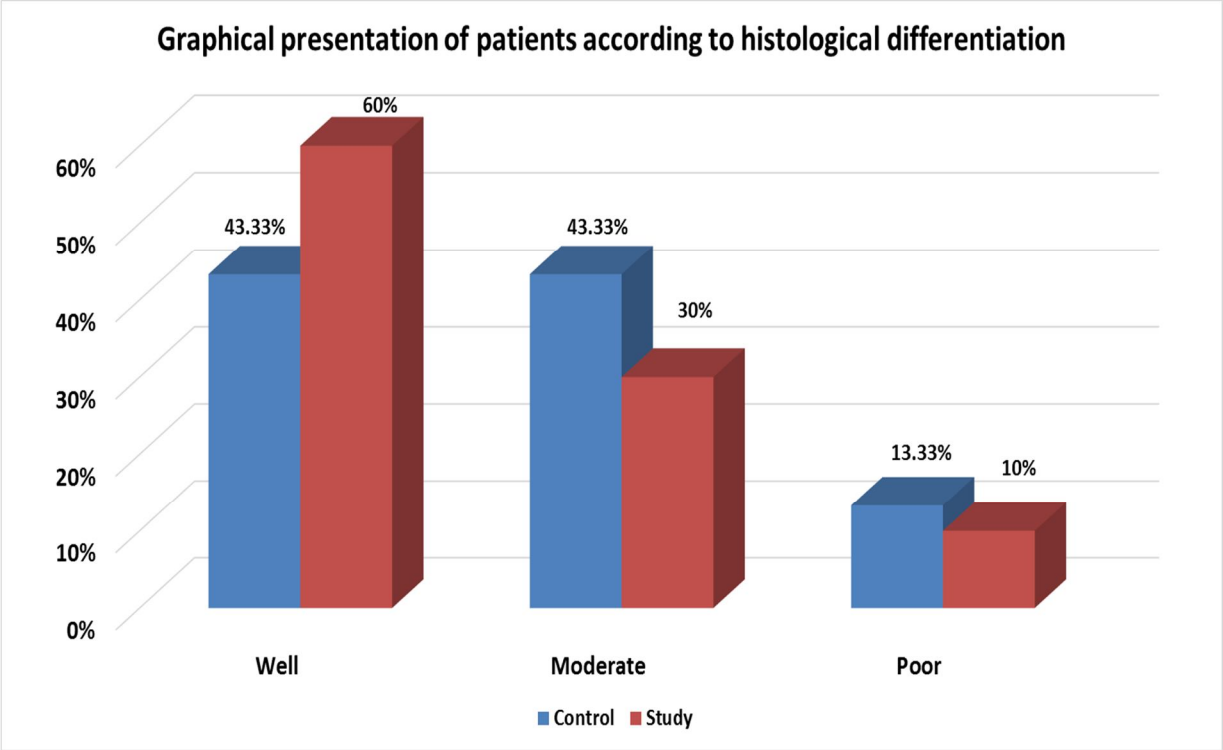

Figure 1: Graphical presentation of patients according to histological differentiation in case (Arm-A, n=30) and control (Arm-B, n=30) groups.

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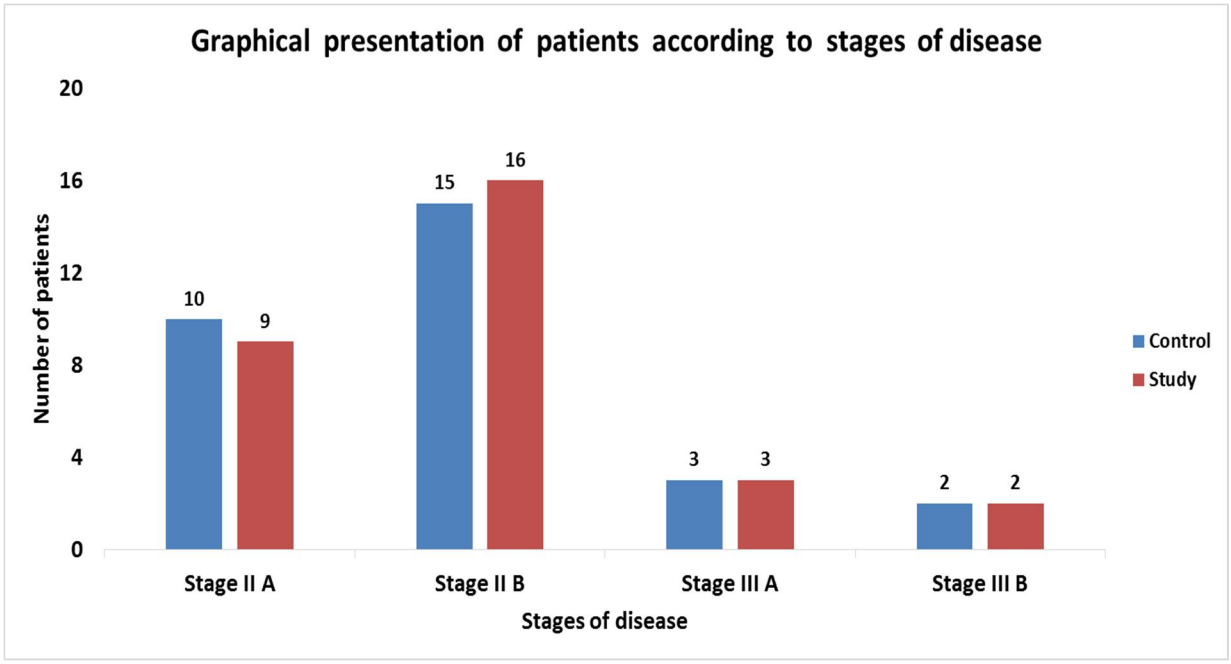


