**Original Article**

**A Prospective Study Comparing Hemoglobin Levels and Response in Patients of Locally Advanced Carcinoma Cervix Receiving Accelerated Chemoradiation versus Conventional Chemoradiation**

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**ABSTRACT**

**Introduction:** Carcinoma cervix still forms a major burden in India; also, anemia is seen commonly in Indian females. Hemoglobin (Hb) level is one of the prognostic factors in carcinoma cervix. The association of Hb levels with response is not well established. However, Hb levels >11 g% have shown good response in a number of studies. **Materials and Methods:** This study enrolled patients with carcinoma cervix, <70 years old with Stage IIA to IVA, histologically squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma. Accelerated concurrent chemoradiotherapy 50 Gy in 25# 6 days a week with weekly cisplatin was given in the study arm. In the control arm, conventional chemoradiation was given, 50 Gy in 25# five fractions per week with weekly cisplatin. Response was compared in both the arms based on Hb levels. Both the arms had 45 patients. **Results:** Combining patients of both the arms, 66% of patients with Hb <11 had complete response (CR) and 81% of patients with Hb >11 had CR which was not significant, but a trend of better response was seen toward patients with higher levels of Hb. However, no significant difference was seen in both the arms. **Conclusion:** Hb levels remain a prognostic factor for carcinoma cervix, but the levels of Hb are still debatable. More prospective studies are needed to assess the effect of Hb. Furthermore, use of erythropoietin and blood transfusions needs to be studied in prognosis of carcinoma cervix.

**KEYWORDS:** Accelerated radiotherapy, chemoradiation, complete response, hemoglobin, partial response

**INTRODUCTION**

Cervical cancer ranks 4th in women worldwide. According to GLOBOCAN, there were 96,922 new cases every year in India.[1] In a country like India, carcinoma cervix still bears a quarter of world’s cervical cancer burden. About 80%–90% of the patients present with locally advanced disease. Most of the patients present with the complaints of postcoital bleeding, intermenstrual bleeding, and discharge per vagina. In advanced stages, the symptoms may increase due to the involvement of adjacent organs.

Early stage tumors are treated by surgery alone or brachytherapy in some cases, and locally advanced cancers are treated with chemoradiation. Chemoradiotherapy (CRT) has been accepted as the standard protocol for treatment of locally advanced cervical cancers with injection cisplatin followed by intracavitary brachytherapy. According to NCCN “in patients with intact cervical cancer, the primary tumor and regional lymphatics at risk are typically treated with definitive external beam radiation therapy (EBRT) to a dose of approximately 45 Gy.”[2]” the primary cervical tumor is then boosted

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using brachytherapy, with an additional 30–40 Gy to point A".[2]

The prognosis of cervical cancers depend on number of factors such as stage, tumor volume, histologic type and lymph node involvement, and hemoglobin (Hb) levels are also seen to contribute in the prognosis of the patient. In developing countries, most of the people are anemic due to poor nutrition. Thus the expected response is poor in such patients. To increase the treatment response, other strategies like extended field radiotherapy and radio-sensitizers have been used, but due to their marginal results they are not routinely used.

Altered fractionated radiotherapy has also been one of the approaches that have shown promise.[3] In conventional fractionation, 1.8–2 Gy per fraction is given as five fractions per week. Any deviation from this regimen is known as altered fractionation. The modalities that have been tried include hyperfractionated radiation therapy (RT) alone, accelerated hyperfractionated radiotherapy (AHRT), and accelerated fractionated RT alone. Accelerated fractionation aims to minimize tumor repopulation during treatment sessions by shortening the overall treatment time, and hyper fractionation RT permits dose escalation. AHRT combines the effects of hyper fractionation and accelerated fractionation. Theoretically hyperfractionation and AHRT are attractive options but none has been proven to be of any benefit over conventional RT, and moreover, there have been reports of more toxicity associated with them.[3-10]

In this study, the response was compared with conventional chemoradiation and accelerated chemoradiation based on Hb levels. Better response was expected with accelerated CRT with high Hb levels. The expected increased tumor control probability with accelerated CRT may become helpful in anemic patients and may bring better response in such patients.

