

Impact of Pre-Radiotherapy and/or Chemoradiotherapy Hemoglobin Level on Response to Treatment in Laryngeal and Hypopharyngeal Squamous Cell Carcinoma

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Abstract

Background: Anemia is reported by many studies as an important risk factor for poor locoregional disease control and survival in head and neck carcinoma. We aimed to study the frequency and prognostic effect of low hemoglobin (Hb) level in head and neck squamous cell carcinoma (HNSCC) before radiotherapy (RT) and/or chemoradiotherapy (CRT). **Material and Methods:** We retrospectively studied the charts of 86 patients diagnosed with laryngeal and hypopharyngeal SCC in a university hospital in Cairo, Egypt. Based on the World Health Organization (WHO), anemia was diagnosed in males at Hb levels < 13 g/dl and <12 g/dl in females. We examined the Hb levels before radiotherapy alone or combined with chemotherapy and its impact on response to treatment and survival. **Results:** The median age was 56 years. 75/86 (87.2%) patients were males with performance status 1 in 73/86 (84.9%) patients. The median Hb level was 13.1 g/dl. The pre-RT/CRT Hb level in female patients (n = 11) was <12g/dl in 4/11 (36.4%) and >12 g/dl in 7/11 (63.6%) patients. Pre-RT/CRT Hb level in male patients was <13 g/dl in 31/75 (41.3%) and >13 g/dl in 44/75 (58.7%). Tumor sites were larynx in 77 (89.5%) and hypopharynx in 9 (10.5%) patients. Disease stage 3, 4 was common in 59/86 (68.6%) patients. Thirty-six (41.8%) patients had surgery. 13/86 (15.1%) patients received induction chemotherapy, while 31/86 (36.0%) had concomitant chemoradiotherapy. Radiotherapy was given in 65/86 (75.58%) patients. The mean RT dose was 66 Gy. Non-anemic patients had significant higher inci-

dence of complete response (CR) to treatment ($p = 0.034$). 25.8% of male patients with Hb < 13 g/dl had higher incidence of recurrence ($p = 0.036$) compared to recurrence in 39.5% of male patients with Hb > 13 g/dl ($p = 0.403$). Female patients whether anemic or non-anemic had no recurrence ($p = 0.036$ and $p = 0.403$ respectively). The median duration of DFS and OS was 6.52 and 9.33 months respectively. Pretreatment Hb level had statistical significant effect on response to treatment and overall survival, but not disease free survival. **Conclusion:** Nutritional anemia is common in developing countries. Our results support the positive prognostic effect of Hb level > 12 g/dl and > 13 g/dl before radiation therapy and/or chemoradiotherapy on response to treatment and overall survival but not the disease free survival.

Keywords

Hemoglobin, Radiotherapy, Chemotherapy, Tumor Hypoxia, Local Control, Survival

1. Introduction

Head and neck squamous cell carcinoma HNSCC is a locoregional disease [1], where radiation therapy has a major role in achieving locoregional control whether alone, after surgery or concurrent with chemotherapy [2] [3].

Anemia is a frequent problem in cancer patients that may develop before, during, or after treatment. The incidence of anemia among cancer patients at diagnosis was more than 40% and 67% of patients developed anemia during chemotherapy [4]. The incidence of cancer related anemia depends on the type of malignancy, disease stage, duration of the disease, type and intensity of treatment, surgery, and infections [5].

Hemoglobin Hb level has been identified as one of the strong prognostic factors for tumor control and survival in HNSCC [6]-[13]. Anemia also has negative effect on the quality of life of cancer patients [14]. The prognostic value of anemia was studied at different treatment times in patients with HNSCC. Findings from most studies in HNSCC have consistently found that a low pretreatment Hb level is a predictor factor of local control and survival after radiotherapy [12]. The incidence of anemia markedly increases when radiation is combined with chemotherapy [15] [16].

Low hemoglobin levels during radiotherapy and post-treatment were also found to affect treatment outcome for HNSCC [17] [18], [11] although not as much investigated as pretreatment anemia. Pre-operative anemia plays a significant role in overall survival [19], where low Hb levels impair tumor oxygenation thus reducing the effect of chemotherapy and radiotherapy [20] [21]. Post-operative anemia was shown to be an independent prognostic factor for local recurrence in locally advanced HNSCC [19] [22].

The range of Hb levels considered optimal for tumor oxygenation was re-

ported by most studies to be 12 - 14 g/dL [12] [23]. The etiology of anemia may be multifactorial; the malignancy itself, a complication of the treatment, or the result of an associated comorbidity [24]. Iron deficiency anemia ID is the most common cause of anemia in both solid and hematologic malignancies [25] [26], particularly in low-middle income countries [26]. The prevalence of ID anemia was higher in patients with poor performance status, advanced tumor stage, after chemotherapy, and in persistent or progressive disease [27].

Anemia contributes to hypoxia. Radiation interacts with oxygen to form labile free radicals to kill tumor cells. Anemia decreases the blood oxygen-carrying capacity, and may result in intratumoral hypoxia which compromises the outcome of radiotherapy in various malignancies even the small tumors [15]. Tumor hypoxia and anemia are both independent prognostic indicators of disease free and overall survival in solid tumors, including HNSCC. Hypoxia promotes progression of tumors via hypoxia inducible factor 1 pathway (HIF-1) which in turn up regulates factors that control angiogenesis, apoptosis, and tumor growth [28] [29].

The aim of this study was to investigate the effect of pre-radiotherapy and/or chemotherapy hemoglobin level on local control and survival of patients with laryngeal and hypopharyngeal SCC.

2. Material and Methods

We retrospectively reviewed the charts of 86 patients diagnosed with laryngeal and hypopharyngeal SCC who presented to the head and neck unit at the Department of Clinical Oncology, Ain-Shams University Hospitals during the period from 2009-2013. The patients were referred from the ENT Department, Ain-Shams University Hospitals where they were diagnosed and some of them were operated on. The approval of the Ethical Committee of the Faculty of Medicine, Ain-Shams University was obtained. The patients were considered anemic if pre-RT/CRT hemoglobin was <12 g/dl in females and <13 g/dl in males according to the WHO criteria for anemia [30]. Performance was assessed using the Eastern Cooperative Oncology Group ECOG. Revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [31] was used to assess response to treatment as complete response CR or no CR. Acute toxicity during radiotherapy was graded according to the RTOG radiation toxicity criteria [32].