Figure 2: Graphical representation of patients according to stages of disease in case (Arm-A, n=30) and control (Arm-B, n=30) groups

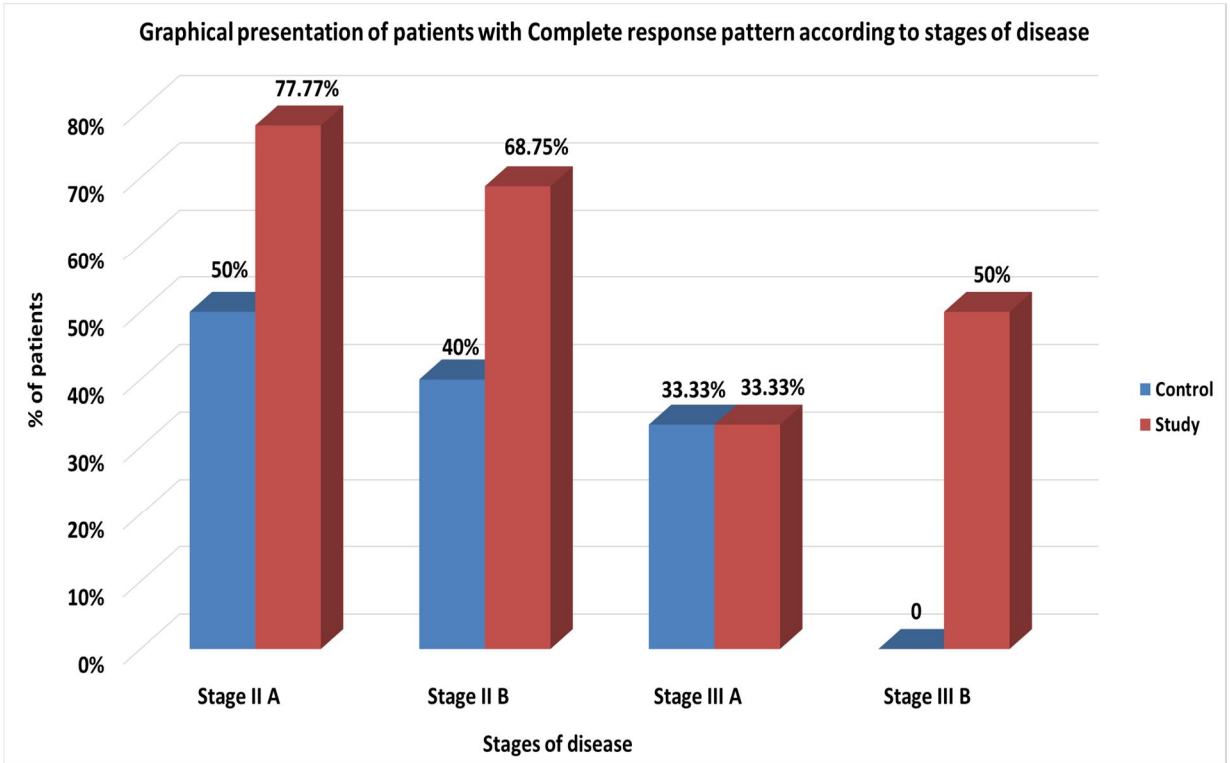


Figure 3: Graphical representation of patients with complete response patterns according to stages of disease in Case (Arm-A, n=30) and Control (Arm-B, n=30) groups.

