·Original Article·

Continuous fall in hemoglobin level is a poor prognostic factor in patients with nasopharyngeal carcinoma treated with radiotherapy

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[**Abstract**] **Background and Objective:** Anemia can not only reduce the quality of life of patients with cancer, but also affect their survival. This study was to investigate the prognostic value of hemoglobin (Hb) level in patients with nasopharyngeal carcinoma (NPC) treated with radiotherapy. **Methods:** Clinical data of 520 NPC patients received definitive radiotherapy between 2000 and 2002 at Sun Yat-sen University Cancer Center were analyzed. Patients were stratified into normal Hb level and anemia groups according to their Hb levels before, during, and after radiation. Anemia was defined according to World Health Organization criteria as Hb level < 130 g/L in men and < 120 g/L in women. Hb continuous decrease group and non-decrease group were defined according to Hb changes in the patients during radiotherapy. Loco-regional recurrence-free survival (LRFS) and overall survival (OS) rates were estimated using the Kaplan-Meier method. Multivariate analysis was performed using the Cox model to analyze the prognostic factors. **Results:** Before radiation, the 5-year LRFS rates were 60.9% in anemia group and 63.9% in normal Hb level group (P = 0.337); the 5-year OS rates were 65.2% and 71.0%, respectively (P = 0.299). During radiation, the 5-year LRFS rates were 56.7% in anemia group and 67.9% in normal Hb level group (P = 0.013); the 5-year OS rates were 61.0% and 75.9%, respectively (P = 0.001). After radiation, the 5-year LRFS rates were 59.6% in anemia group and 64.9% in normal Hb level group (P = 0.169); the 5-year OS rates were 65.0% and 71.9%, respectively (P = 0.090). The 5-year LRFS and OS rates were significantly lower in Hb continuous decrease group than in Hb non-decrease group (59.1% vs. 69.3%, P = 0.032; 66.2% vs. 76.4%, P=0.011). Multivariate analysis showed that the continuous decrease of Hb was an independent prognostic factor for OS. **Conclusion:** The change in Hb level during radiotherapy is an important prognostic factor affecting the OS of NPC patients.

Key words: Nasopharyngeal neoplasm, radiotherapy, hemoglobin

Hemoglobin (Hb) is the main carrier of oxygen in human body and its amount will affect the oxygen content in body and tumor. Decreased Hb level will cause a decline of blood oxygen leading to tumor hypoxia and increased hypoxic cells, which will affect the efficacy of radiotherapy[1]. Rades *et al.*[2] and Schafer *et al.*[3] have found that anemia is an independent prognostic factor affecting the local control rate and survival rate in patients with head and neck squamous cell carcinoma, and emphasized that the patients with anemia should be paid attention to. The same result also appears in the studies of cervical and endometrial cancer[4,5]. However, is the Hb level before treatment[6], during treatment[7] or after treatment[8] affecting the prognosis in the end? Individual reports are not consistent. The reports about the impact of Hb level on the prognosis of patients with nasopharyngeal carcinoma (NPC) are limited. Chua *et al.*[9] studied 334 NPC patients receiving sequential radiotherapy and chemotherapy or radiotherapy alone, and found that the Hb level during radiotherapy was an important prognostic factor affecting the local control rate and survival rate, but the Hb level before radiotherapy did not. However, this study only analyzed the static Hb level before and during treatment, and did not take into account the effect of dynamic changes of Hb level during treatment on the prognosis. Rutkowski *et al.*[10] found that the local control rate of laryngeal cancer patients with decreased Hb level during radiotherapy was significantly lower than that of those without. Therefore, we hypothesized the continuous decline of Hb level during radiotherapy might affect the prognosis of NPC patients. In this study, we analyzed the clinical data of 520 NPC

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patients treated in our hospital to explore the effect of Hb level before, during, and after treatment and its dynamic changes on the prognosis.

