

# Prolonged radiation time and low nadir hemoglobin during postoperative concurrent chemoradiotherapy are both poor prognostic factors with synergistic effect on locally advanced head and neck cancer patients

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**Background:** Anemia, a common complication of head and neck cancer treatment, is regarded as a poor prognostic factor. We evaluated the impact of low hemoglobin (Hb) levels, measured at different time points, on a consecutive cohort of patients with locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) who underwent postoperative concurrent chemoradiotherapy (CCRT).

**Materials and methods:** From 2002 to 2009, 140 patients were enrolled and reviewed retrospectively. Preoperative (pre-op Hb), pre-CCRT Hb, and nadir Hb during CCRT were measured and recorded. The three Hb parameters were analyzed against several well-established pathologic risk factors and radiation-associated variables. Prognostic impacts were investigated with multivariate analysis by Cox proportional hazards model.

**Results:** On Cox regression analysis, significantly higher risk of death was associated with pre-op Hb  $\leq 13$  g/dL (hazard ratio [HR]=1.8; 95% confidence interval [CI], 1.1–3.1;  $P=0.023$ ), nadir Hb  $\leq 11$  g/dL (HR=1.9; 95% CI, 1.1–3.3;  $P=0.020$ ), radiation treatment time (RTT)  $>7$  weeks (HR=1.9; 95% CI, 1.1–3.3;  $P=0.022$ ), and multiple positive lymph nodes (HR=2.1; 95% CI, 1.2–3.7;  $P=0.010$ ), after adjusting for primary tumor site and pathologic lymphovascular invasion. Patients with poor prognosticators including low nadir Hb  $\leq 11$  g/dL and RTT  $>7$  weeks had a higher risk of death (HR=4.0; 95% CI=1.6–10.2;  $P=0.004$ ).

**Conclusion:** In the treatment setting of LA-SCCHN patients who underwent postoperative CCRT, coexistence of lower nadir Hb during CCRT and prolonged RTT resulted in reduced survival.

**Keywords:** anemia, radiation time, concurrent chemoradiotherapy, hemoglobin, head and neck cancer

## Background

A multidisciplinary strategy incorporating surgery, radiotherapy (RT), and chemotherapy improves the treatment outcome in locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). Postoperative adjuvant concurrent chemoradiotherapy (CCRT) has been shown to enhance survival outcome when compared to RT alone.<sup>1–4</sup> However, such combined treatment modalities also incur significant acute side effects and long-term morbidities. Among the acute complications, the occurrence of anemia is common<sup>5</sup> and might be related to surgical blood loss, CCRT, or poor nutritional status.

Besides the direct physiologic consequences of anemia, anemia itself can result in an inferior treatment outcome by causing tumor hypoxia and radioresistance.<sup>6,7</sup> Anemia and the resulting tumor hypoxia also modulate important signaling pathways that enhance expression of stem-like characters, promote metastasis, and result in chemoresistance.<sup>8–10</sup> It has been demonstrated that patients with anemia had inferior treatment outcome in various cancers.<sup>11–13</sup> Several clinical studies have also reported that anemia is a poor prognostic factor in head and neck cancer treatment.<sup>14–19</sup> The optimal timing for hemoglobin (Hb) measurement to be a prognostic indicator was not established.<sup>20</sup> The reported studies measured Hb at various time points and in different treatment settings. Moreover, only a few reports focused on patients receiving the most intense therapy, postoperative CCRT, which is associated with a higher anemia occurrence.<sup>17,21</sup>

We reported a consecutive cohort of stage III/IV SCCHN patients who received postoperative CCRT. Preoperative Hb (pre-op Hb), pre-CCRT Hb, and nadir Hb during CCRT were recorded and analyzed. Other well-established prognostic factors, such as the pathologic features of the tumor and RT-related variables, were also evaluated.

## Materials and methods

### Patient eligibility

This study protocol was approved by the hospital's institutional review board. In this retrospective study, we included patients with newly diagnosed nonmetastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx. Patients with a history of radiation to the head and neck region or any chemotherapy prior to the study were excluded. Patients having bone marrow dysfunction from non-cancer diseases or other hematologic diseases were not eligible for this study. All surviving patients had a minimum follow-up of 2 years. All patients received surgery with curative intent and completed the planned RT doses with concurrent chemotherapy. Each tumor was staged according to the 2002 American Joint Committee on Cancer staging classification.