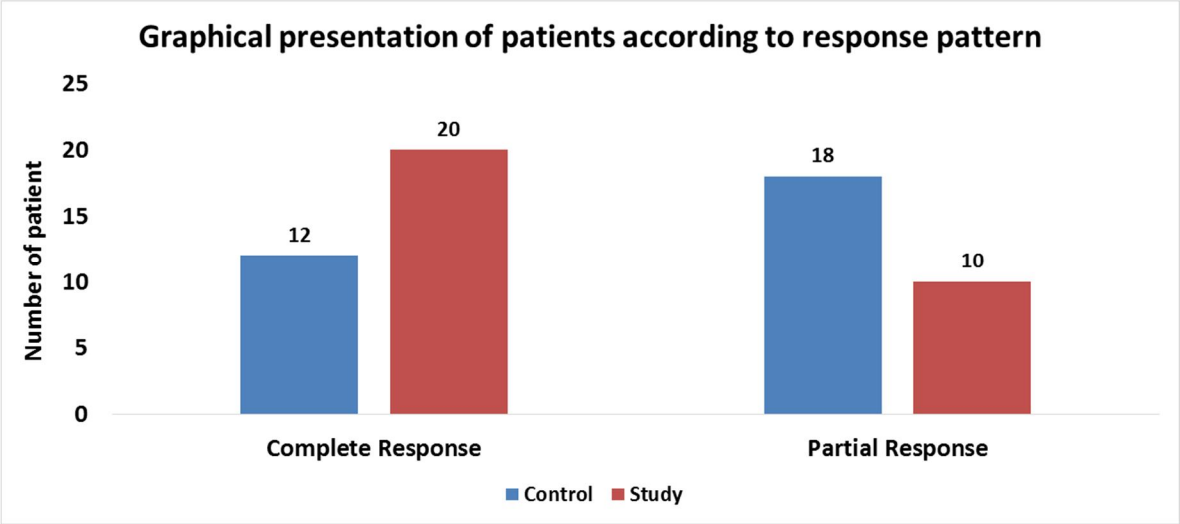


Figure 4: Graphical representation of patients according to response pattern in Case (Arm-A, n=30) and Control (Arm-B, n=30) groups.

Table 1: Distribution of patients according to responses patter in the study group (Arm-A, n=30) and control group (Arm-B, n=30).

Treatment Group	Complete Responses	Partial Responses	X^2 value	P-value
Study Group: Radiotherapy with concurrent Cisplatin (Arm-A, n=30)	20 (66.67%)	10 (33.33%)	4.28	<0.05
Control Group: Radiotherapy Only (Arm-B, n=30)	12 (40%)	18 (60%)		

Table 1 shows the complete responses achieved after completion of the treatment, where 20 (66.67%) cases in Arm-A and 12 (40%) cases in Arm-B showed complete responses. However partial responses were higher in Arm-B group 18 (60%) cases than Arm-A group 12 (40%).

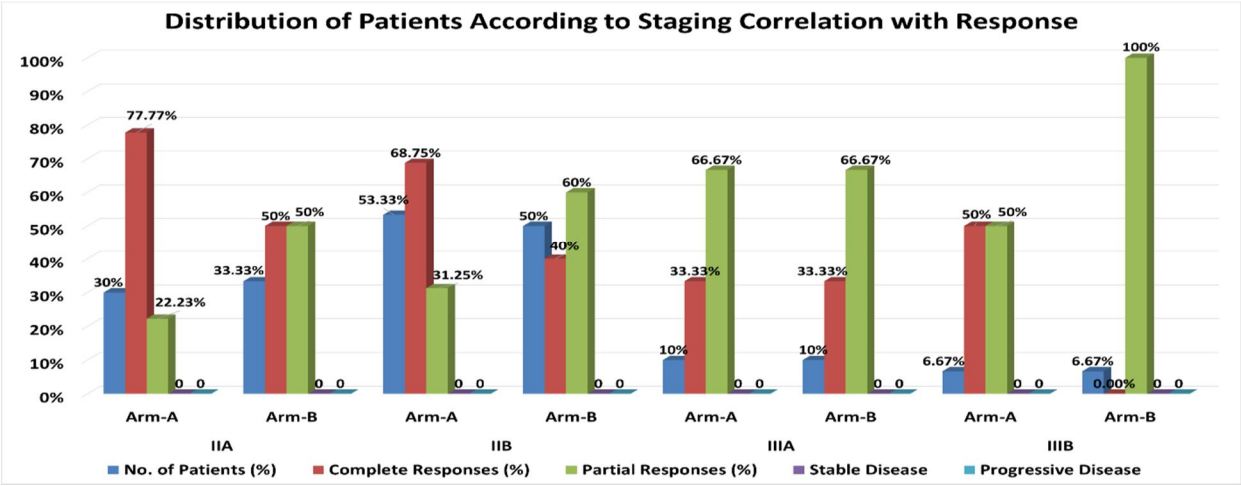


Figure 5: Distribution of patients according to staging correlation with response pattern in the study (Arm-A, n=30) and control (Arm-B, n=30) groups.