Patients and Methods

Clinical information and general characteristics

A total of 600 patients were randomly selected on the computer using SAS software from 2100 NPC patients treated at Sun Yat-sen University Cancer Center between January 1, 2000 and December 31, 2002. The patients meeting the following criteria were enrolled: (1) pathologically proved NPC; (2) at first treatment; (3) receiving radical radiotherapy. A total of 520 patients met the above criteria, including 416 men and 104 women, with a man-to-woman ratio of 4∶1. The median age was 46 years old (range, 18 to 78 years). Of the 520 patients, 518 had poorly differentiated squamous cell carcinoma and 2 had adenoid cystic carcinoma. All patients received routinely nasopharyngeal CT or MRI examination before treatment and were staged according to the 1992 Fuzhou Staging System: 21 (4.1%) at stage I, 113 (21.7%) at stage II, 223 (42.9%) at stage III and 163 (31.3%) at stage IV. A total of 301 patients (57.9%) did not receive chemotherapy and 219 patients (42.1%) received. Other general characteristics of the patients are shown in Table 1.

Table 1 Clinical characteristics of nasopharyngeal carcinoma (NPC) patients with normal or low levels of hemoglobin during radiotherapy

Characteristic	Anemia	No anemia	χ^2	*P*
Total	206	314		
Age (years)			0.021	0.884
< 46	101	156		
⩾ 46	105	158		
Gender			3.891	0.049
Female	50	54		
Male	156	260		
T stage			7.176	0.067
T1	15	34		
T2	56	111		
T3	83	105		
T4	52	64		
N stage			36.742	0.001
N0	37	99		
N1	59	123		
N2	74	75		
N3	36	17		
Treatment modality			67.498	0.001
RT alone	74	227		
RT+CT	132	87		

RT, radiotherapy; CT, chemotherapy.

Standards of hemoglobin measurement and grouping

Hb level was measured before radiotherapy, ranging from 76 to 211 g/L, with a mean value of 143 g/L and a median value of 144 g/L. The Hb level during radiotherapy took the average of Hb values weekly during radiotherapy, ranging from 65 to 181 g/L, with a mean value of 131 g/L and a median value of 132 g/L. Hb level after radiotherapy was defined as the Hb value at the last week of radiotherapy, ranging from 64 to 178g/L, and the mean and median values were both 129 g/L. The patients were stratified into anemia and normal Hb level groups by the Hb level before, during and after radiotherapy according to the anemia standard of World Health Organization (Hb level < 130 g/L in men and < 120 g/L in women). According to the dynamic Hb changes before, during and after radiotherapy, 293 (56.3%) patients were classified as Hb continuous decrease group (before radiotherapy > during radiotherapy > after radiotherapy) and 227 (43.7%) as non-decreased group.

Treatment

Radiotherapy: Most patients received conventional fractionation radiotherapy with high energy 6–8 MV X-ray by linear accelerator. Isocenter radiation by face-neck joint field with low melting point lead block was used, and the radiation field included the skull base, nasopharynx and neck. Face-neck joint field and lower cervical anterior tangent field were irradiated firstly, with anterior nasal field added in some patients, to a total dose of 36 Gy, and then followed by bilateral preauricular fields plus anterior tangent field to a total dose of 60 to 78 Gy.

Chemotherapy: A total of 219 patients received combined radiochemotherapy, including 209 received induction chemotherapy (mostly was cisplatin (DDP) plus 5-fluorouracil (5-FU)) for 1 to 2 cycles and 10 received concurrent chemotherapy with DDP or 5-FU alone for 1 to 3 cycles.

Follow-up

The patients were followed up by re-examination, telephone, letter, and so on. Survival time was calculated from the start of treatment. The 1-, 3- and 5-year follow-up rates were 97.1%, 95.6% and 94.2%.

Statistical methods

SPSS13.0 software was used for statistical analysis. Life table method was used to calculate survival rates, the Kaplan-Meier method was used for survival analysis, a log-rank test was used for the comparison between the groups, and the Cox regression model was used for multivariate prognostic analysis. A *P* value less than 0.05 was considered statistically significant.