After completing treatments, the follow-up schedule was once every month during the first year, and every 3 months, thereafter. Once recurrence occurred, salvage treatments were offered according to individual patient condition. The medical records of all enrolled patients were reviewed in detail and recorded.

### RT

The indications for postoperative adjuvant CCRT were defined by pathologic risk features. CCRT was indicated

for patients having one major risk factor, either positive surgical margin or extracapsular nodal extension, or at least two minor pathologic risk factors. The minor pathologic risk factors included T classification (T3/T4), N classification (N2b; multiple positive lymph nodes or higher), close pathologic surgical margin (1–5 mm), perineural invasion, lymphovascular invasion (LVI), and poor histological differentiation of tumor.<sup>1,5,22–24</sup>

All patients received fractionated RT consisting of five consecutive daily fractions per week with a fraction size of 1.8–2.0 Gy. Radiation was delivered via a linear accelerator using a 6 MV photon beam. Before 2007, the main RT technique was 2D conventional RT with the total dose prescribed ranging between 59.4 Gy and 64.8 Gy (1.8 Gy per fraction) at the main tumor and involved lymph nodes. Thereafter, intensity-modulated RT became the main modality with intent dose of 63 Gy (1.8 Gy per fraction) or 66 Gy (2 Gy per fraction). The RT treatment was mandated to be completed within 7 weeks. The fraction size and total dose were decided at the discretion of treating physician according to each clinical condition. RT dose was prescribed to planning target volumes.

### Chemotherapy

Chemotherapy consisted primarily of cisplatin and 5-FU at two dose levels in our institution.<sup>25</sup> One comprised cisplatin 12 mg/m<sup>2</sup> plus 5-FU 600 mg/m<sup>2</sup> per day administered as a 120-hour continuous infusion on week 1 and week 5 during the course of RT. The other dose level was cisplatin 15 mg/m<sup>2</sup> plus 5-FU 750 mg/m<sup>2</sup> with the same infusion schedule.

In this study, 15 patients received low-dose level cisplatin/5-FU and 105 patients received the high dose-level regimen. Another 20 patients received weekly 30 mg/m<sup>2</sup> cisplatin for at least five or more doses during radiation treatment. All three regimens have been reported in literature,<sup>17,26–28</sup> and were regularly prescribed in our institution. The Hb level was not a criterion in the selection of chemotherapy regimen, total dose, or cycles being prescribed.

### Hb measurement and management

We analyzed Hb levels at three time points. The pre-op Hb and pre-CCRT Hb were measured within 1 week prior to the implemented therapy. Hb was checked weekly during CCRT and the lowest level was defined as the nadir Hb. Anemia was defined as a Hb concentration less than 13 g/dL according to World Health Organization definition. This cut-off value was used for pre-op Hb and pre-CCRT Hb. Since only a few reports contained the nadir Hb,<sup>3,15</sup> it was analyzed as a

categorical variable. The median nadir Hb (11 g/dL) of the study cohort was chosen as the cut point value for further analysis.

No predefined Hb level was maintained and all anemic situations throughout the treatment course were corrected with red blood cell transfusion at the discretion of the treating physician. No patients received erythropoietic stimulating agents (ESAs) or iron supplement before and during CCRT.

## Endpoints and statistical methods

Time to events in this study was counted from the date of surgery to the event occurrence or the end of study, December 31, 2011, whichever came first. Death from any cause accounted for overall survival (OS). Disease recurrence, second primary cancer, and death from any cause were considered events for progression-free survival (PFS). Evidence of locoregional recurrence was specifically recorded as failure to locoregional control (LRC). Patients were recorded as censor if no events occurred until the last follow-up or the end of study.

Survival rates were estimated using the Kaplan–Meier statistical method. Log-rank test was applied to evaluate the possible impact on the OS, PFS, and LRC for age, primary tumor site (oral cavity or non-oral cavity primary tumor), each pathologic risk feature, RT-associated variables, and the three Hb parameters. These factors were also analyzed using the multivariate Cox proportional hazards model to estimate adjusted hazard ratio (HR) and 95% confidence interval (CI). All reported *P*-values were two-tailed and considered to be statistically significant if *P*<0.05. All statistical analyses were performed using SPSS version 12.