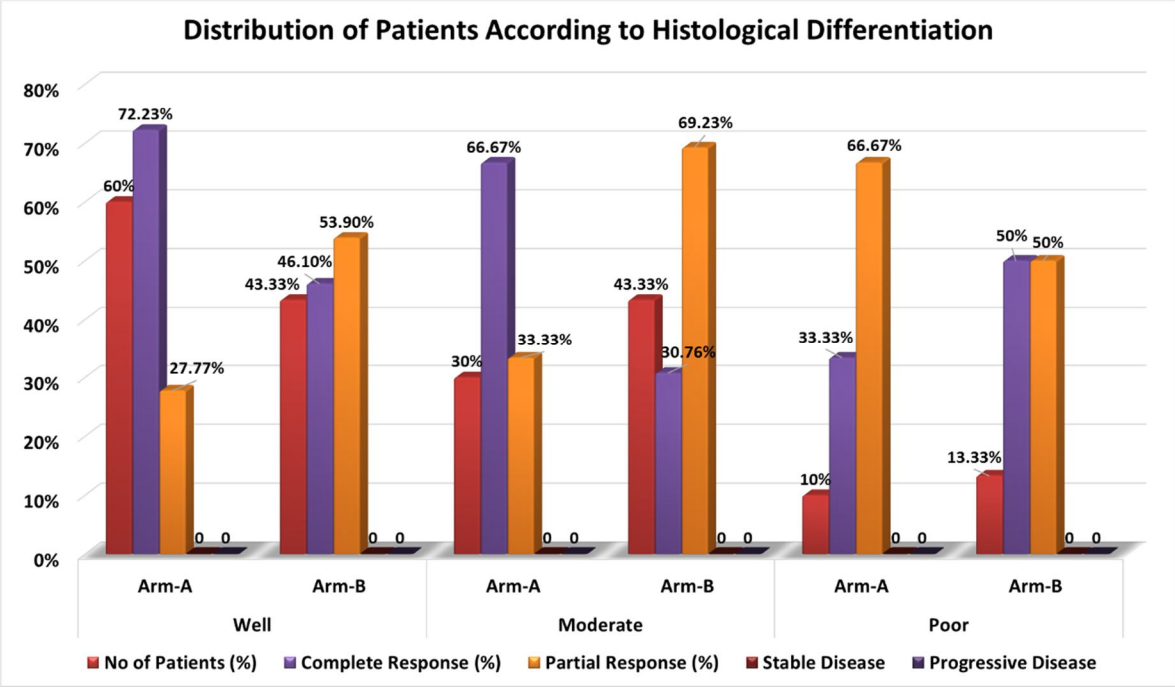
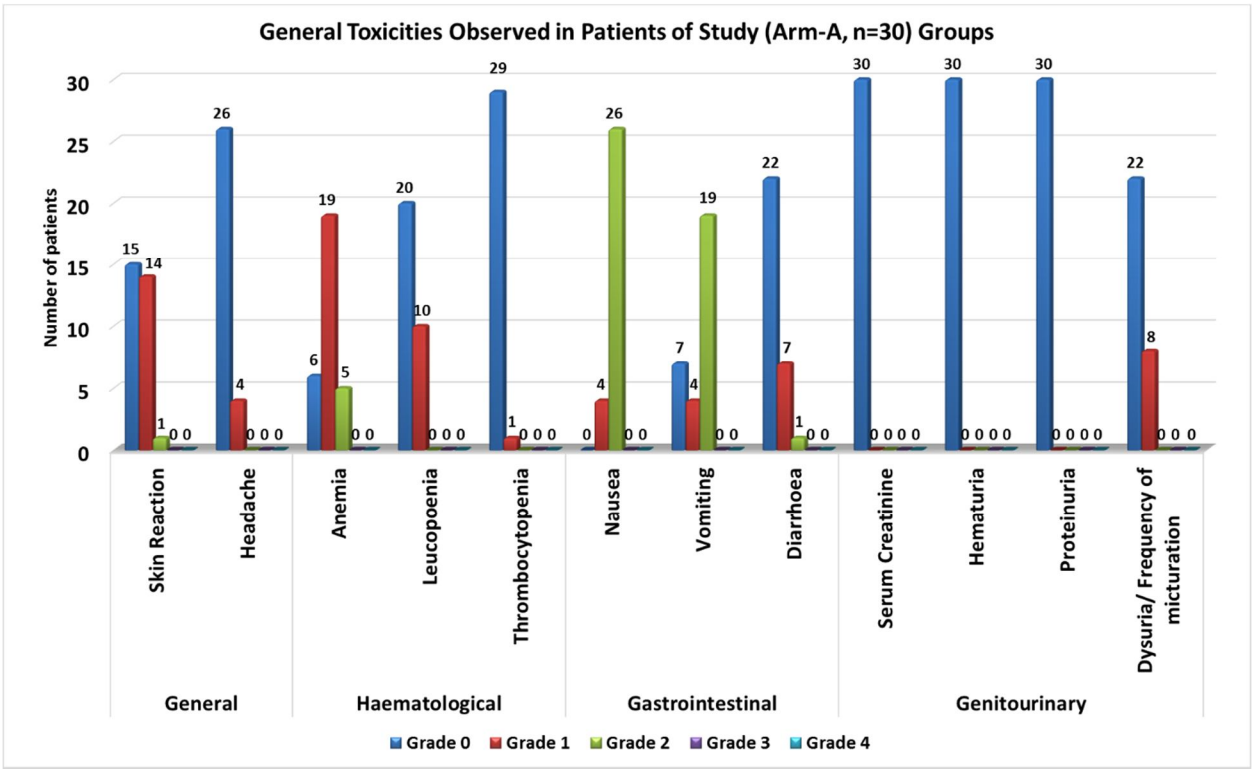