Patient evaluation and staging work-up included complete history, physical examination, endoscopic examination, laboratory and as well as the radiological investigations (chest radiography, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the primary tumor site and the neck). Patients with hemoglobin levels < 9 - 10 g/dL received packed red cell blood transfusion and/or iron supplements. Stage designation was based on the American Joint Committee on Cancer (AJCC) Staging Criteria 7th Edition [33]. CT neck was done 8 - 10 weeks post treatment to assess response, and then repeated during

follow-up.

3. Statistical Analysis

It was done using the Statistical Package for the Social Sciences (SPSS) version 20. The qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges when their distribution was parametric while non-parametric data were presented as median with interquartile range (IQR). Comparison of categorical variables was carried by using Chi-square test. DFS was calculated from date of start of radiotherapy and/or chemoradiotherapy till date of recurrence. OS was calculated from date of pathological diagnosis till date of last follow-up or death. The confidence interval was set to 95%. P-value < 0.05 was considered statistical significance.

4. Results

Eighty-six patients pathologically diagnosed with laryngeal and hypopharyngeal SCC were included in the study. The mean age was 56 years (range 27 - 80). The cohort had more male patients, 75/86 (87.2%) and ECOG performance status (PS) 1 in 73/86 (84.9%) patients. Laryngeal SCC (supraglottic SCC in 42 patients, glottic SCC in 33 patients and subglottic SCC in 2 patients) was the commonest tumor site in 77/86 (89.5%) patients. Tumor characteristics showed predominance of T3 in 33/86 (38.4%) patients, and N0 in 51/86, (59.3%) patients. Only 3 patients (3.5%) had metastatic disease (M1) from the start and 42/86 (48.8%) patients had stage 4. The median pre-RT/CRT Hb was 13.1 g/dl (range 11.9 - 14.2). Most of female patients 7/11 (63.6%) had Hb > 12 g/dl, and most male patients 44/75 (58.7%) had Hb > 13 g/dl (**Table 1**). By the end of the follow-up duration of 9.33 months, 59 patients (86.6%) were alive and 27 (31.4%) patients were dead.

Table 2 shows the summary of treatment. Surgery was the primary treatment in 36/86 (41.8%) patients; total laryngectomy and neck dissection was the commonest type performed in 15/86 (17.4%) patients. Most of the patients 65/86 (76%) received some form of radiotherapy (RT), where RT (adjuvant or definitive) was administered in 34/86 (39.53%) patients while concomitant chemoradiotherapy (CCRT) (adjuvant or definitive) was indicated in 31/86 (36.05%) patients. Fractionation was conventional (200 cGy/fraction) in most of the patients, and hypofractionated (2.25 cGy/fraction) in 4 glottic SCC patients. The mean radiation dose was 66 Gy. Mucositis during radiotherapy occurred in 52/65 (80%) of irradiated patients. The Indications of chemotherapy included induction, and concurrent with radiotherapy. Only 13/86 (15.1%) patients received induction chemotherapy. The induction regimens included TP (taxotere/cisplatin) q 21 days for 3 cycles, TPF (taxotere, cisplatin, 5-fluorouracil 5 FU) q 21 days for 3 cycles, and taxotere/carboplatin q 21 days for 3 cycles. 31/86 (36.0%) patients received concomitant chemotherapy; cisplatin 100 mg/m², weekly cisplatin 30 - 50 mg/m² or weekly carboplatin (AUC 1.5).

Table 1. Patient and tumor characteristics.

Age		
Median (IQR)		56 (50 - 66)
Range		27 - 80
ECOG		
0		1 (1.2%)
1		73 (84.9%)
2		12 (14.0%)
Gender		
Male		75 (87.2%)
female		11 (12.8%)
Site		
Larynx		77 (89.5%)
Hypopharynx		9 (10.5%)
Grade		
1		14 (16.3%)
2		61 (70.9%)
3		11 (12.8%)
Tumor T-stage		
1		11 (12.8%)
2		26 (30.2%)
3		33 (38.4%)
4		16 (18.6%)
Nodal N-stage		
0		51 (59.3%)
1		5 (5.8%)
2		26 (30.2%)
3		4 (4.7%)
AJCC stage		
1		11 (12.8%)
2		16 (18.6%)
3		17 (19.8%)
4		42 (48.8%)
Pretreatment hemoglobin (g/dl)		
Median (IQR)		13.1 (11.9 - 14.2)
<13 (male)		31 (41.3%)
>13 (male)		44 (58.7%)
<12 (female)		4 (36.4%)
>12 (female)		7 (63.6%)
Median follow-up duration		9.33 (4.2 - 17.7)

ECOG: Eastern Cooperative Oncology Group, AJCC: American Joint Committee on Cancer.

Table 2. Treatment characteristics.

	No.	%
Surgery		
Total laryngectomy and ND	15	17.4%
Total laryngectomy	13	15.1%
Other	8	9.3%

Continued

No	44	51.2%
NA	6	7.0%
Induction chemotherapy		
No	65	75.6%
NA	8	9.3%
TPF	6	7.0%
TP	3	3.5%
Cisplatin/5 Fluorouracil	4	4.7%
Carboplatin/5 Fluorouracil	0	0.0%
Concurrent chemotherapy		
No	47	54.7%
NA	8	9.3%
Cisplatin	15	17.4%
Carboplatin	16	18.6%
Radiotherapy RT		
No	13	15.1%
NA	8	9.3%
Alone (Adjuvant-definitive)	34	39.5%
Concurrent (Adjuvant-definitive)	31	36.0%
Acute RT toxicity		
No	17	19.8%
NA	7	8.1%
Mucositis	52	60.5%
Skin reaction	10	11.6%

NA: Not Available, ND: Nodal Dissection.

