Hematological Toxicity of Accelerated Versus Conventional Radiotherapy with or without Concurrent Chemotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma: A Retrospective Study

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Abstract:

Background: Concurrent chemoradiotherapy (CCRT) is the standard treatment for locally advanced head and neck squamous cell carcinoma (LA-HNSCC). While it improves survival, hematologic toxicity remains a major limitation. Accelerated radiotherapy schedules may intensify myelosuppression by shortening bone marrow recovery intervals. This study compared Grade 3 hematologic toxicity between accelerated and conventional CCRT.

Methods: We retrospectively analyzed 83 biopsy-proven LA-HNSCC patients treated between 2012 and 2022. Eligible patients were 18–70 years old, with ECOG 0–2, normal baseline hematologic and biochemical profiles, and no prior malignancy or distant metastasis. Most received weekly cisplatin (40 mg/m²); five received weekly docetaxel (20 mg/m²) due to cisplatin contraindications. Hemoglobin, leukocytes, lymphocytes, and platelets were assessed weekly and graded per CTCAE v4.0. Patients were grouped as non-toxic (Grade 0–2) or Grade 3 toxic. Logistic regression identified predictors of toxicity.

Results: 83 LA-HNSCC patients were analyzed (42 accelerated vs. 41 conventional radiotherapy). Baseline characteristics were comparable. In radiotherapy-only patients, hematologic changes were minimal, with a slightly higher MCH ($p = 0.029$) and limited Grade 3 leukopenia (25% vs. 0%), indicating negligible marrow suppression. In contrast, accelerated concurrent chemoradiotherapy (CCRT) produced significantly greater myelosuppression, with lower mean hemoglobin ($p = 0.044$), leukocytes ($p = 0.035$), and lymphocytes ($p = 0.047$). Grade 3 anemia, leukopenia, and lymphopenia occurred in 15.4%, 69.2%, and 38.5% of accelerated CCRT patients versus 11.1%, 16.7%, and 11.1% in the conventional CCRT group. Multivariate analysis identified fractionation type as the sole independent predictor of both WBC ($p < 0.001$) and lymphocyte ($p = 0.014$) toxicity.

Conclusion: Accelerated CCRT is associated with higher Grade 3 hematologic toxicity, particularly anemia and lymphopenia. Conventional fractionation is more marrow-sparing. Vigilant monitoring and supportive care are essential to maintain treatment compliance and reduce interruptions.

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Introduction:

Concurrent chemoradiotherapy (CCRT) has long been established as the standard of care for patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC).

The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) demonstrated that adding chemotherapy to radiotherapy improves overall survival by approximately 4.5% at 5 years (HR = 0.88, $p < 0.0001$) [2].

Subsequent meta-analyses confirmed that integrating concurrent chemotherapy with altered fractionation schedules yields superior outcomes compared with altered fractionation alone [3].

Despite these survival benefits, the combination of chemotherapy and radiotherapy significantly increases acute toxicities, particularly hematologic toxicity. Adverse effects such as anemia, leukopenia, neutropenia, and thrombocytopenia frequently occur and may necessitate dose reductions or treatment

interruptions, potentially compromising compliance and local control [4].

Both systemic cytotoxic agents and radiation exposure to active bone marrow contribute to myelosuppression, making the hematopoietic system especially vulnerable [5–7].

Accelerated radiotherapy regimens, which deliver six fractions per week, shorten the overall treatment time and improve tumor control by counteracting accelerated repopulation. However, the reduced interval between fractions may also limit bone marrow recovery, thereby enhancing hematologic toxicity.

While previous studies have extensively examined mucosal and skin toxicities, comparative data on hematologic effects of accelerated versus conventional radiotherapy, particularly when delivered concurrently with chemotherapy, remain limited and inconsistent.

Therefore, this study aimed to evaluate and compare the hematologic toxicity profiles of accelerated versus conventional radiotherapy, with or without concurrent chemotherapy, in patients with LA-HNSCC.

The analysis further sought to identify independent predictors of hematologic toxicity and to determine whether accelerated regimens are associated with increased myelosuppression.

Patients and Methods:

Study Design and Patient Selection

This retrospective study included 83 patients with histologically confirmed LA-HNSCC treated at South Egypt Cancer Institute between 2012 and 2022.

Eligible patients had an ECOG performance status of 0–2, no prior history of radiotherapy or chemotherapy, and normal baseline hematologic parameters.

Patients with distant metastasis, prior malignancy, or baseline cytopenia were excluded from analysis.

Clinical staging was determined according to the AJCC 8th edition TNM classification system.

Treatment Protocol

All patients were treated with three-dimensional conformal radiotherapy (3D-CRT) using Elekta linear accelerators.

Two radiotherapy schedules were used:

Conventional fractionation: 70 Gy in 35 fractions (2 Gy/fraction, 5 fractions/week, over 7 weeks).

Accelerated fractionation: 70 Gy in 35 fractions (2 Gy/fraction, 6 fractions/week, over 6 weeks).

Concurrent chemotherapy was administered to eligible patients as cisplatin 40 mg/m² weekly, beginning from the first day of radiotherapy.