Results

Patients' survival

The 1-, 3- and 5-year local recurrence-free survival (LRFS) rates were 82.8%, 66.2% and 59.9%, and the overall survival (OS) rates were 87.8%, 75.2% and 66.2% for all patients.

The impacts of Hb levels in different phases on the LRFS rate and OS rate

Before radiotherapy, the 5-year LRFS rates were 60.9% in anemia group and 63.9% in normal Hb level group ($P = 0.337$), and the 5-year OS rates were 65.2% and 71.0% ($P = 0.299$). During radiotherapy, the 5-year LRFS rates were 56.7% in

anemia group and 67.9% in normal Hb level group (P = 0.013) (Table 2, Figure 1), and the 5-year OS rates were 61.0% and 75.9% (P = 0.001) (Figure 2). After radiotherapy, the 5-year LRFS rates were 59.6% in anemia group and 64.9% in normal Hb level group (P = 0.169), and the 5-year OS rates were 65.0% and 71.9% (P = 0.090).

Table 2 Univariate analysis of the factors related to the loco-regional recurrence-free survival (LRFS) of NPC patients

Prognostic factor	Patient No.	LRFS(%)	χ^2	P
Age (years)			9.573	0.002
<46	257	68.2		
⩾46	263	58.7		
Gender			2.223	0.140
Female	104	70.5		
Male	416	61.8		
T Stage			9.137	0.002
T1–2	216	70.0		
T3–4	304	58.7		
N Stage			0.647	0.420
N0–1	318	67.5		
N2–3	202	63.8		
Treatment modality			0.164	0.685
RT alone	301	66.5		
RT+CT	219	67.6		
Pre-radiation Hb			0.920	0.337
Anemia	83	60.9		
Normal	437	63.9		
Intra-radiation Hb			6.225	0.013
Anemia	206	56.7		
Normal	314	67.9		
Post-radiation Hb			1.896	0.169
Anemia	138	59.6		
Normal	382	64.9		
Hb dynamic change			4.606	0.032
Decrease	293	59.1		
Non-decrease	227	69.3		

Hb, hemoglobin. Other abbreviations as in Table 1.

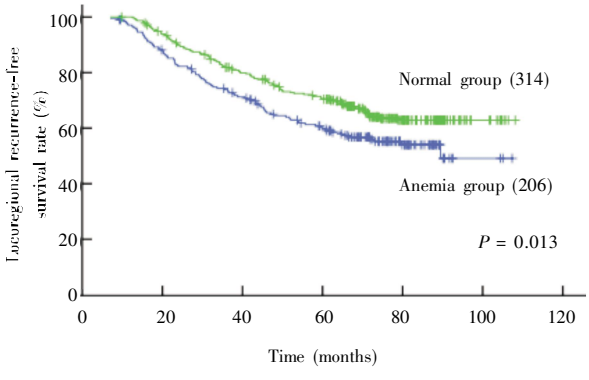

Figure1 Local recurrence-free survival (LRFS) curves of nasopharyngeal cancer (NPC) patients with different levels of hemoglobin (Hb) during radiotherapy

The 5-year LRFS rate is significantly lower in the patients with anemia during radiotherapy than in those without anemia.

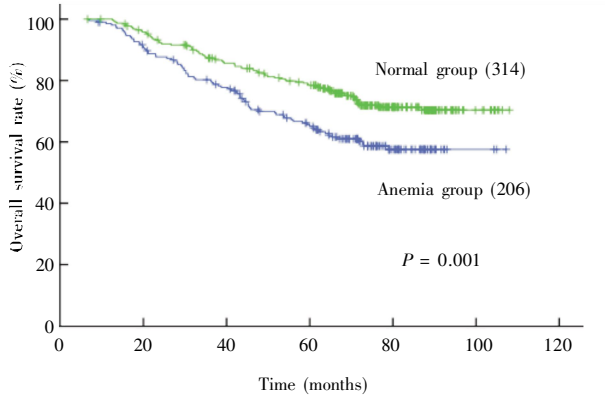

Figure 2 Overall survival (OS) curves of NPC patients with different levels of Hb during radiotherapy

The 5-year OS rate is significantly lower in the patients with anemia during radiotherapy than in those without anemia.