Table 3 depicts the response to treatment where 25/86 (29.1%) patients developed local recurrence. None of the patients developed distant metastases till the end of the study period. After a median follow-up duration of 9.33 months, the median DFS of the patients was 6.52 months while the median OS was 9.33 months.

We studied the prognostic factors affecting response to treatment complete response (CR) versus no CR as shown in (**Table 4**). The treatment data were reported for 80/86 patients as 6/86 (7%) patients' charts were incomplete. 46/86 (53.5%) patients achieved CR whereas 34/86 (39.5%) patients had no CR. Significant factors were T-stage, N-stage, gender and pre-RT/CRT Hb level. The incidence of CR was ($p = 0.010$) higher in male (95.7%) than female patients (4.3%). Both CR and no CR occurred more in patients with pre-RT/CRT Hb levels > 13 and >12 g/dl ($p = 0.034$). 41/46 (89.1%) patients with laryngeal SCC responded

to treatment by CR versus 24/34 (70.6%) patients who had no CR ($p = 0.036$). On the other hand hypopharyngeal SCC tumors had higher rates of no CR 10/34 (29.4%) than CR in 5/46 (10.9%) ($p = 0.036$) patients. AJCC Stage 3, 4 responded to treatment by no CR in 85.3% of patients, whereas stages 1, 2 achieved more CR in 45.7% of patients ($p = 0.003$).

Analysis of the prognostic factors affecting DFS and OS showed that age, gender, performance status at presentation, N-stage and pre-RT/CRT Hb level significantly influenced OS, but none of the studied factors were significantly predictive of DFS (**Table 5, Figures 1-5**). Patients < 56 years had longer median OS of 32.567 months than patients > 56 years who survived for a median of 15.900 months ($p = 0.039$). Median OS of male and female patients was 26.567, and 11.433 months respectively ($p = 0.000$). Patients with N0 and N1 disease had median OS 28.290 months, and 18.227 months respectively ($p = 0.031$). The median DFS of patients with pre-RT/CRT anemia versus no anemia was comparable 19.442, 19.496 months respectively ($p = 0.233$). Non-anemic patients had significantly better median OS compared to anemic patients (44.134 and 38 months respectively, $p = 0.000$).

Table 3. Treatment results.

Variable	Frequency
Complete response (CR)	46 (53.5%)
No complete response (No CR)	34 (39.5%)
NA	6 (7.0%)
Recurrence	25 (29.1%)
Status at last follow-up visit	
Alive	59 (68.6%)
Dead	27 (31.4%)
Disease free survival (DFS) median (IQR)	6.52 (3.27 - 12.37)
Overall survival (OS) median (IQR)	9.33 (4.2 - 17.67)

IQR: Inter Quartile Range.

Table 4. Prognostic factors of response to treatment.

		CR (n = 46)		No CR (n = 34)		Test value	p-value	Significance
		No.	%	No.	%			
Age	<56 years	19	41.3%	18	52.9%	1.065	0.302	NS
	>56 years	27	58.7%	16	47.1%			
Gender	Male	44	95.7%	26	76.5%	6.577	0.010	S
	Female	2	4.3%	8	23.5%			
Site of the tumor	Larynx	46	100.0%	26	76.5%	12.026	0.001	HS
	Hypopharynx	0	0.0%	8	23.5%			
T-staging	T 1 + 2	25	54.3%	10	29.4%	4.94	0.026	S

Continued

	T 3 + 4	21	45.7%	24	70.6%			
N-stage	N0	34	73.9%	13	38.2%	10.269	0.001	HS
	N1, 2, 3	12	26.1%	21	61.8%			
Stage	1 + 2	21	45.7%	5	14.7%	8.534	0.003	HS
	3 + 4	25	54.3%	29	85.3%			
Pre -RT/CRT Hb level	<13	19	41.3%	10	29.4%	8.689	0.034	S
	<12	0	0.0%	3	8.8%			
	>13	25	54.3%	16	47.1%			
	>12	2	4.4%	5	14.7%			

Table 5. Prognostic factors of DFS and OS.

		No.	Mean	SD	OS (median) (months)	p-value	DFS (median) (months)	p-value
Age	<56 years	41	13	2	32.567	0.039	25.000	0.785
	>56 years	45	12.9	1.9	15.900		20.000	
Gender	Male	75	13.1	1.9	26.567	0.000	9.584	0.066
	Female	11	11.7	1.8	11.433		9.545	
Performance at presentation	1	73	13.1	1.9	26.567	0.002	20.000	0.120
	2	12	11.9	1.9	11.567		-	
Treatment	RT	34	13.4	1.6	24.567	0.907	20.200	0.731
	CCRT	31	12.8	2.1	18.667		17.200	
RT dose	<66	45	12.8	1.8	24.567	0.569	-	0.131
	>66	20	13.6	1.9	26.567		20.200	
Surgery	Yes	36	13.1	1.9	25.000	0.059	20.000	0.724
	No	44	12.8	2	14.700		13.200	
Grade	1	14	13.5	1.9	36.571	0.155	30.946	0.306
	2	61	12.9	2	22.175		20.685	
	3	11	12.6	1.9	22.447		20.028	
T-stage	1, 2	37	13.5	2	28.790	0.554	26.621	0.299
	3, 4	49	12.5	1.8	23.530		20.940	
N-stage	0	51	13.2	1.9	28.290	0.031	25.228	0.647
	1	35	12.6	1.9	18.227		17.824	
M	0	83	13	2	23.592	0.365	22.048	0.735
	1	3	13	0.8	27.522		23.889	
AJCC stage	1, 2	27	14.01	1.7	32.019	0.297	33.64	0.085
	3, 4	59	12.48	1.9	23.004		20.15	
Pre-RT/CRT Hb level	<12	4	9.9	1.9	11.433	0.000	11.292	0.233
	<13	31	11.4	1.3	26.567		8.150	
	>12	8	12.8	0.5	11.567		8.925	
	>13	43	14.4	1.1	32.567		10.571	