A small subset of patients (n = 5) received docetaxel 20 mg/m² weekly instead of cisplatin due to renal impairment or intolerance.

Supportive care, including hydration, antiemetics, and hematologic monitoring, followed institutional protocols.

Hematologic Monitoring and Toxicity Assessment

Complete blood counts (CBCs) were performed at baseline and weekly during treatment. The parameters analyzed included hemoglobin (Hb), white blood cell count (WBC), and lymphocyte levels.

Hematologic toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Both mean and median values were calculated to evaluate hematologic changes. Patients were grouped as non-toxic (Grade 0–2) or Grade 3 toxic, and logistic regression identified predictors of toxicity.

Statistical Analysis

All data were analyzed using SPSS software version 20.0 (Armonk, NY: IBM Corp, released 2011).

Continuous variables were expressed as mean ± standard deviation (SD) or median (IQR), and compared using Student's t-test or Mann–Whitney U test as appropriate.

Categorical variables were compared using the Chi-square test or Fisher's exact test.

Variables with $p < 0.10$ in univariate analysis were entered into a multivariate logistic regression model to identify independent predictors of hematologic toxicity.

Statistical significance was set at $p < 0.05$.

Results:

Patient Characteristics

A total of 83 patients with LA-HNSCC were analyzed. 42 patients received accelerated radiotherapy (26 with CCRT and 16 radiotherapy alone), while 41 received conventional radiotherapy (18 CCRT and 23 radiotherapy alone). The two groups were comparable in baseline demographic and clinical characteristics, including age, sex, and performance status ($p > 0.05$). Early-stage disease was more frequent in the accelerated arm (26.2% vs. 2.4%, $p = 0.002$) (Table 1).

Hematologic Parameters in Radiotherapy-Only Patients

In patients treated with radiotherapy (RT) alone, hematologic indices were largely similar between accelerated and conventional schedules. As shown in Tables 2 and 3, the only statistically significant difference was a higher mean corpuscular hemoglobin (MCH) in the accelerated RT group (31.08 ± 3.95 pg vs. 28.42 ± 2.83 pg, $p = 0.029$). All other parameters, including hemoglobin, hematocrit, white blood cells (WBCs), lymphocytes, and platelets, showed no significant differences ($p > 0.05$).

Hematologic toxicity in radiotherapy-only patients was generally mild (Table 6). Grade 3 leukopenia occurred in 25% of patients receiving accelerated RT compared with none in the conventional RT group, while Grade 3 anemia and lymphopenia were negligible (0–4.3%). Although this finding suggests a slight marrow stress with treatment acceleration, the overall toxicity remained limited and clinically insignificant. Therefore, accelerated fractionation without

chemotherapy appears to have minimal impact on bone marrow suppression.

Hematologic Parameters in Concurrent Chemoradiotherapy (CCRT) Patients

In the CCRT subgroup, accelerated fractionation was associated with significantly greater hematologic suppression compared with conventional schedules. Mean hemoglobin (9.35 ± 1.13 g/dL vs. 10.32 ± 1.65 g/dL, $p = 0.044$), total WBC count (3.09 ± 0.68 × 10^3/μL vs. 3.89 ± 1.30 × 10^3/μL, $p = 0.035$), and lymphocyte count (1.18 ± 0.75 × 10^3/μL vs. 2.01 ± 1.32 × 10^3/μL, $p = 0.047$) were all significantly lower in the accelerated arm (Tables 4 and 5). Platelet, basophil, eosinophil, and monocyte count showed no significant differences ($p > 0.05$). These findings confirm that the combination of chemotherapy with an accelerated radiotherapy schedule produces a more pronounced myelosuppressive effect.

Grade 3 Hematologic Toxicity (CTCAE v4.0)

Grade 3 hematologic toxicities were rare among patients receiving RT alone but occurred much more frequently in those treated with concurrent chemoradiotherapy (Table 6).

In the accelerated CCRT arm, Grade 3 anemia, leukopenia, and lymphopenia were observed in 15.4%, 69.2%, and 38.5% of patients, respectively.

In contrast, the conventional CCRT group showed markedly lower rates of 11.1%, 16.7%, and 11.1%, respectively.

Among radiotherapy-only patients, Grade 3 events were minimal: anemia (0% vs. 4.3%), leukopenia (25% vs. 0%), and lymphopenia (0% vs. 0%) for the accelerated and conventional schedules, respectively.

These results demonstrate that hematologic toxicity was predominantly treatment-related and significantly aggravated by the concurrent use of chemotherapy and acceleration of radiotherapy delivery.

Comparative Statistical Analysis

As presented in Tables 7–9, no significant associations were found between hemoglobin toxicity and treatment group, sex, age, or stage ($p > 0.05$).

However, WBC toxicity was significantly associated with both fractionation type ($p < 0.001$) and sex ($p = 0.032$), while lymphocyte toxicity was significantly higher in the accelerated group compared with the conventional group ($p = 0.014$). Disease stage and age were not significant predictors for either parameter.