Further stratified analysis found that for T1–2N0–3 patients, the OS rate was significantly lower in anemia group during radiotherapy than in normal Hb level group (P = 0.001) (Figure 3), while for T1–2N0–1 (clinical stages I and II) and T3–4N0–3 patients, no significant differences were observed between the two groups (P = 0.590, P = 0.500).

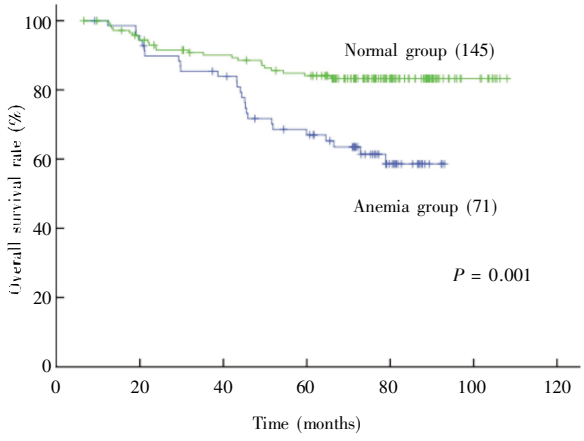

Figure 3 OS curves of stage T1–2N0–3 NPC patients with different levels of Hb during radiotherapy

The 5-year OS rate is significantly lower in the stage T1–2N0–3 patients with anemia during radiotherapy than in those without anemia.

The impacts of dynamic Hb level changes on the LRFS rate and OS rate

The 5-year LRFS rates were 59.1% in Hb continuous decrease group and 69.3% in non-decrease group (P = 0.032), and the 5-year OS rates were 66.2% and 76.4% (P = 0.011), respectively (Figures 4 and 5).

Further stratified analysis found that for the patients without anemia before radiotherapy, the LRFS and OS rates were significantly lower in Hb continuous decrease group than in in non-decrease group (P = 0.012, P = 0.005); while for those with anemia before radiotherapy, no significant differences were observed between the two groups (P = 0.920, P = 0.530).

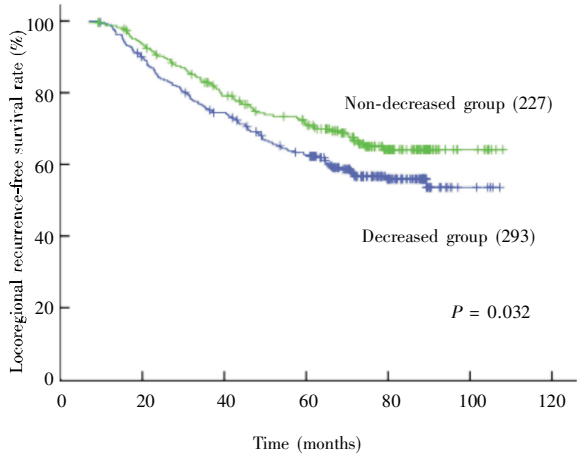

Figure 4 LRFS curves of patients with different Hb dynamic change trends

The 5-year LRFS rate is significantly lower in the patients in Hb decreased group than in those in Hb non-decreased group.