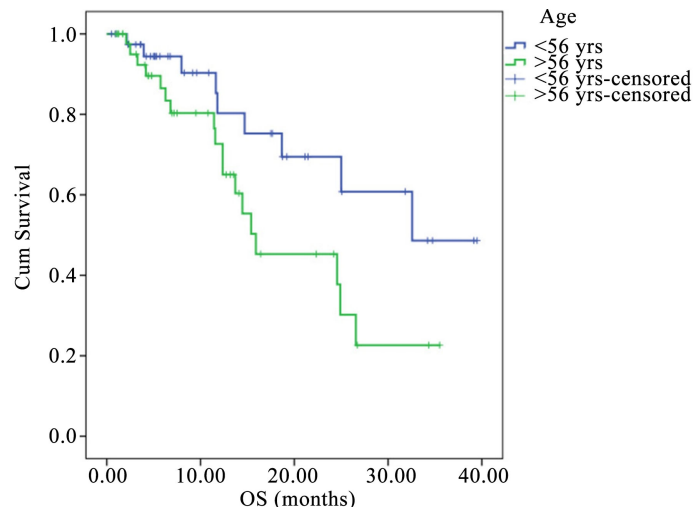


Figure 1. Effect of age on OS.

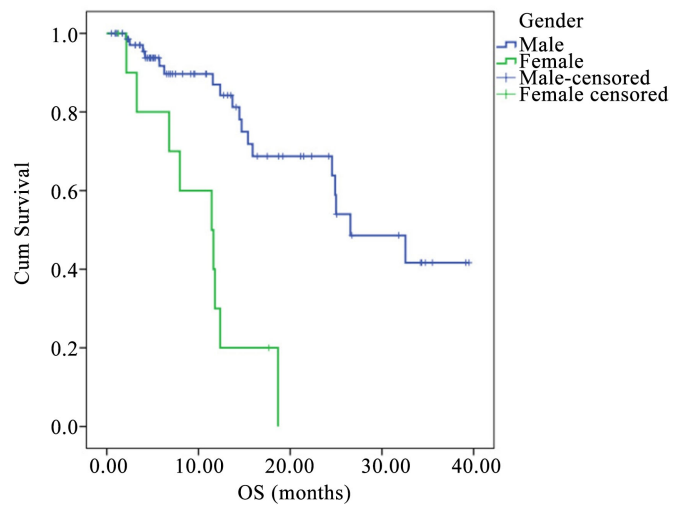


Figure 2. Effect of gender on OS (n = 86).

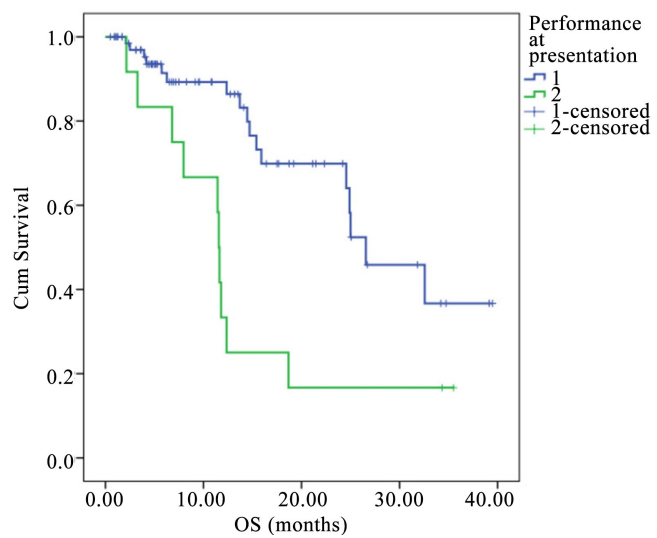


Figure 3. Effect of performance on OS (n = 86).

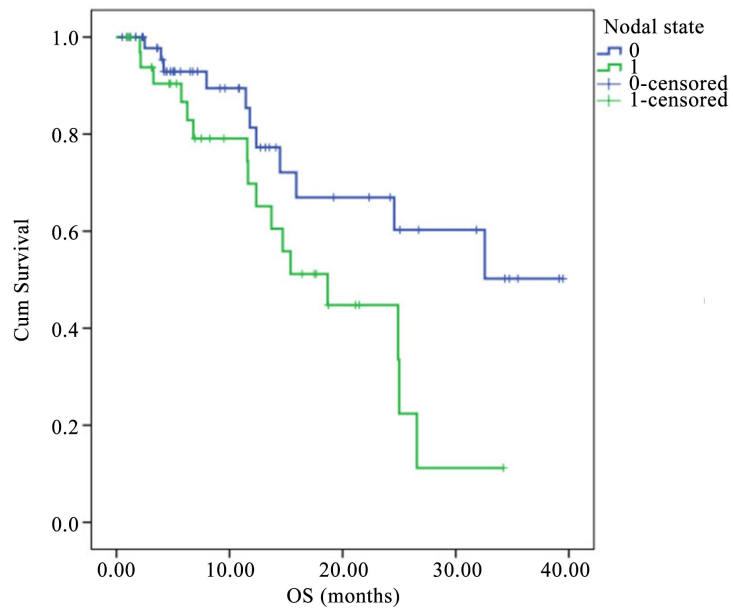


Figure 4. Effect of nodal stage on OS (n = 86).

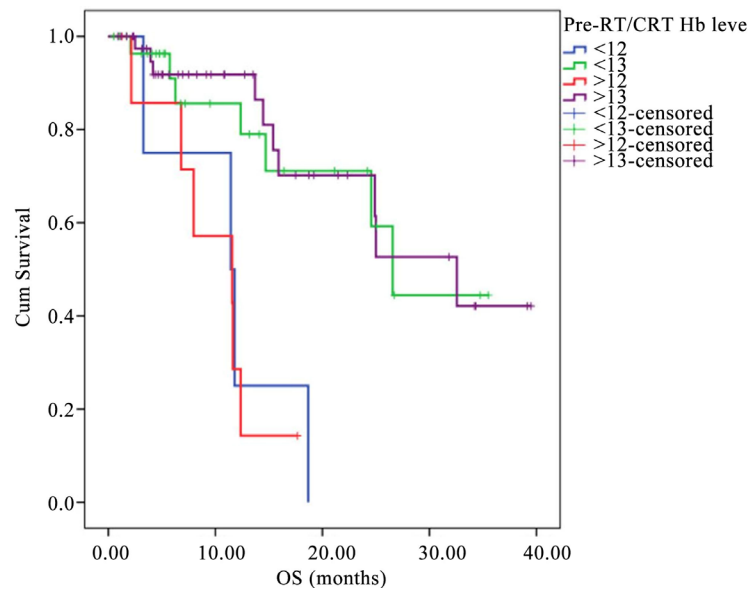


Figure 5. Effect of pre-RT/CRT hemoglobin level on OS (n = 86).