Figure 6: Distribution of patients according to histological differentiation and correlation with response pattern both in the study (Arm-A, n=30) and control (Arm-B, n=30) groups.



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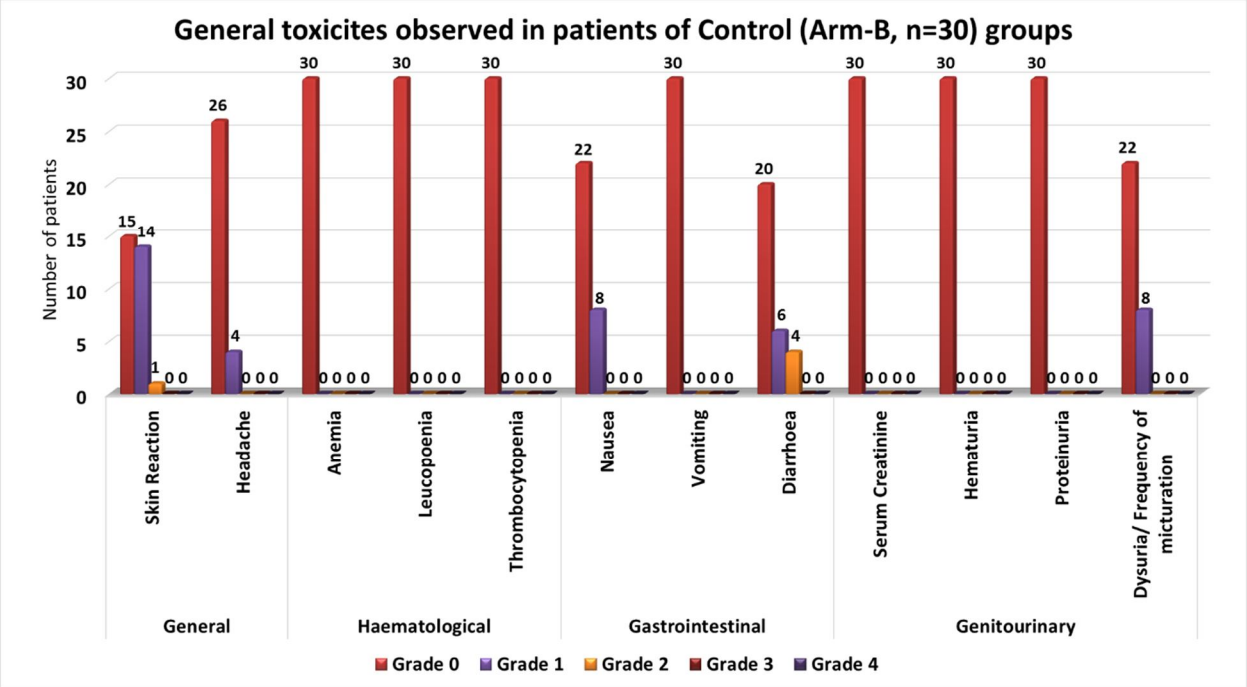

Figure 8: General toxicities observed in patients of Control (Arm-B, n=30) group. According to common Toxicity Criteria Version 2, April 1999). Figure 8 shows most of the grade 1 and grade 2 toxicities are of gastrointestinal origin [25].