**Materials and Methods**

This prospective comparative study was conducted in the Department of Radiation Oncology TCC, IGMC, Shimla in patients suffering from locally advanced carcinoma of cervix. The patients were enrolled in the study starting from July 2016 to June 2017. Cases included in this study were previously untreated, staged by Federation of Gynecology and Obstetrics (FIGO) staging 2008, Stage IIA–IVA, histologically proven invasive squamous cell carcinoma (SCC), adenocarcinoma and adenosquamous carcinoma, age ≤70 years, normal renal and liver function tests, and Karnofsky Performance Status score ≥70. Hb levels were measured before the commencement of treatment and weekly during the treatment. Hb levels before starting the treatment were considered for evaluation.

Randomization was carried out by stratification; the treatment assignment was stratified according to clinical stages of disease. Patients were randomized into two groups, one study and one control group based on treatment they received.

**Control arm**

Patients were subjected to standard conventional concurrent CRT with EBRT 50 Gy in 25# over 5 weeks with injection cisplatin 40 mg/m² on D1 of every week. Intracavitary brachytherapy (ICBT) was used after a gap of 1–2 weeks using Selectron IRIDIUM based HDR system, to give a dose of 18–21 Gy in 2 or 3 divided fractions to point A. If they were not fit for ICBT, the patients were subjected to supplement radiation therapy. 20 Gy was given over ten fractions @ 200 cGy/# over 2 weeks with injection cisplatin weekly.

**Study arm (accelerated concurrent chemoradiotherapy arm)**

Patients were subjected to six fractions per week (accelerated) RT 50 Gy in 25# over 4 weeks and 1 day along with injection cisplatin 40 mg/m² on D1 of every week for a total 25#. Brachytherapy given was the same. Supplementary treatment includes 20 Gy in 10 fractions in one and a half weeks @ 200cGy/# with injection cisplatin weekly for the patients who were unfit for ICBT.

**Assessment of status and toxicity**

Patients were assessed every week for toxicities and for suitability of brachytherapy 1–2 weeks after completion of EBRT. Patients were assessed as complete response (CR), partial response (PR), NR, and progressive disease. Toxicities were monitored, and Eastern Cooperative Oncology Group toxicity criteria was utilized to assess and document hematologic toxicities and the radiotherapy and oncology group (RTOG) acute morbidity criteria to assess toxicities from radiotherapy.

**Follow-up**

First follow-up was done at 6 weeks. A complete gynecological examination accompanied with systemic examination was performed, and subsequent follow-up was done at every 2 months. Patients were examined locally and for any acute and late toxicity. Late toxicities were graded according to RTOG criteria.

**Secondary treatment**

Patients who had persistent tumor on completion of treatment were considered for salvage surgery if resectable. Adjuvant chemotherapy was administered in patients with unresectable disease.
**Statistical analysis**

Response rate was the primary end point for analysis. The data obtained from both arms were analyzed by Student’s t-test and Chi-square test. *P* < 0.05 was taken as significant. The statistical significance was defined as: *P* > 0.05 - nonsignificant, *P* = 0.05 to 0.01 - significant, and *P* < 0.01 - highly significant.

**RESULTS**

Patient characteristics were balanced in both the arms on the basis of age, stage, and histology [Table 1]. 130 patients of carcinoma cervix were assessed for eligibility, of which 90 patients were enrolled in the study. 45 patients were randomized in each conventional and accelerated radiotherapy arm. Age of the enrolled patients ranged between 34 and 70 years, the median age at presentation being 55 years in both the study as well as the control arm.

Majority of the patients belonged to Stage IIIB in both the groups (55.5% in study and 42.2% in the control group). The number of patients in Stage IIIB in study group was sixteen (35.5%) and twenty in the control group (46.6%). Biopsy proven Squamous Cell Carcinoma (SCC), adeno and adenosquamous carcinoma cervix patients were enrolled in the study. Majority of patients were having SCC histology in both the arms. Forty-two (93.3%) patients in the study arm had SCC while the number in the control arm was forty-one (91.1%). Thus, both the arms of this study were balanced as per histology of the disease. The number of patients with well-differentiated, moderately differentiated, and poorly differentiated tumors in the study arm were nine (20%), twenty-one (46.6%), and five (11.1%) and in the control group were eight (17.7%), twenty-four (53.3%), and four (8.8%), respectively.