Patient, tumor and treatment characteristics in Pre-RT/CRT Hb > 12 g/dl and > 13 g/dl versus Pre-RT/CRT Hb < 12 g/dl and < 13 g/dl (Table 6):

The total number of anemic patients was 35/86 (40.7%) (Hb < 12 g/dl in 4 female patients and Hb < 13g/dl in 31 male patients,) (p = 0.000). 51/85 patients were non-anemic (Hb > 12 g/dl in 7 female patients, and Hb > 13 g/dl in 43 male patients (p = 0.000).

Anemic patients had predominance of PS 2 in 4/4 (100%) of patients with Hb < 12 g/dl, versus PS 1 in 30/31 (96.8%) of patients who had Hb < 13 g/dl (p = 0.000). 6/8 (75%) of patients with Hb > 12 g/dl had PS 2, compared to PS 1 in 41/43 (95.3%) of patients with HB > 13 g/dl (p = 0.000).

Table 6. Patient, tumor and treatment characteristics in anemic and non-anemic patients.

		<12 (n = 4)		<13 (n = 31)		P-value	>12 (n = 8)		> 13 (n = 43)		p-value
		No.	%	No.	%		No.	%	No.	%	
Age	<56 years	2	50.0%	11	35.5%	0.762	4	50.0%	24	55.8%	0.572
	>56 years	2	50.0%	20	64.5%		4	50.0%	19	44.2%	
Performance at presentation	0	0	0.0%	0	0.0%	0.000	0	0.0%	1	2.3%	0.000
	1	0	0.0%	30	96.8%		2	25.0%	41	95.3%	
	2	4	100.0%	1	3.2%		6	75.0%	1	2.3%	
Gender	Male	0	0.0%	31	100.0%	0.000	1	12.5%	43	100.0%	0.000
	Female	4	100.0%	0	0.0%		7	87.5%	0	0.0%	
Site of the tumor	Larynx	0	0.0%	31	100.0%	0.000	3	37.5%	43	100.0%	0.000
	Hypopharynx	4	100.0%	0	0.0%		5	62.5%	0	0.0%	
T-stage	1, 2	0	0.0%	12	38.7%	0.124	3	37.5%	22	51.2%	0.477
	3, 4	4	100.0%	19	61.3%		5	62.5%	21	48.8%	
N0	0	2	50.0%	18	58.1%	0.759	1	12.5%	30	69.8%	0.002
	1, 2	2	50.0%	13	41.9%		7	87.5%	13	30.2%	
Metastases	M0	4	100.0%	30	96.8%	0.715	7	87.5%	42	97.7%	0.173
	M1	0	0.0%	1	3.2%		1	12.5%	1	2.3%	
Stage	1, 2	0	0.0%	7	22.6%	0.092	1	12.5%	19	44.2%	0.288
	3, 4	4	100.0%	24	77.4%		7	87.5%	24	55.8%	
Surgery	Yes	0	0.0%	15	48.4%	0.362	2	25.0%	19	44.2%	0.092
	No	4	100.0%	13	41.9%		6	75.0%	21	48.8%	
Induction chemotherapy	NA	0	0.0%	3	9.7%	0.000	0	0.0%	3	7.0%	0.044
	Yes	2	50.0%	3	9.7%		5	62.5%	3	7.0%	
	No	1	25.0%	25	80.6%		3	37.5%	36	83.7%	
Radiation (alone or concurrent)	NA	1	25.0%	3	9.7%	0.132	0	0.0%	4	9.3%	0.436
	Yes	3	75.0%	21	67.7%		4	50.0%	31	72.1%	
	No	0	0.0%	7	22.6%		4	50.0%	8	18.6%	
RT dose	<66	3	100.0%	20	83.3%	0.159	1	25.0%	21	61.8%	0.444
	>66	0	0.0%	4	16.7%		3	75.0%	13	38.2%	
Concurrent chemoradiation CCRT	Yes	2	50.0%	10	32.3%	0.402	2	25.0%	17	39.5%	0.413
	No	1	25.0%	18	58.1%		6	75.0%	22	51.2%	
	NA	1	25.0%	3	9.7%		0	0.0%	4	9.3%	
Acute RT toxicity	No	0	0.0%	4	12.9%	0.156	4	50.0%	9	20.9%	0.646
	NA	1	25.0%	3	9.7%		0	0.0%	3	7.0%	
	Mucositis	3	75.0%	21	67.7%		2	25.0%	26	60.5%	
	Skin reaction	0	0.0%	3	9.7%		2	25.0%	5	11.6%	

Continued

Response	NA	1	25.0%	2	6.5%	0.101	0	0.0%	3	7.0%	0.060
	CR	0	0.0%	19	61.3%		2	25.0%	25	58.1%	
	No CR	3	75.0%	10	32.3%		6	75.0%	15	34.9%	
Recurrence	No	3	75.0%	20	64.5%	0.036	8	100.0%	22	51.2%	0.403
	Yes	0	0.0%	8	25.8%		0	0.0%	17	39.5%	
	NA	1	25.0%	3	9.7%		0	0.0%	4	9.3%	
DFS	Median (IQR)	11.62 (7.35 - 15.23)		5.3 (3.1 - 12.37)		0.351	9.77 (4.47 - 12)		5.67 (3.4 - 13.2)		0.978
	Range	3.27 - 18.67		0.5 - 26.73			1.27 - 17.67		0.9 - 39.5		
OS	Median (IQR)	11.62 (7.35 - 15.23)		6.77 (4.07 - 21.13)		0.876	9.77 (4.47 - 12)		9.6 (4.2 - 19.2)		0.396
	Range	3.27 - 18.67		0.5 - 35.5			1.27 - 17.67		0.9 - 39.5		

4/4 (100%) of patients with Hb < 12 g/dl had hypopharyngeal SCC and 31/31 (100%) of patients with < 13 g/dl had laryngeal SCC ($p = 0.000$). Whereas, 5/8 (62.5%) of patients with Hb > 12 had hypopharyngeal SCC versus 43/43 (100%) of patients with Hb > 13 g/dl who had laryngeal SCC ($p = 0.000$).