IV. DISCUSSION

Cervical cancer is the most common cancer in Bangladesh. The prevalence of cancer cervix is about 26% of all types of female cancers [26].

This study was carried out –

1) To increase the duration of locoregional control.

2) To compare the effects of the two regimens in locoregional control & their toxicities.

This study contained 60 patients of carcinoma cervix. They were divided equally into two groups and each group contained 30 patients. The majority of the patients in this study were between the ages of 35 to 50 years with a mean of 45.50 years and a median of 52.50 years. 2 cases below 35 years and 11 cases were more than 50 years. Bardaxoglou et al. 1993 reported that the peak age incidence for cervical carcinoma is between 48 and 55 years with a mean of 53.8 years and a median of 51.5 years [27].

The study observed, most of the patients present are having squamous cell carcinoma. In Control group squamous cell carcinoma is 28 (93.33%) and adenocarcinoma is 2 (6.67%). In this Arm-A group squamous cell carcinoma is 29 (96.57%) and adenocarcinoma is 1 (3.33%). This figure is similar to Bomford et. al 2003 [28]. In the case of responsiveness to treatment in the control group, it has been observed that complete response was achieved in 12 (40%) cases and partial response was observed in 18 (60%) [Figure 4, Table 1]. Achariya D.K. et al, 1994 found that the complete regression was achieved in 49.4% of cases and partial regression occurred in 32.2% cases [29]. On the other hand, the study group observed complete response was achieved in 20 (66.67%) cases and partial response was observed in 10 (33.33%), mentioned in Figure 4 and Table. 1.

In our study, concurrent chemotherapy with Cisplatin along with external beam irradiation was used to treat the patient of carcinoma cervix in the study group. In an attempt to improve survival, several investigators had tried chemotherapeutic agents as radio-sensitizers in standard radiation treatment [17, 30]. Multiple agents have been evaluated for efficacy in patients with advanced or recurrent disease. With a single agent, the response rates vary from 6% to 40%. The single agent with the most activity is Cisplatin. However, a randomized trial by the Southwest Oncology Group (SWOG) revealed no advantage of combination drug over Cisplatin alone [30-32].

The National Cancer Institute (NCI) issues Clinical announcement on cervical cancer as Chemotherapy along with Radiation improves survival. In three of the studies, women were randomly divided into groups or arms that received either radiation alone or

radiation plus concomitant chemotherapy. The chemotherapy agents used were Cisplatin and 5-FU (two studies) and Cisplatin alone (one study). In all three trials, the proportion of women alive after about three years of follow-up was higher in the groups receiving chemotherapy plus radiation than in those receiving only radiation therapy. [33] In two other studies, all patients received concomitant chemotherapy and radiation. However, the chemotherapy drugs differed between the arms. In one arm of each of these trials, the chemotherapy used was hydroxyurea while in the other arms the chemotherapy included Cisplatin. In both trials, the groups who received Cisplatin had better survival rates. NCI's clinical announcement states that, although the best chemotherapy regimen for cervical cancer has not been determined, "significant results were seen using Cisplatin alone or Cisplatin in combination with 5-FU and other agents" [33]. There are several reports on the result of concomitant use of Cisplatin, 5-FU, mitomycin-c, combined with irradiation to treat patients with locally advanced or recurrent carcinoma of the cervix. The first series of studies of Cisplatin combined with irradiation in carcinoma of the uterine cervix were conducted by Potish and colleagues and Twiggs and co-workers, who administered Cisplatin weekly (10 mg/m2, gradually escalating to 20 mg/m2) in combination with standard irradiation. Of 815 patients treated with Cisplatin as a single agent, 782 were part of GOG trials. An objective response was observed in 23% of patients [34].

An Indian study on 102 patients staged as IIA-IIIB squamous cell carcinoma of the cervix were randomized in two groups. The control group was treated with radiotherapy alone while the study group was treated with concurrent chemo-radiation. External radiotherapy was given to a dose of 45 Gy/20/4 wk. The study group received Inj. Cis-platinum 40 mg/m2 every week / 4 cycles. Two to four weeks after radiation, if patients found suitable intracavitary LDR brachytherapy was given to a dose of 35 Gy to point A. Patients not suitable was further treated with external radiation to a dose of 20 Gy/10/2 wk. The overall response rate in CRT and RT alone arm was 86.5% and 78%. The complete response was 65% and 58% respectively in CRT and RT alone arm ($P > .005$). Similarly, the partial response was 21.2% and 20% [35].