Univariate and Multivariate Logistic Regression

Univariate logistic regression showed that fractionation type, sex, and treatment modality were potential predictors of WBC toxicity. After adjustment, accelerated fractionation remained the only independent predictor of WBC toxicity (OR = 13.7, 95% CI: 3.6–52.1, $p < 0.001$) (Table 11).

Logistic regression analysis revealed that conventional fractionation was significantly associated with a lower risk of lymphocyte toxicity compared with the accelerated schedule ($p = 0.026$, OR = 0.164, 95% CI = 0.034–0.804) (Table 12).

None of the analyzed factors (age, sex, or stage) significantly influenced hemoglobin toxicity (Table 10).

Summary

Accelerated CCRT was associated with the highest degree of hematologic suppression, particularly leukopenia and lymphopenia. Logistic regression confirmed fractionation type as the main independent predictor of both WBC and lymphocyte toxicities. In contrast, accelerated radiotherapy alone produced minimal hematologic effects, emphasizing that the combined acceleration and chemotherapy regimen is the primary driver of Grade 3 hematologic toxicity.

Discussion:

Altered fractionation and concurrent chemotherapy have been widely examined as RT intensification strategies for HNSCC [1,3,8,9]. These interventions primarily aim to counteract accelerated tumor repopulation during treatment, thereby improving locoregional control and overall survival [10]. Despite these benefits, intensification is consistently linked to increased acute toxicity, which may compromise compliance and long-term outcomes [1]. Among the spectrum of adverse events, mucocutaneous and hematologic toxicities are particularly significant [3,9].

Evidence from randomized and non-randomized trials shows that accelerated RT results in higher rates and severity of acute mucosal and cutaneous reactions compared with conventional fractionation [3,8]. Concurrent chemotherapy further increases systemic toxicity due to its cytotoxic and myelosuppressive effects [1,9]. The combined influence of altered fractionation and chemotherapy highlights the need for a therapeutic balance between achieving tumor control and minimizing morbidity [10].

Large clinical trials have clarified these patterns. The DAHANCA 6 and 7 studies demonstrated that administering six weekly fractions at 2 Gy each improved locoregional control and survival without a rise in late complications [8]. The IAEA-ACC trial also supported accelerated RT as both feasible and beneficial for tumor control, although accompanied by a predictable increase in acute toxicity [10]. Findings from the GORTEC 99-02 trial further showed that chemotherapy was the main driver of hematologic and gastrointestinal toxicities, whereas acceleration primarily contributed to mucosal and skin reactions [9]. Collectively, these results suggest that while altered fractionation amplifies acute effects, systemic chemotherapy remains the dominant contributor to hematologic suppression.

Table 1 shows comparable baseline characteristics between groups, with a higher frequency of early-stage disease in the accelerated arm (p = 0.002).

Table 1. Baseline Patient Characteristics According to Treatment Group

	Accelerated (n = 42)	Conventional Radiotherapy (n = 41)	Test of Sig.	p
Sex				
Male	30 (71.4%)	21 (51.2%)	χ^2= 3.577	0.059
Female	12 (28.6%)	20 (48.8%)		
Age (years)				
Min. – Max.	30.0 – 70.0	35.0 – 70.0	t= 0.790	0.432
Mean ± SD.	52.79 ± 11.90	54.66 ± 9.54		
Median (IQR)	55.0 (44.0 – 61.0)	54.0 (50.0 – 60.0)		
PS				
0	13 (31.0%)	18 (43.9%)	χ^2= 1.528	0.466
1	22 (52.4%)	18 (43.9%)		
2	7 (16.7%)	5 (12.2%)		
Tumor stage				
I	3 (7.1%)	1 (2.4%)	χ^2= 11.076*	^{MC}p= 0.014*
II	8 (19.0%)	0 (0.0%)		
III	18 (42.9%)	25 (61.0%)		
IV A	12 (28.6%)	13 (31.7%)		
IV B	1 (2.4%)	2 (4.9%)		
Stage				
Early	11 (26.2%)	1 (2.4%)	χ^2= 9.464*	0.002*
Late	31 (73.8%)	40 (97.6%)		
ccRTH				
No	16 (38.1%)	23 (56.1%)	χ^2= 3.517	0.181
Cisplatin	22 (52.4%)	17 (41.5%)		
Docetaxel	4 (9.5%)	1 (2.4%)		

IQR: Inter quartile range SD: Standard deviation t: Student t-test
χ^2: Chi square test FE: Fisher Exact test MC: Monte Carlo test
p: p value for comparing between the two studied groups
*: Statistically significant at $p \leq 0.05$

As shown in Tables 2 and 3, hematologic parameters were largely comparable between accelerated and conventional radiotherapy schedules. Aside from a higher MCH in the accelerated arm (p = 0.029), no significant differences were observed across other indices (p > 0.05). These results suggest that accelerated fractionation alone does not significantly impact marrow function

Table (2): Comparison between the two studied groups according to different parameters in RTH only cases