Node positive disease occurred in 4/4 (100%) of patients who had Hb < 12 g/dl and in 18/31 (58.1%) of patients who had Hb < 13 g/dl ($p = 0.759$). While, 7/8 (87.5%) of patients with Hb > 12 g/dl and 13/34 (30.2%) of patients with Hb > 13 g/dl had nodal positive disease ($p = 0.002$). Disease stage 3, 4 was diagnosed in 4/4 (100%) of patients with Hb < 12g/dl and in 24/31 (77.4%) of patients who had Hb < 13 g/dl ($p = 0.092$). On the other hand, 7/8 (87.5%) of patients who had Hb > 12 g/dl and 24/43 (55.8%) of patients who had Hb > 13 g/dl were diagnosed with advanced stage disease ($p = 0.288$).

More patients with Hb < 12 g/dl 2/4 (50%) received induction chemotherapy than patients with Hb < 13 g/dl 3/31 (9.7%), ($p = 0.000$). Also more patients with Hb > 12 g/dl 5/8 (62.5%) had induction chemotherapy than those with Hb > 13 g/dl 3/43 (7%), ($p = 0.044$). Concurrent chemoradiotherapy (adjuvant or definitive) was administered in 2/4 (50%) and in 10/31 (32.3%) of patients with Hb < 12 and <13 g/dl ($p = 0.402$) respectively, whereas CRT was given in 2/8 (25%) and 17/43 (39.5%) of patients with pretreatment Hb > 12 and >13 g/dl respectively ($p = 0.413$). Most of the anemic patients received RT (50% of patients with Hb < 12 g/dl, and 67% of cases with Hb < 13 g/dl, $p = 0.132$). Similarly, patients with Hb > 12 and >13 g/dl were treated with RT (50% and 72.1% respectively, $p = 0.436$). Although non-significant acute mucositis tended to occur more in anemic patients (75.0% of patients with Hb < 12 g/dl, and 61.7% of patients with Hb < 13 g/dl, $p = 0.156$), versus acute mucositis in 25% of patients with Hb > 12 g/dl and 60.5% of patients who had Hb > 13 g/dl ($p = 0.646$).

Comparing response to treatment, 0/4 of patients with Hb < 12 g/dl had CR, while 19/31 (61.3%) of Hb < 13 g/dl patients achieved CR ($p = 0.101$). The incidence of CR was 2/8 (25.0%) of patients who had Hb > 12 g/dl versus 25/31 (58.1%) CR achieved in patients with Hb > 13 g/dl ($p = 0.060$). No recurrence developed in anemic patients with Hb < 12 (0/4), however 8/31 (25.8%) of anemic patients with Hb < 13 g/dl ($p = 0.036$) had local recurrence. As regards

the non-anemic group, patients who had Hb > 12 g/dl (0/8) developed no recurrence but it occurred in 17/43 (39%) of patients with Hb > 13 g/dl ($p = 0.403$).

Table 7 demonstrates that non-anemic female patients had relatively longer mean DFS than non-anemic male patients (7.97 and 6.30 months respectively, $p = 0.127$); anemic females also achieved longer mean DFS compared to anemic male patients (11.62 and 5.30 months respectively, $p = 0.301$). In general males (anemic and non-anemic) had better mean OS than females (anemic and non-anemic). Where, males with Hb > 13 g/dl survived for 32.567 months and females who had Hb > 12 g/dl survived for 7.967 months ($p = 0.001$). Similarly males with Hb < 13 g/dl compared to females with Hb < 12 g/dl had better mean OS (26.567 months and 11.433 months respectively, $p = 0.004$) (**Table 8**, **Figure 6** and **Figure 7**).

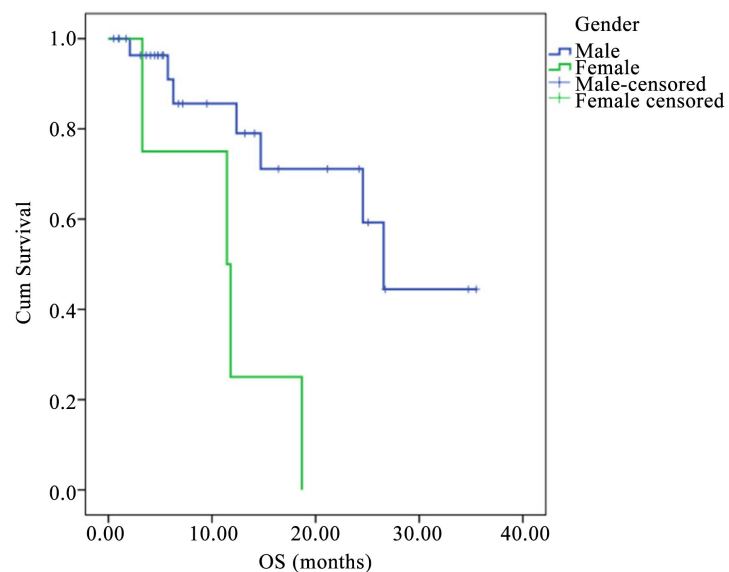


Figure 6. Effect of gender on OS in anemic patients ($n = 35$).