## Results

### Patient demographics and general treatment outcome

From January 2002 to December 2009, 140 patients were eligible for the study analysis. The median follow-up time was 33.5 months (interquartile range: 16–65 months). The median age of all patients in this study was 51 years (interquartile range: 44–57 years), including 135 (96.4%) male and 4 (3.6%) female patients. One hundred and 6 patients (75.7%) had their primary tumors located in the oral cavity. The pathologic stage distribution was as follows: stage III =17.9%, stage IVa =71.4%, and stage IVb =10.7%. Positive surgical margin was noted in 22.9% and nodal extracapsular extension in 14.3% of patients. The median total RT dose was 6,480 cGy (interquartile range: 6,300–6,600 cGy). Seventy-four patients

(52.9%) received 2D conventional RT and the others were treated by intensity-modulated RT mode. The median time interval between operation and RT (OP–RT interval) was 6.3 weeks (interquartile range: 4.8–8.0 weeks). The median total RT treatment time (RTT) was 7.4 weeks (interquartile range: 6.7–8.3 weeks). The median treatment time between operation and the end of RT (OP–RT package time) was 13.6 weeks (interquartile range: 12.4–15.6 weeks).

The overall 5-year OS, PFS, and LRC were 52.1%, 44.9%, and 73.2%, respectively. During the study period, there were 33 and 37 events of locoregional recurrences and distant metastasis, respectively. The detailed patient demographics and tumor characters are listed in Table 1.

### Hb parameters and impacts on outcome

The median pre-op Hb was 14.3 g/dL (interquartile range: 13.1–15.1 g/dL) and median pre-CCRT Hb was 11.9 g/dL (interquartile range: 11.1–12.8 g/dL). We observed that a lower pre-op Hb correlated with a higher N classification and non-oral cavity primary tumor site (Table 2). The median nadir Hb was 10.7 g/dL (interquartile range: 9.4–11.7 g/dL). Eighty-two (58.6%), 31 (22.1%), and 27 (19.3%) patients had the nadir Hb  $\leq$ 11.0 g/dL, 11.1–12.0 g/dL, and >12.0 g/dL.

The 5-year OS, PFS, and LRC of patients with a pre-op Hb  $\leq$ 13 g/dL were 29.1%, 20.7%, and 61.4%, respectively. These results were significantly worse compared to patients in the pre-op Hb >13 g/dL group (OS = 59.5%, *P*<0.001 [Figure 1A]; PFS =51.2%, *P*<0.001; LRC =77.0%, *P*=0.019). The corresponding values, however, were not significantly different when comparing pre-CCRT Hb  $\leq$ 13 g/dL versus >13 g/dL patient groups (Table 1).

Patients whose nadir Hb was  $\leq$ 11.0 g/dL, between 11.1 g/dL and 12.0 g/dL, and >12.0 g/dL had a 5-year OS of 42.4%, 61.6%, and 70.6%, respectively (*P*=0.004; Figure 1B). The three groups of patients had a 5-year PFS of 36.6%, 49.1%, and 54.9%, respectively (*P*=0.012) and a 5-year LRC of 70.0%, 86.4%, and 61.7%, respectively (*P*=0.224). Although not statistically significant for LRC, patients with nadir Hb below 11 g/dL had more events of locoregional recurrence, distant metastasis, second primary tumors, and non-cancer death (data not shown).

Among the 82 patients with nadir Hb  $\leq$ 11 g/dL, 21 (25.6%) received red blood cell transfusion during CCRT. The 5-year OS of the 82 patients with and without transfusion was 28.6% and 47.3%, respectively (*P*=0.095), the PFS was 22.9% and 41.6%, respectively (*P*=0.166), and the LRC was 64.0% and 71.7%, respectively (*P*=0.558; Table 1).