Majority of the patients had a baseline Hb level between 10 and 12 g% (thirty-nine patients [86.6%] in study and thirty-eight [84.4%] in the control group). Few patients with Hb levels below 10 had subsequently been given blood transfusions for correction of the Hb levels. The distribution of patients with different Hb levels is shown in Figure 1.

**Effect of hemoglobin level on response**

Among patients of the control arm, patients with Hb <11 g% tend to perform worse compared to patients in the study arm, eighteen (56.25%) patients with Hb <11 had CR in the control arm [Table 2] as compared to twenty-two (64.70%) in the study arm [Table 3], *P* = 0.254. Beyond Hb of 11 g%, the difference had persisted between the study and the control arm in response rates, twelve in study arm (35.29%) versus fourteen in control arm (43.75%, *P* = 0.471) [Figure 2].

**Effect of hemoglobin levels on response irrespective of arm**

When patients of both arms (overall) with Hb <11 g% were compared with patients with those with Hb >11 g%, there was a nonsignificant difference in CR rates with

### Table 1: Patient characteristics in both the arms (n=90); 45 in each arm

| Characteristics | Study arm | Control arm |
|-----------------|-----------|-------------|
| **Age (years)** |           |             |
| Median           | 55        | 55          |
| Range            | 37-70     | 34-70       |
| **Stage**        |           |             |
| II              | 27        | 21          |
| III             | 17        | 22          |
| IVA             | 1         | 2           |
| **Histology**    |           |             |
| SCC             | 42        | 41          |
| Adenocarcinoma  | 2         | 2           |
| Adenosquamous carcinoma | 1 | 2 |
| **Grade**        |           |             |
| Well differentiated | 9     | 8           |
| Mod differentiated | 21     | 24          |
| Poorly differentiated | 5     | 4           |
| Unknown         | 10        | 9           |

SCC: Squamous cell carcinomas

### Table 2: Effect of Haemoglobin on response in control group

| HB in GM% | CR | PR | PD | Total |
|-----------|----|----|----|-------|
| in CRT ARM | No | %Age | No | %Age | No | %Age | No |
| <10       | 4  | 57.14 | 2  | 28.57 | 1  | 14.28 | 7  |
| 10.1-10.5 | 7  | 58.33 | 1  | 8.3 | 4  | 33.33 | 12 |
| 10.6-11   | 7  | 63.63 | 2  | 18.18 | 2  | 18.18 | 11 |
| 11.1-11.5 | 5  | 100  | 0  | 0 | 0  | 0 | 5  |
| 11.6-12   | 5  | 100  | 0  | 0 | 0  | 0 | 5  |
| >12       | 4  | 80  | 1  | 20 | 0  | 0 | 5  |
| Total     | 32 | 6 | 7 | 45 |

Hb: Hemoglobin, CRT: Chemoradiation, CR: Complete response, PR: Partial response, PD: Progressive Disease

![Figure 1: Comparison of hemoglobin levels in both the arms](image1.png)
a $P = 0.097$. 66% of the patients with Hb <11 had a CR whereas 81% of patients with hemogram >11 had CR [Table 4]. This suggested that patients with Hb >11 had a better clinical response than the patients with anemia with a median follow-up of 5 months. Figure 3 shows the diagrammatic representation of patients with complete and PR as per Hb levels.

**Acute toxicities compared in both the arms**

Figure 4 shows tabulated form of different toxicities seen in both the arms. Grade 2 and 3 toxicities were seen more in adaptive RT (ART) arm than CRT arm. No grade 4 toxicity was seen in both the arms.