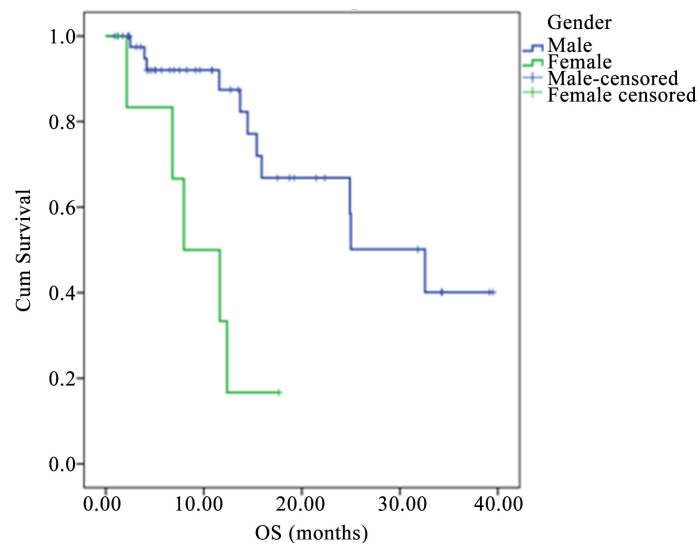


Figure 7. Effect of gender on OS in non-anemic patients ($n = 51$).

Table 7. Comparison of DFS between anemic and non-anemic patients.

	No.	DFS		95% CI		Log rank test	
		Mean	SE	Lower	Upper	X ²	P-value
No anemia							
Male Hb > 13	44	6.30	10.39	3.48	12.97	2.331	0.127
Female Hb > 12	7	7.97	5.84	2.13	12.37		
Anemia							
Male Hb < 13	31	5.30	6.89	3.10	12.37	1.070	0.301
Female Hb < 12	4	11.62	6.30	7.35	15.23		
Overall	86	20.200	2.314	15.664	24.736		

Table 8. Comparison of OS in anemic and non-anemic patients.

	No.	OS		95% CI		Log rank test	
		Mean	SE	Lower	Upper	X ²	p-value
No anemia							
Male Hb > 13	44	32.567	5.665	21.463	43.671	10.648	0.001
Female Hb > 12	7	7.967	2.960	2.165	13.768		
Anemia							
Male Hb < 13	31	26.567	2.265	22.126	31.007	8.125	0.004
Female Hb < 12	4	11.433	4.267	3.071	19.796		
Overall	86	24.900	4.301	16.469	33.331		

5. Discussion

Regardless of the etiology of anemia, its existence in cancer patients can impair treatment effectiveness and outcome and also negatively impact the quality of life of cancer patients [8]. Nutritional anemia, namely iron deficiency anemia (ID), has three- to four-times higher prevalence in the developing world than the developed world especially in population with more physiologic needs [34].

The incidence of ID anemia increases after 50 years of age [35]. The median age of patients in our study was 56 years which is the same age reported by Narayanaswamy RK *et al.* [13] in their analysis of pre-CRT anemia in 91 patients with HNSCC. Anemia was diagnosed in 36.4% of our female patients and 41.3% of our male patients. In contrast, Dubray *et al.* [7] who defined anemia as hemoglobin level < 13.5 g/dl in men and < 12.0 g/dl in women, diagnosed anemia in 31% of men and 17% of women.

The incidence of anemia varies by tumor site. Dubray *et al.* [7] reported that the incidence of pre-RT anemia was 40% (20 of 50) for supraglottic SCC versus 12% (25 of 205) for glottic SCC. In the current study the incidence of pre-RT/CRT Hb < 12 g/dl was 100% in hypopharyngeal SCC and pre-RT/CRT Hb < 13 g/dl had 100% incidence in laryngeal SCC.

Pretreatment anemia was significantly associated with higher T- or N-stage in

patients with HNSCC studied by Dubray *et al.* [7]. Blitzer *et al.* [36] reported that low Hb levels were associated with advanced T-stage HNSCC treated with definitive radiation. We also observed that patients diagnosed with T3 - 4 tumor tended to have low pretreatment Hb levels < 12 and <13 g/dl (100% and 61.3% respectively, $p = 0.124$). Advanced nodal disease was detected in 50% of patients with Hb levels < 12 g/dl, whereas 58.1% of cases with Hb < 13 g/dl were node negative ($p = 0.759$). Node positive disease was diagnosed in 87.5% of patients with Hb > 12 g/dl, while 69.8% of Hb level > 13 g/dl was detected in patients with node negative tumors ($p = 0.002$).

With the increased use of concurrent chemotherapy with definitive radiation in HNSCC, most patients developed anemia [37] [38]. The incidence of pre-CRT Hb < 12 g/dl was 67%, while pre-CRT Hb \geq 12 g/dl was 24% in 91 Indian patients with different sites head and neck SCC [13]. In the current study we found a higher incidence of pre-RT/CRT Hb < 12 g/dl in 50% of patients who received CRT, compared to 32.3% incidence in patients with Hb < 13 g/dl treated with CRT ($p = 0.402$). On the other hand only 25% and 39.5% of patients who were given CRT had Hb levels > 12 and >13 g/dl respectively ($p = 0.413$). 75% of our patients who were treated with induction chemotherapy also had a high incidence of Hb < 12 g/dl, but much less incidence in patients who had pretreatment Hb < 13 g/dl ($p = 0.000$).

Narayanaswamy *et al.* [13] compared toxicity of CRT below and above Hb 10.7 g/dl which is the common mean Hb level in India. The authors found that patients with pre-RT Hb \geq 10.7 g/dl had lesser grade of mucositis compared to patients with pre-RT Hb < 10.7 g/dl. Mucositis reaction associated with pre-RT Hb level showed statistical significance ($p < 0.0001$). In agreement, our anemic cohort developed acute mucositis during radiotherapy (alone or combined with chemotherapy) in 75% of patients with pretreatment Hb < 12 g/dl and 67.75% of patients with Hb < 13 g/dl ($p = 0.156$). Acute mucositis tended to occur less with pre-RT/CRT Hb levels > 12 and >13 g/dl ($p = 0.646$).