In another study, Souhami and co-workers treated 50 patients with bulky locally advanced carcinoma of the cervix with a combination of weekly Cisplatin (30 mg/m2) concurrent with radiation therapy (46 Gy to the whole pelvis plus three HDR intracavitary insertions once weekly to a total dose of 30 Gy to point A). The complete tumor response rate was 88% (44 of 50) [34].

In comparison regarding the response rate between the study group and the control group the difference is statistically significant ($P<0.05$). It indicates that the patients of the study group have an approximately 30.00% higher complete regression rate than that of the control group.

About toxicity, no severe untoward reactions were noticed in any of the patients of the study group. All the patients experienced grade 0 to grade 2 systemic toxicities (according to common toxicity criteria version 2.0). The study group developed side reactions (Figure 7) mainly anemia, leucopenia, nausea & vomiting more in comparison to the control group (Figure 8). In the study group 24 (80%) patients developed anemia, 10 (33%) patients developed leucopenia, 30 (100%) patients developed nausea and 23 (76%) patients developed vomiting which is 0, 0, 8 (27%) & 0 respectively in control group. The side reactions were duly overcome by conservative management.

Thus, after careful analysis, it is very much clear that the patients who were administered Inj. Cisplatin during external irradiation had a better treatment response in terms of locoregional tumor control in comparison to the patients who are not under Cisplatin control. This indicates that in the study group the irradiation worked in a much better way than that of the control group. All other parameters were kept the same as far as possible both in the study group and the control group, so it is only Cisplatin that shows a better treatment response. After careful consideration of the above-mentioned facts and figure it is concluded that Cisplatin can be administered at a dose of 30 mg/m2 weekly safely along with external beam irradiation in the patients of carcinoma cervix with the existing facilities to get better treatment response.

Lastly, for future studies, survival seems to be a more suitable parameter to appreciate the value of Cisplatin in the management of carcinoma cervix along with external beam irradiation.

V. CONCLUSION

The presence of hypoxic cells in a tumor limits the success of radiotherapy. Current areas of the investigation were undertaken to observe the duration of locoregional control and to compare the effects of the two regimens in locoregional control & their toxicities in cervical cancer patients. In this prospective study cervical carcinoma from stages, IIA to IIIB was included. All patients during treatment were examined and interviewed. They were again interviewed, examined and evaluated in subsequent months during follow-up visits. In the study group, complete response (CR) was found in 20 (66.67%) and partial response (PR) was found in 10 (33.33%). In the control group, Complete response (CR) was found in 12 (40%) and partial response (PR) was found in 18 (60%).

The overall response (CR & PR) rate was 100%. The calculated x2 value was 4.28 which was greater than the table value of x^2 i.e. 3.84. It corresponds to the probability of 0.05 in the x^2 table (P <0.05). Statistically, the result was significant. After completion of the treatment, it was observed that the patients receiving a combination of Cisplatin and radiotherapy had a better treatment response than the patient who received only external radiotherapy. So it can be concluded that the patients of carcinoma cervix from stages IIA to IIIB may be treated by external beam irradiation and concurrent chemotherapy (Inj. Cisplatin).

VI. ACKNOWLEDGEMENT

This prospective study was performed at the Department of Radiotherapy, Rajshahi Medical College Hospital, Rajshahi, Bangladesh.

VII. AUTHOR CONTRIBUTIONS

Dr. Ashim Kumar Ghosh (AKG) designed the study and executed the experiments along with Dr. Julekha Khatun (JK) and Dr. Md. Shafayat Habib (MSH). Three of them contributed equally to experimental data analysis. AKG wrote the manuscript. Both co-authors JK and MSH approved the final version of the manuscript.

A. *Conflicts Of Interest*

The authors declared that they have no conflict of interest.

VIII. SUPPLEMENTARY DATA

A. *Calculation (X^2 test)*

Treatment group	CR %	PR%	Total
Study Group (Arm-A)	20	10	30
Control Group (Arm-B)	12	18	30
Total	32	28	60 (total)

We Knows, $X^2 = \sum \frac{(O-E)^2}{E}$

Where, O = Observed value; E = Expected value

$E = \frac{\text{Row total x Column total}}{\text{Grand Total}}$

For Study group CR E value = $\frac{30 \times 32}{60} = 16$

For Study group PR E value = $\frac{30 \times 28}{60} = 14$

And For Control group CR E value = $\frac{30 \times 32}{60} = 16$

For Control group PR E value = $\frac{30 \times 28}{60} = 14$

O	E	O-E	$(O-E)^2$	$(O-E)^2/E$
20	16	4	16	1.0
12	16	-4	16	1.0
10	14	-4	16	1.14
18	14	4	16	1.14

Total

X^2 = 1.0+1.0+1.14+1.14 = 4.28

df= (Row – 1) x (Column -1) = (2-1) x (2-1) = 1

For df.= 1 table value of X^2 =3.84 at p = 0.05 level. Here calculated value of X^2 = 4.28 which is greater than table value.