	Accelerated RTH only (n = 16)	Conventional RTH only (n = 23)	Test of Sig.	p
RBCs (10^6uL)				
Min. – Max.	3.90 – 6.40	3.50 – 6.70	t= 1.309	0.199
Mean ± SD.	5.27 ± 0.67	4.94 ± 0.82		
Median (IQR)	5.35 (4.85 – 5.85)	4.80 (4.25 – 5.50)		
Hemoglobin (g/dl)				
Min. – Max.	9.30 – 14.20	8.0 – 13.20	t= 1.841	0.074
Mean ± SD.	11.66 ± 1.62	10.76 ± 1.42		
Median (IQR)	11.40 (10.05 – 12.95)	10.50 (9.95 – 11.85)		
Hematocrit (%)				
Min. – Max.	38.20 – 54.0	38.40 – 54.0	t= 1.543	0.131
Mean ± SD.	47.07 ± 6.22	44.30 ± 4.96		
Median (IQR)	48.70 (40.70 – 52.95)	43.70 (39.80 – 48.0)		
MCV (fl)				
Min. – Max.	79.50 – 98.40	79.0 – 97.60	t= 1.021	0.314
Mean ± SD.	89.82 ± 7.28	87.60 ± 6.21		
Median (IQR)	91.20 (82.85 – 97.25)	85.70 (82.10 – 93.70)		
MCH (pg)				
Min. – Max.	25.40 – 36.30	24.90 – 35.10	t= 2.310	0.029
Mean ± SD.	31.08 ± 3.95	28.42 ± 2.83		
Median (IQR)	32.55 (26.30 – 34.10)	27.80 (26.55 – 30.30)		
MCHC (g/dl)				
Min. – Max.	31.60 – 36.70	31.40 – 36.60	t= 0.566	0.575
Mean ± SD.	34.41 ± 1.78	34.08 ± 1.80		
Median (IQR)	34.40 (32.90 – 36.05)	34.80 (32.45 – 35.75)		
RDW (%)				
Min. – Max.	11.30 – 14.70	11.20 – 14.50	t= 0.132	0.896
Mean ± SD.	13.09 ± 1.24	13.14 ± 1.10		
Median (IQR)	13.30 (11.90 – 14.35)	13.50 (12.25 – 14.10)		
Platelets (x 1000/Ul)				
Min. – Max.	75.0 – 570.0	85.0 – 475.0	U= 182.500	0.966
Mean ± SD.	267.6 ± 132.4	266.3 ± 115.8		
Median (IQR)	260.0 (197.0 – 332.50)	245.0 (180.0 – 348.0)		
MPV (fl)				
Min. – Max.	7.20 – 12.40	7.0 – 12.40	t= 0.667	0.509
Mean ± SD.	9.70 ± 1.80	10.06 ± 1.52		
Median (IQR)	9.65 (7.95 – 11.40)	10.30 (9.0 – 11.25)		
WBCs (x1000/uL)				
Min. – Max.	3.90 – 10.50	2.60 – 12.10	U= 178.000	0.877
Mean ± SD.	7.07 ± 2.23	6.93 ± 3.17		
Median (IQR)	7.70 (4.70 – 8.90)	8.40 (3.85 – 9.40)		
Neutrophils (x 1000/u)				
Min. – Max.	1.0 – 6.70	0.50 – 6.70	U= 168.500	0.662
Mean ± SD.	3.50 ± 1.94	3.36 ± 2.25		
Median (IQR)	3.0 (1.50 – 5.35)	3.50 (1.35 – 5.35)		

IQR: Inter quartile range SD: Standard deviation t: Student t-test

U: Mann Whitney test

p: p value for comparing between the two studied groups

*: Statistically significant at $p \leq 0.05$

Table (3): Comparison between the two studied groups according to different parameters in RTH only cases

Parameter	Accelerated RTH only (n = 16)	Conventional RTH only (n = 23)	U	p
Lymphocytes (x1000/u)				
Min. – Max.	0.90 – 3.70	0.70 – 4.0		
Mean ± SD.	2.37 ± 1.04	2.40 ± 1.12	176.500	0.832
Median (IQR)	2.10 (1.75 – 3.55)	2.40 (1.40 – 3.45)		
Basophils (x 1000/u)				
Min. – Max.	0.0 – 0.10	0.0 – 0.10		
Mean ± SD.	0.03 ± 0.04	0.01 ± 0.03	162.000	0.544
Median (IQR)	0.0 (0.0 – 0.05)	0.0 (0.0 – 0.0)		
Eosinophils (x 1000/u)				
Min. – Max.	0.0 – 0.60	0.10 – 0.50		
Mean ± SD.	0.28 ± 0.17	0.27 ± 0.15	176.500	0.832
Median (IQR)	0.30 (0.15 – 0.35)	0.20 (0.10 – 0.40)		
Monocytes (x 1000/u)				
Min. – Max.	0.20 – 1.0	0.20 – 1.0		
Mean ± SD.	0.60 ± 0.29	0.52 ± 0.29	154.500	0.404
Median (IQR)	0.65 (0.35 – 0.80)	0.50 (0.20 – 0.80)		

IQR: Inter quartile range SD: Standard deviation U: Mann Whitney test
p: p value for comparing between the two studied groups

In the concurrent chemoradiotherapy (CCRT) subgroup, as shown in Tables 4 and 5, these findings highlight the hematologic impact of accelerated CCRT, which is primarily manifested as leukopenia and lymphopenia, while erythroid and platelet parameters remained largely preserved.