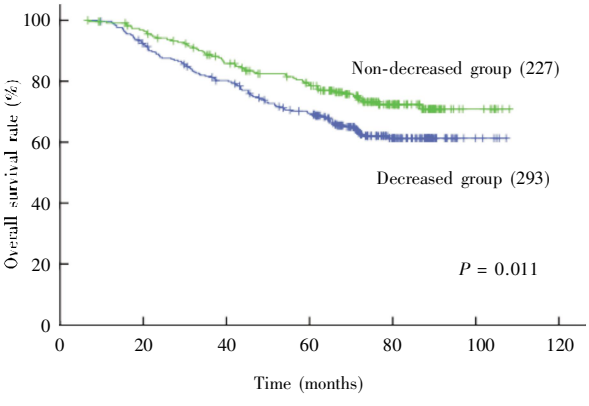

Figure 5 OS curves of patients with different Hb dynamic change trends

The 5-year OS rate is significantly lower in the patients in Hb decreased group than in those in Hb non-decreased group.

The patients with continuously decreased Hb were stratified into two groups according to the Hb level before treatment. No significant differences in LRFS rates (P = 0.871) and OS rates (P = 0.574) were observed between the patients with and those without anemia before radiotherapy.

Univariate analysis of other prognostic factors for LRFS

Univariate analysis showed that age and T stage were prognostic factors affecting the LRFS rate. The patients younger than 46 years had a higher LRFS rate than those no less than 46 years old, and T1–2 patients had a significantly higher LRFS rate than T3–4 patients (Table 2, Figure 6).

Multivariate analysis of local recurrence-free survival rate and overall survival rate

Multivariate analysis revealed that T stage, age and the Hb level during radiotherapy were potential independent prognostic factors affecting the LRFS rate (Table 3); T stage, age, N stage and Hb dynamic change were potential independent prognostic factors affecting the OS rate (Table 4).

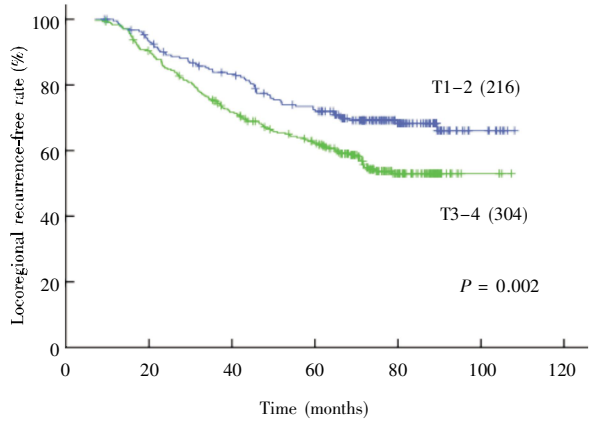

Figure 6 LRFS curves of patients at different T stages

The 5-year LRFS rate is significantly lower in the patients at stages T3–4 than in those at stages T1–2.

Table 3 Multivariate analysis of LRFS using the Cox proportional hazards regression model

Variable	B	SE	Wald	EXP(B)	*P*
T stage	0.434	0.153	8.115	1.544	0.004
Age	0.448	0.145	9.593	1.565	0.002
Intra-radiation Hb level	−0.320	0.144	4.959	0.726	0.026

Table 4 Multivariate analysis of overall survival using the Cox proportional hazards regression model

Variable	B	SE	Wald	EXP(B)	*P*
T stage	0.517	0.171	9.085	1.677	0.003
Age	0.349	0.159	4.820	1.417	0.028
N stage	0.688	0.157	19.143	1.990	0.000
Hb dynamic change	−0.367	0.165	4.973	0.693	0.026

Discussion

In this article, we studied the impacts of Hb level on the prognosis of NPC patients, and found that only the Hb level during radiotherapy was a prognostic factor affecting the LRFS and OS rates. The patients with anemia during treatment had significantly lower LRFS rate and OS rate than those without. Multivariate analysis showed that anemia during radiotherapy might be an independent prognostic factor affecting the LRFS rate. Our results are similar with that Chua *et al.*[9] reported. We also found that age and T stage might be independent prognostic factors affecting the LRFS rate, and that the patients with continuously decreased Hb during radiotherapy had lower LRFS rate and OS rate.