**Table 1** Patient characteristics and treatment outcome

	N=140, number (%)	Overall survival		Disease-free survival		Locoregional control rate	
		5-year (%)	P-value*	5-year (%)	P-value*	5-year (%)	P-value*
Age (years)							
<50	64 (45.7)	45.8	0.194	37.6	0.185	66.0	0.233
50+	76 (54.3)	57.5		51.1		78.5	
Primary tumor site							
Oral cavity	106 (75.7)	60.3	0.001	54.1	<0.001	79.1	0.002
Pharynx/larynx	34 (24.3)	26.4		15.1		52.4	
Surgical margin							
Positive	32 (22.9)	43.8	0.184	31.7	0.064	66.5	0.202
Negative	108 (77.1)	54.6		48.9		75.2	
Extracapsular extension							
No	120 (85.7)	53.6	0.278	45.4	0.438	73.3	0.612
Yes	20 (14.3)	42.9		45.0		73.7	
Pathological T stage							
2	36 (25.7)	55.6	0.915	46.3	0.779	67.6	0.470
3–4	104 (74.3)	50.7		44.3		75.6	
Pathologic N stage							
N0–N2a	69 (49.3)	67.1	<0.001	55.7	0.001	78.7	0.060
≥N2b	71 (50.7)	35.1		34.2		67.3	
Histology differentiation							
Well/moderate	125 (89.3)	52.0	0.572	45.4	0.573	74.8	0.664
Poor	15 (10.7)	53.3		42.7		62.7	
Lymphovascular invasion							
No	83 (59.3)	59.3	0.045	52.9	0.019	80.8	0.022
Yes	57 (40.7)	41.6		32.4		60.4	
Perineural invasion							
No	93 (66.4)	52.5	0.697	45.8	0.705	79.1	0.083
Yes	47 (33.6)	51.5		43.7		62.2	
OP–RT interval (weeks)							
≤6	66 (47.1)	51.1	0.962	47.6	0.667	72.5	0.961
>6	74 (52.9)	53.2		41.0		74.9	
RTT (weeks)							
≤7	49 (35.0)	64.6	0.039	62.0	0.020	87.2	0.020
>7	91 (65.0)	45.2		36.1		65.5	
Pre-op Hb (g/dL)							
≤13.0	34 (24.3)	29.1	<0.001	20.7	<0.001	61.4	0.019
>13.0	106 (75.7)	59.5		51.2		77.0	
Pre-CCRT Hb (g/dL)							
≤13.0	112 (80.0)	49.2	0.151	41.5	0.110	73.1	0.995
>13.0	28 (20.0)	62.6		60.3		74.4	
Nadir Hb (g/dL)							
≤11.0	82 (58.6)	42.4	0.004	36.6	0.012	70.0	0.224
11.1–12.0	31 (22.1)	61.6		49.1		86.4	
>12.0	27 (19.3)	70.6		54.9		61.7	
Transfusion status during CCRT**							
Not transfused	61 (74.4)	47.3	0.095	41.6	0.166	71.7	0.558
Received transfusion	21 (25.6)	28.6		22.9		64.0	

**Notes:** \*P-value based on the Log-rank test; \*\*including only 82 patients with Hb ≤11.0 g/dL during CCRT.

**Abbreviations:** OP–RT interval, interval between operation and radiotherapy; RTT, radiation treatment time; Hb, hemoglobin; pre-op Hb, preoperative hemoglobin – hemoglobin within 1 week before operation; CCRT, concurrent chemoradiotherapy; pre-CCRT Hb, hemoglobin within 1 week before CCRT; nadir Hb, the lowest hemoglobin concentration during CCRT.

## Multivariate analyses for treatment outcome OS

A significantly worse OS was observed in patients with non-oral cavity primary tumor ( $P=0.001$ ), N classification  $\geq$  N2b ( $P<0.001$ ), and the presence of LVI ( $P=0.045$ ) (Table 1).

With the increasing duration of RTT, which was presumed to be  $\leq$ 7 weeks, there was a trend of worse OS for patients with RTT 7–8 weeks and  $>8$  weeks ( $P=0.085$ ; Figure 1C and Table 1). We dichotomized the RTT into  $\leq$ 7 weeks and  $>7$  weeks for multivariate analysis. After adjusting for

**Table 2** Association of preoperative hemoglobin level with pathological T, N stage, and primary tumor site

	Pre-op Hb (g/dL)		P-value*
	≤13.0 (N=34), number (%)	>13.0 (N=106), number (%)	
Pathological T stage			
2	7 (20.6)	29 (27.4)	0.713
3	8 (23.5)	21 (19.8)	
4	19 (55.9)	56 (52.8)	
Pathological N stage			
0	3 (8.8)	32 (30.2)	0.009
1	6 (17.6)	21 (19.8)	
2	21 (61.8)	51 (48.1)	
3	4 (11.8)	2 (1.9)	
Primary tumor site			
Oral cavity	21 (61.8)	85 (80.2)	0.029
Pharynx/larynx	13 (38.2)	21 (19.8)	

Note: \*P-value based on the chi-square test.