Table (4): Comparison between the two studied groups according to different parameters in ccRTH cases

	Accelerated ccRTH (n = 26)	Conventional ccRTH (n = 18)	Test of Sig.	p
RBCs (10^6uL)				
Min. – Max.	4.10 – 6.70	2.80 – 6.70	t= 2.327*	0.025*
Mean ± SD.	5.18 ± 0.72	4.59 ± 0.97		
Median (IQR)	5.0 (4.70 – 5.80)	4.50 (4.20 – 5.0)		
Hemoglobin (g/dl)				
Min. – Max.	7.40 – 11.50	8.0 – 13.20	t= 2.156	0.044*
Mean ± SD.	9.35 ± 1.13	10.32 ± 1.65		
Median (IQR)	9.0 (8.70 – 10.20)	10.20 (9.0 – 11.70)		
Hematocrit (%)				
Min. – Max.	38.70 – 54.0	38.70 – 54.0	t= 0.233	0.817
Mean ± SD.	44.22 ± 5.20	43.83 ± 5.75		
Median (IQR)	42.35 (39.70 – 47.80)	40.20 (39.40 – 49.0)		
MCV (fl)				
Min. – Max.	78.90 – 99.10	78.20 – 98.60	t= 0.028	0.978
Mean ± SD.	87.03 ± 6.85	87.09 ± 6.90		
Median (IQR)	84.0 (81.50 – 94.70)	84.90 (81.40 – 94.30)		
MCH (pg)				
Min. – Max.	23.40 – 36.10	24.90 – 33.80	t= 1.311	0.197
Mean ± SD.	30.02 ± 3.93	28.57 ± 3.09		
Median (IQR)	30.25 (26.20 – 33.60)	27.85 (25.70 – 31.60)		
MCHC (g/dl)				
Min. – Max.	31.30 – 39.70	31.20 – 36.20	t= 0.223	0.825
Mean ± SD.	34.16 ± 2.09	34.03 ± 1.58		
Median (IQR)	33.95 (32.40 – 35.50)	34.40 (32.40 – 35.30)		
RDW (%)				
Min. – Max.	11.50 – 14.50	11.20 – 14.50	t= 1.238	0.223
Mean ± SD.	12.85 ± 1.03	12.47 ± 0.97		
Median (IQR)	12.55 (11.90 – 13.70)	12.35 (11.70 – 12.90)		
Platelets (x 1000/Ul)				
Min. – Max.	60.0 – 364.0	65.0 – 420.0	U= 209.000	0.549
Mean ± SD.	165.0 ± 108.2	148.6 ± 105.8		
Median (IQR)	92.50 (80.0 – 247.0)	95.0 (90.0 – 250.0)		
MPV (fl)				
Min. – Max.	7.0 – 11.70	7.20 – 12.50	t= 2.002	0.052
Mean ± SD.	9.12 ± 1.36	9.99 ± 1.49		
Median (IQR)	8.95 (7.90 – 10.10)	9.95 (9.20 – 10.70)		
WBCs (x1000/uL)				
Min. – Max.	2.0 – 4.30	2.30 – 7.30	U= 146.000*	0.035*
Mean ± SD.	3.09 ± 0.68	3.89 ± 1.30		
Median (IQR)	3.0 (2.50 – 3.50)	3.85 (2.90 – 4.60)		
Neutrophils (x 1000/u)				
Min. – Max.	0.40 – 2.0	0.50 – 3.50	U= 146.500*	0.035*
Mean ± SD.	0.85 ± 0.40	1.16 ± 0.69		
Median (IQR)	0.70 (0.50 – 1.20)	0.95 (0.80 – 1.40)		

IQR: Inter quartile range SD: Standard deviation t: Student t-test

U: Mann Whitney test

p: p value for comparing between the two studied groups

*: Statistically significant at $p \leq 0.05$

Table (5): Comparison between the two studied groups according to different parameters in ccRTH cases "Continue"

	Accelerated ccRTH (n = 26)	Conventional ccRTH (n = 18)	U	p
Lymphocytes (x1000/u)				
Min. – Max.	0.30 – 2.90	0.60 – 4.10		
Mean ± SD.	1.18 ± 0.75	2.01 ± 1.32	151.000*	0.047*
Median (IQR)	1.15 (0.50 – 1.90)	1.25 (0.90 – 3.20)		
Basophils (x 1000/u)				
Min. – Max.	0.0 – 0.10	0.0 – 0.10		
Mean ± SD.	0.01 ± 0.03	0.03 ± 0.05	196.000	0.175
Median (IQR)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)		
Eosinophils (x 1000/u)				
Min. – Max.	0.0 – 0.50	0.0 – 0.50		
Mean ± SD.	0.19 ± 0.15	0.26 ± 0.15	173.000	0.135
Median (IQR)	0.15 (0.10 – 0.30)	0.25 (0.10 – 0.40)		
Monocytes (x 1000/u)				
Min. – Max.	0.10 – 1.0	0.10 – 1.0		
Mean ± SD.	0.52 ± 0.31	0.53 ± 0.27	224.000	0.810
Median (IQR)	0.40 (0.30 – 0.90)	0.45 (0.30 – 0.80)		