**Disease response as per stage**

With regard to CR rates, Stage IIB patients did worse in the CRT group as compared to the ART group-CR (14 patients, 73.6%) versus (22 patients, 88%). However, the difference was not statistically significant ($P = 0.124$). But, Stage IIB patients in CRT group did as well as compared to ART group – CR (15 patients, 71.4% vs. 9 patients, 56.25%).

**DISCUSSION**

According to GLOBOCAN, with an estimated 570,000 cases and 311,000 deaths in 2018 worldwide, cervical cancer ranks as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women. Carcinoma of cervix still pose a major problem in developing countries.\[11\]

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**Table 3: Effect of hemoglobin on response in study group**

| Hb (g %) | ART | CR, n (%) | PR, n (%) | PD, n (%) | Total, n |
|---------|-----|-----------|-----------|-----------|----------|
| <10     | 4   | 66.6      | 2 (33.3)  | 0         | 6        |
| 10.1-10.5 | 8  | (57.14)   | 3 (21.4)  | 3 (21.4)  | 14       |
| 10.6-11 | 10  | (100)     | 0         | 0         | 10       |
| 11.1-11.5 | 5  | (71.42)   | 1 (14.28) | 1 (14.28) | 7        |
| 11.6-12 | 4   | (80)      | 1 (20)    | 0         | 5        |
| >12     | 3   | (100)     | 0         | 0         | 3        |
| Total   | 34  | 7         | 4         | 45        |

Hb: Hemoglobin, ART: Accelerated radiotherapy, CR: Complete response, PR: Partial response, PD: Progressive disease

**Table 4: Response as per hemoglobin irrespective of arm**

| Hb | CR (overall), n (%) | PR (overall), n (%) |
|----|---------------------|--------------------|
| <10| 8 (61.53)           | 4 (30.76)          |
| 10-10.5 | 15 (57.69)     | 4 (15.38)          |
| 10.6-11 | 17 (80.95)     | 2 (9.5)            |
| 11.1-11.5 | 10 (83.33)   | 1 (8.3)            |
| 11.6-12 | 9 (90)            | 1 (10)             |
| >12 | 7 (87.5)          | 1 (12.5)           |
| Total | 66                | 13                 |

Hb: Hemoglobin, CR: Complete response, PR: Partial response

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**Figure 2:** Complete response in both the arms as compared with hemoglobin levels

**Figure 3:** Complete and partial response as per hemoglobin levels

**Figure 4:** Tabulation of all toxicities in chemoradiotherapy and adaptive radiotherapy groups

Anemia is also a major problem in the developing countries with 56% of girls being anemic in India.\[12\] In patients of cervical cancer, anemia can be due to abnormal bleeding, poor nutrition, and anemia due to chronic disease. Hb has been proven to be a prognostic factor in patients of carcinoma cervix where Hb more than 11 g% results in good prognosis. Disease-related anemia is a common hematological manifestation in patients of carcinoma cervix. An independent impact of baseline Hb level on both survival and local control (LC) in cervical cancer has been demonstrated in a number of studies.\[13-16\] where definitions of anemia varied from <10 to <12 g/dl.
According to a study by Yildirim et al.,[17] the 5-year overall survival (OS) was 44% for carcinoma cervix, 71% for Stage IB, 60% for Stage II, and 28% for Stage III. The 5-year disease-free survival (DFS) probabilities were 70%, 59%, and 26%, respectively.[17] On univariate analysis, patients with baseline Hb ≥12 g/dl had significantly better OS than those with baseline Hb of <12 g/dl (median survival was 66.2 vs. 22.2 months, respectively, \( P = 0.0001 \), highly significant). Furthermore, initial Hb level of ≥12 g/dl was also predictive of longer DFS and improved LC (\( P = 0.001 \) and 0.0043, respectively). Distant metastases occurred in 25% and 40% of patients with baseline Hb ≥12 g/dl and <12 g/dl, respectively (\( P = 0.001 \)). A relative decline of Hb level was predictive for DFS (\( P = 0.0132 \)) and for LC (\( P = 0.0222 \)) but not for OS (\( P = 0.262 \)). In multivariate Cox analysis, pretreatment Hb level was the second (after stage of disease and parametrial tumor extension in Stage III) predictive factor for OS and the first for DFS, whereas its effect on LC was at the borderline level (\( P = 0.057 \)). Relative changes of Hb values during RT did not significantly affect survival and LC.[17]