Abbreviation: Pre-op Hb, preoperative hemoglobin – hemoglobin within 1 week before operation.

other confounders, significant HR for death was observed in patients with N classification  $\geq$  N2b (adjusted HR =2.1; 95% CI, 1.2–3.7), RTT >7 weeks (adjusted HR =1.9, 95% CI, 1.1–3.3), pre-op Hb  $\leq$ 13 g/dL (adjusted HR =1.8; 95% CI, 1.1–3.1), and nadir Hb  $\leq$ 11 g/dL (adjusted HR =1.9; 95% CI, 1.1–3.3) (Table 3).

### PFS

Patients with non-oral cavity primary tumor ( $P<0.001$ ), N classification  $\geq$  N2b ( $P=0.001$ ), and the presence of LVI ( $P=0.019$ ) had significantly reduced PFS by univariate analysis (Table 1). In multivariate analysis, non-oral cavity primary tumor, RTT >7 weeks, and pre-op Hb  $\leq$ 13 g/dL were associated with worse PFS (Table 3). Nadir Hb  $\leq$ 11 g/dL remained a trend toward inferior PFS (adjusted HR =1.6; 95% CI, 0.95–2.6;  $P=0.079$ ).

### LRC

In univariate analysis, non-oral cavity primary tumor ( $P=0.002$ ) and the presence of LVI ( $P=0.022$ ) were associated with inferior LRC (Table 1). A trend of worse LRC with prolonged RTT

was still observed ( $P=0.065$ ; Table 1). Only RTT >7 weeks strongly predicted worse LRC using multivariate analysis (Table 3). Patients with non-oral cavity primary tumor and pre-op Hb  $\leq$ 13 g/dL also had a higher risk of local recurrence.

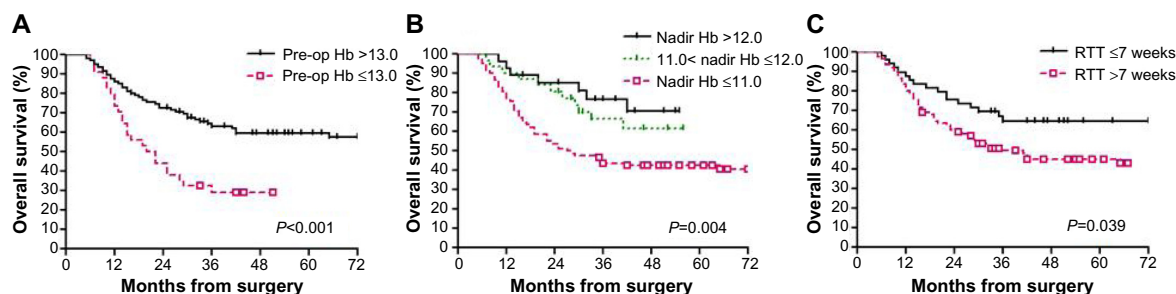
### Additive effect of prolonged RTT and nadir Hb

We investigated if there was a possible interaction between prolonged RTT and low nadir Hb, both of which might attenuate CCRT efficacy. We found that patients with both nadir Hb  $\leq$ 11 g/dL and RTT >7 weeks had a markedly worse 5-year OS (36.0%), PFS (27.8%), and LRC (60.3%), when compared to patients with neither of the two factors (5-year OS =77.3%,  $P=0.001$  [Figure 2]; PFS =68.7%,  $P=0.002$ ; LRC =85.9%,  $P=0.026$ ). Patients with both poor prognosticators had risk of death four times higher than those with none of the two factors (HR =4.0; 95% CI, 1.6–10.2;  $P=0.004$ ).