IQR: Inter quartile range SD: Standard deviation U: Mann Whitney test
p: p value for comparing between the two studied groups

As shown in Table 6, Hematologic toxicities were graded according to CTCAE version 4.0. Grade 3 events were uncommon in radiotherapy-only arms but occurred more frequently among patients receiving concurrent chemoradiotherapy (CCRT).

Table (6): Comparison of Hematologic Toxicities Between Accelerated and Conventional Treatment Groups using CTCAE v4.0

Parameter	Treatment Group	Subgroup	No. of Patients	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)
Hemoglobin (g/dl)	Accelerated (n = 42)	Radiotherapy only (n = 16)	16	2 (12.5%)	3 (18.8%)	0 (0%)
		CCRT (n = 26)	26	6 (23.1%)	10 (38.5%)	4 (15.4%)
	Conventional (n = 41)	Radiotherapy only (n = 23)	23	5 (21.7%)	4 (17.4%)	1 (4.3%)
		CCRT (n = 18)	18	3 (16.7%)	5 (27.8%)	2 (11.1%)
WBCs ($\times 10^3/\mu L$)	Accelerated (n = 42)	Radiotherapy only (n = 16)	16	0 (0%)	0 (0%)	4 (25%)
		CCRT (n = 26)	26	3 (11.54%)	5 (19.23%)	18 (69.23%)
	Conventional (n = 41)	Radiotherapy only (n = 23)	23	1 (4.3%)	0 (0%)	0 (0%)
		CCRT (n = 18)	18	2 (11.1%)	2 (11.1%)	3 (16.7%)
Lymphocytes ($\times 10^3/\mu L$)	Accelerated (n = 42)	Radiotherapy only (n = 16)	16	3 (18.8%)	2 (12.5%)	0 (0%)
		CCRT (n = 26)	26	13 (50.0%)	3 (11.5%)	10 (38.5%)
	Conventional (n = 41)	Radiotherapy only (n = 23)	23	4 (17.4%)	3 (13.0%)	0 (0%)
		CCRT (n = 18)	18	10 (55.6%)	5 (27.8%)	2 (11.1%)

CTCAE v4.0: *Common Terminology Criteria for Adverse Events, version 4.0*

No significant associations were found between hemoglobin toxicity and treatment group, sex, age, or tumor stage ($p > 0.05$) as shown in Table 7. Toxicity was slightly more frequent with accelerated radiotherapy and in males, but the differences were not statistically significant.

Table (7): Relation between Toxicity profile of hemoglobin with different parameters in total sample (n = 83)

	Toxicity profile of hemoglobin		Test of Sig.	p
	Non-Toxic (n = 76)	Toxic (n = 7)		
Groups				
Accelerated	38 (50.0%)	4 (57.1%)	χ^2= 0.131	^{FE}p= 1.000
Conventional Radiotherapy	38 (50.0%)	3 (42.9%)		
Sex				
Male	46 (60.5%)	5 (71.4%)	χ^2= 0.322	^{FE}p= 0.701
Female	30 (39.5%)	2 (28.6%)		
Age (years)				
Min. – Max.	30.0 – 70.0	35.0 – 70.0	t= 1.289	0.201
Mean ± SD.	52.79 ± 11.90	54.66 ± 9.54		
Median (IQR)	55.0 (44.0 – 61.0)	54.0 (50.0 – 60.0)		
Stage				
Early	12 (15.8%)	0 (0.0%)	χ^2= 1.292	^{FE}p= 0.586
Late	64 (84.2%)	7 (100.0%)		

IQR: Inter quartile range SD: Standard deviation t: Student t-test
χ^2: Chi square test FE: Fisher Exact test MC: Monte Carlo test
p: p value for Relation between toxicity profile of hemoglobin with different parameters

As shown in Table 8, Accelerated fractionation, female sex, and advanced disease stage are key factors associated with increased WBC toxicity, underscoring the multifactorial nature of hematologic suppression during intensified treatment protocols.