The calculated value X^2 i.e 4.28 is greater than the table value of X^2 i.e 3.84. It corresponds to the probability of .05 in the x^2 table; it is significant ($p<0.05$). Hence the concurrent chemo-radiotherapy is effective than radiotherapy alone.

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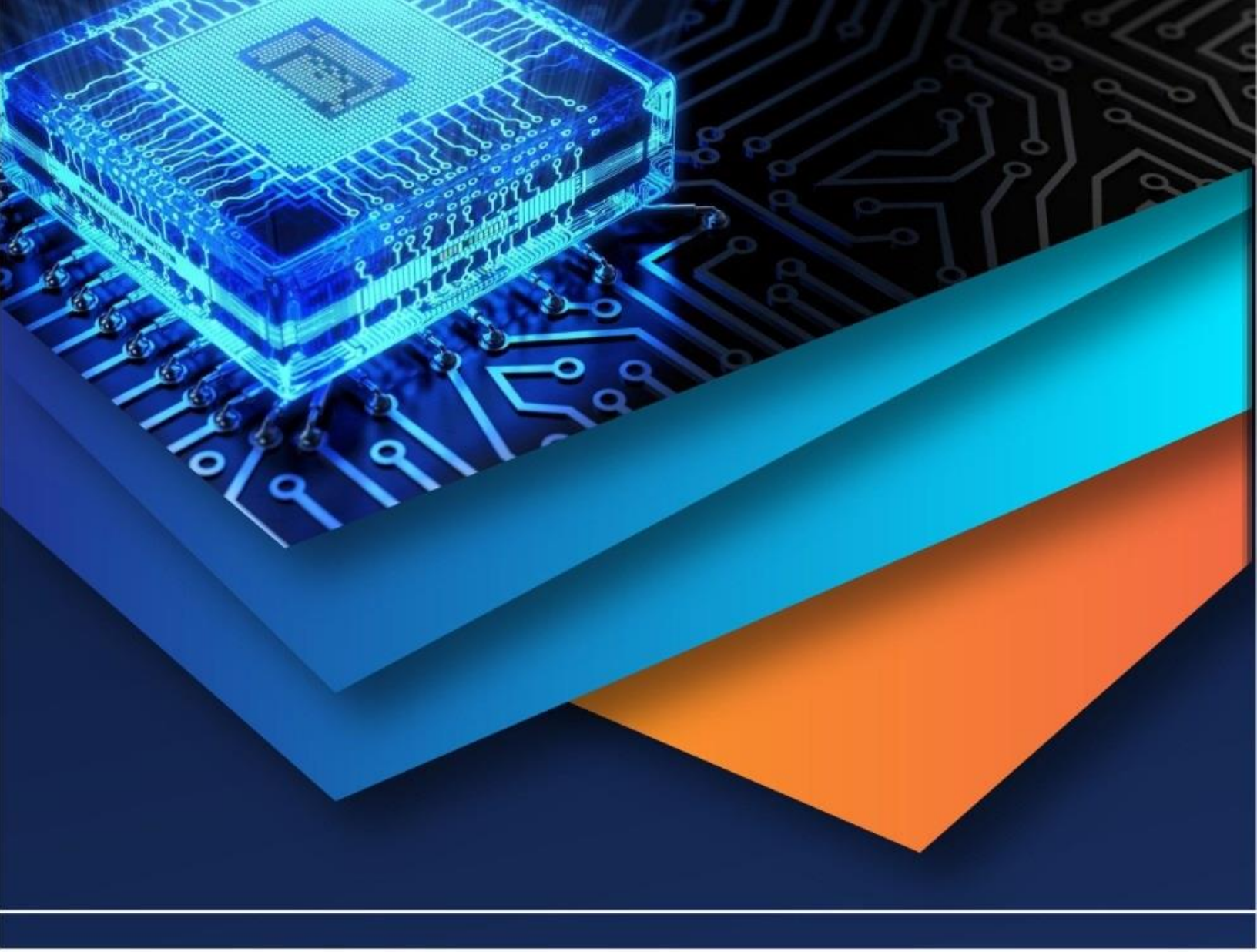

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