## Discussion

In this study, we found that pre-op Hb  $\leq$ 13 g/dL and lower nadir Hb during CCRT predicted a poorer outcome among patients with LA-SCCHN treated by postoperative CCRT. The adverse impact of anemia persisted after controlling for several well-accepted pathologic and radiation-related prognostic factors. Anemia proved to be an unfavorable factor in this patient cohort comprising predominantly of oral cancer, which was a quite different demographic compared to other reported series.<sup>14–19</sup> However, our retrospective study design and single institutional experience were limitations of this study. Moreover, though all the chemotherapy regimens used in our study have been reported<sup>17,25–28</sup> in the literature, this might be a limitation while interpreting and generalizing our results. Though only 8 patients had their primary tumor located at oropharynx, human papillomavirus status analysis was not investigated in this study. Our results should be verified with larger case series or clinical trials.

Only one study evaluated the influence of Hb on patients all of whom received postoperative CCRT.<sup>20</sup> Reichel et al investigated the impact of Hb before and



**Figure 1** Kaplan–Meier curve of overall survival according to pre-op Hb level (g/dL) (A), nadir Hb (g/dL) during CCRT (B), and RTT (C).

Abbreviations: pre-op, preoperative; Hb, hemoglobin; CCRT, concurrent chemoradiotherapy; RTT, radiation treatment time.

**Table 3** Results of multivariate analysis with regard to overall survival, disease-free survival, and locoregional control rate

	Overall survival			Disease-free survival			Locoregional control rate		
	Adj HR	95% CI	P-value*	Adj HR	95% CI	P-value*	Adj HR	95% CI	P-value*
Primary tumor site									
Oral cavity	1.0	–		1.0	–		1.0	–	
Pharynx/larynx	1.3	0.8–2.3	0.278	1.7	1.0–2.8	0.036	2.1	0.99–4.4	0.053
Pathological N stage									
N0–N2a	1.0	–		1.0	–		1.0	–	
$\geq$ N2b	2.1	1.2–3.7	0.010	1.5	0.9–2.5	0.116	1.1	0.5–2.5	0.867
LVI									
No	1.0	–		1.0	–		1.0	–	
Yes	1.1	0.6–1.8	0.831	1.3	0.8–2.1	0.314	1.8	0.8–3.9	0.156
RTT (weeks)									
$\leq$ 7	1.0	–		1.0	–		1.0	–	
$>$ 7	1.9	1.1–3.3	0.022	1.9	1.1–3.2	0.015	3.0	1.2–7.5	0.016
Hb parameter (g/dL)									
Pre-op Hb $>$ 13.0	1.0	–		1.0	–		1.0	–	
Pre-op Hb $\leq$ 13.0	1.8	1.1–3.1	0.023	1.9	1.2–3.2	0.010	2.1	0.96–4.4	0.067
Nadir Hb $>$ 11.0	1.0	–		1.0	–		1.0	–	
Nadir Hb $\leq$ 11.0	1.9	1.1–3.3	0.020	1.6	0.95–2.6	0.079	1.2	0.6–2.7	0.573

**Note:** \*P-value based on the Cox proportional hazards model.

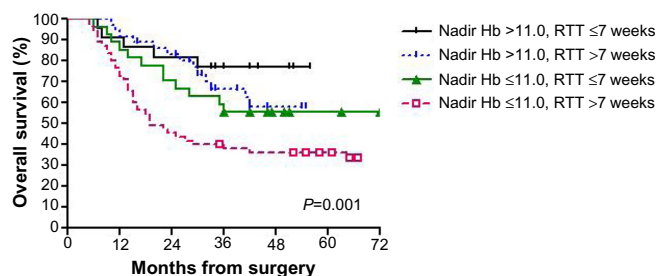
**Abbreviations:** Adj HR, adjusted hazard ratio; CI, confidence interval; LVI, lymphovascular invasion; RTT, radiation treatment time; pre-op Hb, preoperative hemoglobin – hemoglobin within 1 week before operation; nadir Hb, the lowest hemoglobin concentration during concurrent chemoradiotherapy.

48 hours after surgery, and Hb right before and after CCRT. They found that only Hb measured before surgery and Hb measured 48 hours after surgery were unfavorable factors. However, the study enrolled 12% of patients with stage I/II disease and the Hb parameters were not analyzed with other important pathologic or RT variables which might influence the true impact of anemia in this treatment setting.