Table (8): Relation between Toxicity profile of WBCs with different parameters in total sample (n = 83)

	Toxicity profile of WBCs		Test of Sig.	p
	Non-Toxic (n = 58)	Toxic (n = 25)		
Groups				
Conventional Radiotherapy	39 (67.2%)	3 (12.0%)	χ^2= 21.328*	<0.001*
Accelerated	19 (32.8%)	22 (88.0%)		
Sex				
Male	40 (69.0%)	11 (44.0%)	χ^2= 4.596*	0.032*
Female	18 (31.0%)	14 (56.0%)		
Age (years)				
Min. – Max.	30.0 – 70.0	39.0 – 70.0	t= 0.625	0.534
Mean ± SD.	53.22 ± 11.24	54.84 ± 9.74		
Median (IQR)	54.50 (45.0 – 61.0)	55.0 (50.0 – 60.0)		
Stage				
Early	12 (20.7%)	0 (0.0%)	χ^2= 6.047*	^{FE}p= 0.015*
Late	46 (79.3%)	25 (100.0%)		

IQR: Inter quartile range SD: Standard deviation t: Student t-test
χ^2: Chi square test FE: Fisher Exact test MC: Monte Carlo test
p: p value for Relation between toxicity profile of WBCs with different parameters
*: Statistically significant at $p \leq 0.05$

As demonstrated in Table 9, Lymphocyte toxicity was significantly higher in the accelerated treatment group compared with the conventional group (p = 0.014). No significant associations were observed with sex, age, or disease stage.

Table (9): Relation between Toxicity profile of lymphocytes with different parameters in total sample (n = 83)

	Toxicity profile of lymphocytes		Test of Sig.	p
	Non-Toxic (n = 71)	Toxic (n = 12)		
Groups				
Accelerated	32 (45.1%)	10 (83.3%)	χ^2= 6.012*	0.014*
Conventional Radiotherapy	39 (54.9%)	2 (16.7%)		
Sex				
Male	41 (57.7%)	10 (83.3%)	χ^2= 2.837	FEp= 0.117
Female	30 (42.3%)	2 (16.7%)		
Age (years)				
Min. – Max.	31.0 – 70.0	30.0 – 70.0	t= 0.042	0.966
Mean ± SD.	53.69 ± 10.71	53.83 ± 11.65		
Median (IQR)	54.0 (45.0 – 61.0)	55.0 (47.0 – 60.50)		
Stage				
Early	11 (15.5%)	1 (8.3%)	χ^2= 0.425	FEp= 1.000
Late	60 (84.5%)	11 (91.7%)		

IQR: Inter quartile range SD: Standard deviation t: Student t-test
χ^2: Chi square test FE: Fisher Exact test MC: Monte Carlo test
p: p value for Relation between toxicity profile of lymphocytes with different parameters
*: Statistically significant at $p \leq 0.05$

As shown in Table 10, None of the evaluated factors significantly influenced hemoglobin toxicity (p > 0.05). Although higher odds were noted with accelerated radiotherapy and male sex, these associations were not statistically significant.

Table (10): Logistic regression for hemoglobin toxicity.

	Univariate	
	p	OR (LL – UL 95%C.I)
Groups		
Conventional Radiotherapy®		1.000
Accelerated	0.718	1.333 (0.279 – 6.364)
Male	0.574	1.630 (0.297 – 8.953)
Age (years)	0.206	1.053 (0.972 – 1.141)
Tumor Stage		
Early		1.000
Late	NA	–

OR: Odd`s ratio
C.I: Confidence interval LL: Lower limit UL: Upper Limit
#: All variables with p<0.05 was included in the multivariate

As shown in Table 11, logistic regression analysis demonstrated that accelerated fractionation remained a strong and independent predictor of WBC toxicity, regardless of patient sex or age.

Table (11): Logistic regression analysis for the parameters affecting Toxicity profile of WBCs (No. of toxic =25 vs. no. of Non-toxic=58)

	Univariate		Multivariate	
	p	OR(LL – UL 95%C.I)	p	OR(LL – UL 95%C.I)
Groups				
Conventional®		1.000		1.000
Accelerated Radiotherapy	<0.001*	15.053(4.001 – 56.634)	<0.001*	13.696 (3.600 – 52.104)
Female	0.035*	2.828 (1.077 – 7.431)	0.175	2.152 (0.710 – 6.518)
Age (years)	0.529	1.014 (0.970 – 1.060)		
Tumor Stage				
Early®		1.000		
Late	NA			

OR: Odd`s ratio
C.I: Confidence interval LL: Lower limit UL: Upper Limit
#: All variables with p<0.05 was included in the multivariate

As demonstrated in Table 12, logistic regression analysis showed that conventional fractionation was significantly associated with a lower risk of lymphocyte toxicity compared with accelerated schedules.

Table (12): Univariate Logistic regression analysis for the parameters affecting Toxicity profile of lymphocytes (No. of toxic =12 vs. no. of Non-toxic=71)

	Univariate	
	p	OR (LL – UL 95%C.I)
Groups		
Accelerated®		1.000
Conventional Radiotherapy	0.026*	0.164 (0.034 – 0.804)
Female	0.110	0.273 (0.056 – 1.340)
Age (years)	0.966	1.001 (0.946 – 1.060)
Tumor Stage		
Early®		1.000
Late	0.522	2.017 (0.236 – 17.238)

OR: Odd`s ratio
C.I: Confidence interval LL: Lower limit UL: Upper Limit
#: All variables with p<0.05 was included in the multivariate

Hematological toxicity represents a frequent and clinically significant adverse effect of radiotherapy, particularly when combined with chemotherapy in patients with HNSCC. In the present study, hematological toxicities were more pronounced in the accelerated chemoradiotherapy group compared with the conventional arm, suggesting that treatment intensification exacerbates myelosuppression. This observation is consistent with prior reports indicating that shortening overall treatment time limits bone marrow recovery and thereby amplifies hematological toxicity [11–13].