Nordsmark *et al.*[11] thought that Hb was an important prognostic factor affecting the LRFS rate in head and neck cancer patients treated by radiotherapy. Similarly, we also found that the patients with anemia during radiotherapy had a lower LRFS rate. The reason may be anemia promotes tumor

angiogenesis and causes tumor cells resisting apoptosis signal [12,13], and thus affects the efficacy of cancer treatment. In addition, anemia leads to an increase of hypoxic cells, which are resistant to radiotherapy and are considered as a main reason of local uncontrolled disease or recurrence after radiotherapy. Evans *et al.* [14] found that hypoxic cells exist in almost all solid tumors, generally account for 10% to 20% of all tumor cells, some as high as 50%. Most of hypoxic cells are in the G_0 phase of cell cycle, tend to have no or slow proliferation and be insensitive to radiotherapy and chemotherapy, and become one of the reasons why cancer is difficult to cure and easy to relapse. It may also be one of the reasons why NPC patients have a rising survival rate but the local recurrence rate is still as high as 20% to 40%[15].

Significantly, we found that for patients with stage-I and -II diseases, anemia during radiotherapy had no significant effect on their survival rate; while for patients at stage T1–2, anemia affected the survival rate obviously. This may be because patients with stage-I and -II diseases have relatively early N stages, N0 or N1, while some of patients at stage T1–2 have late N stages, N2 or N3. The latter patients have relatively poor performance status, as well as easily suffer from anemia because of tumor infiltration, so the prognosis is relatively poor and the survival rate decreases.

During treatment, Hb level will decrease due to the myelosuppression caused by radiotherapy and chemotherapy, tumor infiltration, as well as loss of appetite and nutritional deficiency caused by the reactions of chemotherapy and radiotherapy. The reason for the poor efficacy in patients with continuously decreased Hb is considered that the continuously decreased Hb during radiotherapy leads to reduced level of blood oxygen and causes tissue hypoxia, which increases hypoxic tumor cells and thus affects the efficacy of radiotherapy[1]. Rudat *et al.* [16] found that hypoxic tumor cell was an unfavorable factor affecting the local control rate and survival rate in head and neck cancer patients treated by radiotherapy. Tumor cells in hypoxic condition will highly express hypoxia-inducible factor-1 (HIF-1) which plays regulatory roles through binding to hypoxia-responsive elements that regulate downstream target genes (VEGF, p53, EPO, and so on). For example, HIF-1 induces cell cycle arrest by inhibiting proto-oncogene, and leads to the enhancement of malignant behavior of tumor cells[17], which become radiation resistant and thus affect the therapeutic effect.

Multivariate analysis found that continuously decreased Hb during radiotherapy might be an independent prognostic factor affecting the OS rate, suggesting that we should observe the changes of Hb during radiotherapy. Active treatments should be used for patients with continuously decreased Hb to treat anemia and prevent the decline of Hb. Common clinical treatments of anemia include blood transfusion, erythropoietin, and so on. However, it has been reported [18] that blood transfusion might cause immune suppression and increase the risk of infection from blood transfusion, and the shortage of blood also restricts the application. Therefore, erythropoietin is more and more used in clinic. Glaser *et al.*[19] studied 191 patients with oral cancer and oropharyngeal cance r, and found that erythropoietin could significantly improve the LRFS and OS rates. Similarly, Rades *et al.*[20] used erythropoietin in 42 patients with esophageal cancer, as compared with the control group, the 2-year OS rates were 32% and 8% (P = 0.009) and 2-year LRFS rates were 67% and 15% (P = 0.001), both of which were significantly improved. Charu *et al.*[21] also found that erythropoietin could increase Hb level, reduce blood transfusion and significantly improve patients' quality of life. Nevertheless, Smith *et al.*[22] thought that erythropoietin cannot prolong the survival time and benefit patients. Therefore, for the patients with low Hb level during radiotherapy, the specific treatment for anemia needs further clinical study.

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