Pre-op Hb, defined as pretreatment Hb in other studies, was the most common Hb parameter investigated.<sup>14–19,29–33</sup> Our results were consistent with previous findings that low pretreatment Hb predicted a poor prognosis. In our study, we also found that non-oral cavity tumor site and higher N classification were associated with lower pre-op Hb. Only two studies had similar investigation. One revealed that lower pretreatment Hb was related to higher T classification and

primary tumor site<sup>16</sup> and the other showed an association with older age and poorer performance status.<sup>17</sup>

In this study, we would like to focus on one specific Hb parameter, nadir Hb during CCRT. It might contribute to tumor hypoxia during CCRT which is an important aspect to cause radioresistance and treatment failure. Our data showed that the lower the nadir Hb (especially for nadir Hb  $\leq$ 11 g/dL), the worse the OS. Also, it might reflect a poor general condition and nutritional status of patients that non-cancer death increased with nadir Hb  $\leq$ 11.0 g/dL. The occurrence of second primary malignancy as well increased in this patient group (data not shown). Only two studies investigated this Hb parameter.<sup>14,19</sup> Both results confirmed that low nadir Hb was an unfavorable prognostic factor. However, one of the studies enrolled patients who underwent either surgery or RT as the primary treatment<sup>14</sup> and the other study did not analyze the nadir Hb against other prognostic contributors.<sup>19</sup> In addition, Bhide et al found that patients who received transfusions and who needed more units of blood to maintain Hb  $>$ 12 g/dL during CCRT had poorer outcomes.<sup>19</sup> Our results suggested that performing blood transfusions only when clinically necessary probably might be a rational strategy in maintaining Hb level. However, our data also showed a trend toward inferior survival in those who received blood transfusion. The optimal methods and the target level of Hb to be maintained during head and neck squamous cell carcinoma treatment were not clearly demonstrated.<sup>34,35</sup> ESA was once considered promising but has been proven to be of



**Figure 2** Adverse survival outcome interaction between lower nadir Hb ( $\leq$ 11 g/dL) and the presence of prolonged RTT ( $>$ 7 weeks) during postoperative CCRT.

**Abbreviations:** Hb, hemoglobin; RTT, radiation treatment time; CCRT, concurrent chemoradiotherapy.

no survival benefits in several clinical trials.<sup>36,37</sup> Exogenous ESA might activate an aggressive phenotype of cancer cells through the erythropoietin receptor and its downstream pathway.<sup>38,39</sup> On the other hand, practice with blood transfusion to correct anemia also did not improve the outcome.<sup>40,41</sup> In contrast to the pretreatment Hb, several factors contributed to anemia during CCRT in our treatment setting, including surgical blood loss, radiation- and chemotherapy-induced anemia, and impaired nutritional status. In our study cohort, neither nasogastric nor gastroenterostomy tube was mandated which might contribute to the severity of anemia observed. We believe nadir Hb during CCRT is a factor deserving more emphasis. Best supportive care should be provided to prevent a low nadir Hb and improve the clinical outcome.

Different RT-related time factors have been investigated to affect treatment outcome in LA-SCCHN, including interval between surgery and RT,<sup>42</sup> RT treatment time,<sup>43–45</sup> and treatment package time.<sup>43,46</sup> We included all three variables and observed that longer RT treatment time was the only factor being associated with inferior outcomes. It has been hypothesized that prolonged RT periods may result in cancer cell repopulation and subsequent treatment failure.<sup>47</sup> The causes of prolonged RTT in this study were CCRT-related side effects, such as mucositis, dermatitis, fatigue, or infection. These factors should be solved with more delicate supportive care and patient education. Also, more precise radiation delivery and normal tissue protection might be helpful. Moreover, our data suggest that there may be synergistic effect of the two poor prognostic factors, prolonged RT treatment time and low nadir Hb, both of which might contribute to cancer cell repopulation and radioresistance.

In conclusion, both low nadir Hb during CCRT and prolonged RTT should be avoided in the clinical practice to maximize the efficacy of adjuvant CCRT and improve the treatment outcome in patients with locally advanced head and neck cancer.

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## Disclosure

The authors have declared no conflicts of interest.

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