Several comparative studies have evaluated the hematological impact of altered or accelerated fractionation. Chauhan et al [11] reported no significant overall differences between altered fractionation and conventional CRT, although grade 1 anemia and leukopenia occurred more often in the conventional arm. Specifically, 17.3% of patients in the altered fractionation arm developed grade 1 anemia compared with 25.3% in the conventional group, and grade 2 anemia was observed exclusively in the conventional group (5.5%, p = 0.039). Likewise, leukopenia was slightly more frequent in the conventional arm (13.3% vs 8%), though the difference was not statistically significant.

In contrast, Sharma et al [12] demonstrated that hematological toxicities (grades I–IV) were significantly higher in the CRT group compared with concomitant boost RT (p = 0.0004). Similarly, Wozniak et al [13] reported that postoperative CRT resulted in greater hematologic suppression, including significantly lower mean hemoglobin and WBC counts, compared

with accelerated postoperative RT alone ($p < 0.00001$ for both parameters).

Our findings are consistent with other studies demonstrating that CRT induces significant reductions in hemoglobin, leukocytes, lymphocytes, and platelets [14–16]. However, a slightly higher RBC count accompanied by lower hemoglobin was observed, likely reflecting incidental variation related to timing differences or incomplete hematologic follow-up rather than a true physiological effect of treatment. Ahmadsei et al [14] observed that patients undergoing multiple radiotherapy courses had significantly reduced hemoglobin and lymphocyte levels compared with healthy controls ($p \leq 0.03$), changes that correlated with higher fatigue scores and impaired quality of life. Romdhoni et al [15] similarly reported significant declines in MCHC, total leukocytes, lymphocytes, and platelets after a full RT course (all $p < 0.05$).

Notably, reductions in hemoglobin and lymphocyte counts have been linked to increased fatigue and reduced treatment tolerance [14]. Mashhour et al [16] reported that 27.5% of patients developed grade 3 neutropenia, and induction chemotherapy significantly increased the likelihood of both severe hematologic and non-hematologic toxicities ($p = 0.001$ and 0.058, respectively). These results parallel our observation that the addition of chemotherapy further intensified marrow suppression in the accelerated RT setting.

Radiation-induced lymphopenia (RIL) warrants special emphasis, as it is one of the most consistently observed hematologic sequelae of RT, with grade ≥3 lymphopenia reported in up to 70% of patients [17,18]. Lymphocytes are highly radiosensitive, with a 50% lethal dose of only 1–2 Gy [19], explaining why significant declines often occur as early as the first treatment week [18]. High-grade RIL has been linked to inferior survival across several tumor types, including HNSCC [20–22]. Its severity is influenced by baseline lymphocyte count, chemotherapy use, tumor volume, dose to lymphoid organs, and treatment duration [18,23]. Our finding of significantly lower lymphocyte counts in the accelerated arm supports this evidence, suggesting that shorter interfraction intervals may exacerbate lymphocyte depletion and compromise immune competence.

The clinical consequences of hematological toxicity are substantial. Severe cytopenias often necessitate treatment interruptions, chemotherapy dose reductions, or omission of cycles, which can undermine tumor control and survival [13]. Although accelerated fractionation theoretically improves tumor control by limiting repopulation, this advantage may be negated if toxicity-related breaks occur, as reported in both HNSCC and cervical cancer populations [1,11].

Strategies to mitigate hematological toxicity include weekly hematologic monitoring, early use of supportive measures such as transfusions or growth factors, and the application of bone marrow-sparing RT techniques [24,25]. Konnerth et al [24], in a systematic review of cervical cancer CRT, reported that sparing active pelvic bone marrow significantly reduced grade ≥3 hematologic toxicity. Although evidence in HNSCC remains limited, similar avoidance strategies targeting vertebral bone marrow and circulating blood pools may be feasible. Though these approaches have been more extensively studied in pelvic and thoracic malignancies, their principles are increasingly applicable to HNSCC, given the cumulative myelosuppressive effects of chemoradiotherapy.

These findings highlight the importance of close hematologic monitoring during accelerated CCRT. Regular weekly complete blood count assessments, along with early intervention using growth factors or transfusions when indicated, may help prevent treatment interruptions and maintain chemotherapy dose intensity.

Conclusion:

Hematologic toxicity is a significant consideration in head and neck radiotherapy, especially with concurrent chemotherapy. Its severity depends on radiation technique, chemotherapy regimen, and individual patient factors. Careful monitoring, minimizing unnecessary marrow exposure, and judicious selection of systemic agents can mitigate risks and support optimal treatment outcomes.

Limitations:

The main limitations of this study include its retrospective design, single-center data source, and moderate sample size, which may restrict the generalizability of the findings. However, both univariate and multivariate logistic regression analyses were conducted to control for potential confounders, confirming that fractionation type independently predicts hematologic toxicity.

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