In our study, 60 patients (66.7%) were anemic at presentation and had Hb <11 g%. Of them, 30 patients (50%) were in study arm and rest 30 in control arm. 73% of the patients in accelerated CRT arm with Hb <11 g% had CR while 80% of the patients with Hb >11 g% had CR. In control arm with anemic patients (Hb <11 g%), CR was seen in 60% as compared to 73% patients in study arm and those with Hb >11 g% had CR of 93% as compared to 80% in study arm.

The overall CR was seen in 73% and partial response was seen in 17% of total patients. Irrespective of the arm among the patients with response, CR was seen in 80% of the anemic patients and 89% of the patients with Hb >11 g%.

Some authors[18] reported that anemia does not exert an independent prognostic impact but represents only an epiphenomenon linked to known adverse prognostic factors such as tumor advancement. Tumor hypoxia is considered a possible and attractive radiobiological explanation for increased failure rates in anemic patients, including those with cervical cancer. Hypoxia is known to mediate molecular changes related to cellular processes which may result in increased spontaneous aggressiveness through clonal selection and genomic changes, increased tumor angiogenesis, and relative tumor resistance to therapy. According to some authors, hypoxia-induced treatment failure in advanced SCC of the cervix is primarily caused by hypoxia-induced radiation resistance rather than hypoxia-induced metastases.[19] However, recent data indicate that the relationships between anemia and tumor hypoxia (as well as the effect of transfusion) in patients with cancer are much more complex than considered initially.[18,20]

In a study by Mayr et al.,[15] local recurrence predominated in the group with both a low mean Hb (<11.2 g/dL) and low perfusion, with a 5-year LC rate of 60% versus 90% for all other groups (\( P = 0.001 \)) and a disease-specific survival rate of 41% versus 72% (\( P = 0.008 \)), respectively. In the group with both high mean Hb and high perfusion, the 5-year LC rate and disease-specific survival rate was 100% and 78%, respectively.[15]

The prognostic impact of pretreatment Hb level and its changes during definitive radiotherapy was evaluated by univariate and multivariate analysis in the group of 453 FIGO IB-IIIB cervical cancer patients. Pretreatment anemia (Hb <12 g/dl) was present in 148 patients (33%), and anemia at the end of irradiation in 48%; in 64% of patients Hb level declined during therapy. Median OS in patients with initial Hb ≥12 g/dl was 66 months compared to 22 months in those with lower baseline Hb levels (\( P = 0.0001 \)). This difference was mainly due to increased risk of distant spread in anemic patients (40% compared to 25% in individuals with pretreatment Hb ≥12 g/dl; \( P = 0.001 \)).[21]

In some studies, the change of Hb level during radiotherapy was the strongest prognostic factor for LC and survival in cervical cancer.[13,18] However, the difference of initial and final Hb levels does not predict the Hb levels throughout the treatment. Thus, in a study by Grogan et al.,[14] average weekly nadir Hb levels (calculated by averaging the weekly nadir Hb) during RT was shown to be the second (after tumor stage) most important predictor of survival.

In a study by Thakur et al.,[22] accelerated hyperfractionated radiotherapy with Hb >11 showed better CR than with Hb 10–10.9 g/dL (80% vs. 21.1%) which was statistically significant (\( P = 0.0045 \)). Within the CRT group, there was no significant difference in the outcomes within Hb subgroups (CR rates of 80% vs. 61.9%, \( P = 0.4285 \)).

**Conclusion**

There still remains the controversy that what should be the baseline Hb levels and whether increasing Hb levels with blood transfusions overcome the poor prognostic impact of anaemia. Also, chemoradiation using cisplatin is the standard of treatment for locally advanced cancers of cervix which further cause anemia. These problems

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can be tackled by the use of altered fractionation or it worsens the condition needs to be studied at a higher level. Newer agents for increasing Hb are still investigational.

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**Conflicts of interest**

There are no conflicts of interest.

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