The occurrence of anemia also varies by timing of measurements, where Dubray *et al.* [7], showed that the incidence of pretreatment anemia was 40% (20 of 50) for supraglottic laryngeal SCC versus 12% (25 of 205) for glottic SCC. The incidence of post-RT anemia was 56% (25 of 45) for supraglottic SCC versus 23% (41 of 175) for glottic SCC. Welsh *et al.* [39], prospectively studied 20 patients with HNSCC, the pre-CRT Hb was in the normal range but dropped to < 11.5 g/dl in 15% and > 11.5 g/dl in 85% of patients after treatment. Chua *et al.* [11], randomized 334 patients with advanced nasopharyngeal SCC into RT alone arm and induction chemotherapy followed by RT arm. In the chemotherapy arm, the mean baseline, pre-radiation, and mid-radiation Hb levels were 13.6, 11.0, and 11.8 g/dL, respectively. In the radiotherapy arm, the mean baseline pre-radiation and mid-radiation Hb levels were 13.7 and 12.9 g/dL, respectively. Multivariate analysis showed that a low mid-radiation Hb level, but not a low baseline or pre-radiation Hb level, was an independent predictor of local disease recurrence and malignancy-related death. We did not assess post-treatment Hb

level in this report.

Our analysis of prognostic factors influencing treatment response noted that gender, site of the tumor, T-stage, N-stage and pre-RT/CRT Hb level were significant factors. Significant factors of overall survival included age, gender, performance status, N-stage and pretreatment Hb. No factors influenced the DFS ($p > 0.05$). Narayanaswamy *et al.* [13], in their analysis of 91 patients with HNSCC for the effect of pre-RT Hb levels in locally advanced HNSCC treated with CCRT, the authors found that performance status, pre-RT hemoglobin level, radiotherapy interruptions > 5 days and non-development of grade III mucositis were significantly associated with good locoregional control. Pre-RT Hb in HNSCC was shown by many studies to be an independent significant prognostic factor of response and survival [10] [36] [40]. Lower levels of pretreatment Hb were significantly associated with reduced local control and response at the tumor primary site [7] [9] [36]. Warde *et al.* [41] studied pre-RT anemia in 735 patients with T1-2N0 glottic SCC. Patients diagnosed with a pretreatment Hb < 12 g/dL were found through multivariate analysis to have a 1.8-fold increased risk for locoregional failure (95% confidence interval, 1.2 - 2.5) compared to patients with Hb 15.0 g/dL. Similarly, we demonstrated that pretreatment Hb was among the significant prognostic factors predicting response to treatment, where 58.7% of Hb levels > 12 g/dl and > 13 g/dl were associated with CR compared to 41.3% of Hb levels < 12 and 13 g/dl ($p = 0.034$). Narayanaswamy RK *et al.* [13] detected significantly better response (CR versus no CR) to treatment in patients with pre-RT Hb ≥ 12 g/dl than Hb < 12 g/dl ($p < 0.001$). Blitzer *et al.* [36] demonstrated that low Hb levels were associated with local recurrence in advanced T-stage HNSCC patients treated with definitive radiation. The authors predicted an approximately 10% drop in locoregional control for every 2-g/dL drop (estimated 2-year locoregional control 26% for Hb = 12g/dL, 37% for Hb = 14g/dL, and 47% for Hb = 16). Few studies showed no correlation between local tumor control and pretreatment Hb in glottic SCC [42] [43] [44]. In a multivariate analysis of 116 patients with advanced unresectable HNSCC treated with CRT Haddad *et al.* [9] reported that pre-CRT Hb < 12 g/dl was associated with a worse response rate at the primary site ($p = 0.05$).

Pre-treatment Hb levels have been shown to be associated with overall and disease-free survival in HNSCC among other solid tumors [8] [15]. This correlation of pre-treatment anemia and outcome is documented with radiation therapy and surgery in HNSCC patients [45]. The majority of studies found that a low pre-treatment Hb level is a significant prognostic factor of local control and survival after curative radiotherapy independent of tumor factors as T-stage and N-stage. Low Hb levels were associated with worse survival [42] [43]. The levels of pre-treatment Hb in head and neck carcinomas that corresponded with poor OS and DFS outcome have been defined by retrospective studies to be 9, 12, 13, and 14.5 g/dl [7] [8] [10] [46]. According to Vaupel P *et al.* [23] the range of Hb levels considered optimal for tumor oxygenation was 12 - 14 g/dl. It is likely that the Hb threshold depends on the specific type of malignancy, the timing of Hb

measurement, and addition of chemotherapy [11]. In accordance we identified pre-RT/CRT Hb level as one of the significant prognostic factors determining incidence of OS, where Hb levels < 12 and 13 g/dl versus Hb levels > 12 and >13 g/dl were associated with 21.3 and 27.2 months median OS ($p = 0.000$). However, the pretreatment Hb levels did not affect the incidence of median DFS of anemic and non-anemic patients (19.442, 19.496 months respectively, $p = 0.23$). Haddad *et al.* [9] did not observe a statistically significant impact of pretreatment Hb level on survival of HNSCC patients, where patients with Hb < 12 g/dl had a relatively better DFS ($p = 0.109$), while patients with Hb > 12 g/dl had better OS ($p = 0.656$).

The shortcomings of our study include the retrospective nature of the study, and the small number of patients in comparison to many similar studies in the literature. However, to the best of our knowledge this is the first study in Egypt of the frequency of anemia in head and neck SCC patients before radiotherapy and/or chemoradiotherapy and its effect on response to treatment and survival.

6. Conclusion

Anemia is a frequent problem in patients with head and neck squamous cell carcinoma. Evidence from the literature emphasizes the independent prognostic role of anemia for recurrence and survival which calls for formal protocol for hemoglobin monitoring before, during and after treatment. The Hb threshold which affects treatment outcome needs to be defined where it may vary according to the tumor site, from patient to patient, and timing of measurement. The hematologic definition of anemia may not necessarily be the oncologic definition [12]. In Egypt nutritional iron deficiency anemia is prevalent and is a common laboratory finding in head and neck carcinoma patients presenting to our institution.

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