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ORIGINAL RESEARCH

Anemia is a Prognostic Factor for Overall Survival Rate in Patients with Non-Small Cell Lung Cancer Treated with Stereotactic Body Radiation Therapy

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Purpose: Anemia has been associated with poor prognosis in patients with cancer across several cancer types. It has been identified as a prognostic factor in patients with non-small cell lung cancer (NSCLC) who have undergone surgery or chemoradiotherapy. However, there are only a few reports that have evaluated the prognostic significance of anemia in patients with NSCLC undergoing stereotactic body radiation therapy (SBRT).

Patients and Methods: A total of 77 patients were enrolled in this study. The pretreatment hemoglobin (Hb) levels, within 2 weeks before SBRT, were available for all patients. The median age of the participants (56 men, 21 women) was 80 (range, 50–90) years. The median Hb level was 12.8 (range, 7.8–18.3) g/dL. The median follow-up period was 24 (range, 1–87) months.

Results: Local recurrence was observed in 8 (10.4%) cases during the follow-up period. The 1- and 2-year local control (LC) rates were 94.8% and 86.4%, respectively. Seventeen (22.1%) patients died during the follow-up period. The 1- and 2-year overall survival (OS) rates were 93.1% and 85.2%, respectively. Univariate analysis identified anemia and body mass index as significant prognostic factors for predicting OS. On multivariate analysis, anemia was confirmed to be the only significant factor ($p = 0.02469$).

Conclusion: Our data suggest that anemia is a prognostic factor for predicting the OS rate in patients with early-stage NSCLC treated with SBRT.

Keywords: anemia, hemoglobin, non-small cell lung cancer, stereotactic body radiation therapy, stereotactic ablative body radiotherapy

Introduction

Among all cancers, lung cancer had the highest estimated incidence and mortality rates in 2018 worldwide.[1] An estimated 2,094,000 people worldwide were diagnosed with lung cancer in 2018, resulting in 1,761,000 deaths. Stereotactic body radiation therapy (SBRT) is an important treatment option for early-stage non-small cell lung cancer (NSCLC) with results comparable to surgery.[2] Nagata et al reported favorable outcomes in both operable and inoperable NSCLC cases treated by SBRT.[3] Chang et al reported good results of SBRT in a pooled analysis of patients enrolled in two phase-III trials that compared surgery with SBRT.[4]

Anemia has been associated with a poor prognosis in patients with cancer across various types of cancer.[5–10] In patients with NSCLC who undergo surgery.[11–13] or radiation therapy or chemoradiotherapy,[14–17] anemia has been reported as a poor prognostic factor. However, there is limited literature available on the prognostic

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significance of anemia in patients with NSCLC undergoing SBRT.[18,19] The purpose of this study was to evaluate the association between pre-treatment anemia and prognosis in patients with NSCLC treated with SBRT.

Materials and Methods

Patients

This retrospective study was conducted with the approval of institutional review board of Yamaguchi University Hospital, and all patients provided written informed consent before treatment. This study was conducted in accordance with the Declaration of Helsinki.

The inclusion criteria were as follows: patients with localized NSCLC, N0M0 disease, who were clinically inoperable or refused surgery, and were treated with SBRT, and for whom the hemoglobin (Hb) levels were available within 2 weeks before SBRT. Between September 2009 and September 2019, 77 patients meeting the inclusion criteria were identified and included in the study. Cases where the pathological diagnosis could not be confirmed were treated as NSCLC if the joint conference of respiratory surgeons, pulmonologists, radiologists, and radiation oncologists came to that consensus.

Planning and Irradiation

Before radiation treatment planning, patients were evaluated by four-dimensional computed tomography (4DCT) using Somatom (SIEMENS, Germany) for the amount of movement of the tumor caused by respiration. For 4DCT, real-time positioning management (RPM) system (Varian Medical Systems, USA) was used. Patients with respiratory motion of the tumor ≥1.0 cm were planned for the implantation of a fiducial marker which were implanted by bronchoscopy near the tumor. For every such patient, three markers were implanted.

All patients underwent CT scan under light exhalation breath-hold, and 4DCT were also performed using RPM. The slice thickness was 1.0 or 2.0 mm. Patients were immobilized using Vac-Loc Cushion (CIVCO Medical Solution, USA) with both their arms up. The clinical target volume (CTV) was defined as equal to the gross tumor volume (GTV). In patients with implanted fiducial markers, the internal target volume (ITV) was equal to the CTV. In contrast, summation of the GTVs defined at every respiratory phase of the 4DCT gave the ITV in patients without the fiducial marker. The planning target volume (PTV) was generated by adding 5 mm around the ITV. In principle, the prescribed dose for peripherally situated tumors was 50 Gy in 5 fractions until September 2016 and 48 Gy in 4 fractions after October 2016. The tumors with a central location near organs at risk were treated with 60 Gy in 8 fractions. A central tumor was defined as a tumor whose distance from the proximal bronchial tree was ≤2 cm. The dose was prescribed to the isocenter. Leaf margins were modified to cover the PTV by 80% of the prescribed dose. The linear accelerator used was MHCL-15DP (Mitsubishi Electronics, Japan) until September 2015, and TrueBeam (Varian Medical Systems, USA) after October 2015. Treatment planning used of 6–8 beams, including 4–6 non-coplanar beams.

The treatment for patients with implanted fiducial markers was performed under motion tracking using a real-time tumor tracking system (Mitsubishi Electronics, Japan) until September 2015 and SyncTraX (Shimadzu Corporation, Japan) after October 2015. In brief, the system consists of two sets of X-ray tubes under the floor and image intensifiers on the ceiling. The fiducial marker implanted near the tumor is easily visible on the radiograph and is tracked in real time. The position of the marker is recognized as a surrogate of the tumor position. The treatment beam turns on only when the marker is located within designated area. The detailed method has been described in literature earlier.[20]

The treatment for patients without fiducial marker was performed under light-free breathing.

Evaluation

The medical charts were reviewed and data pertaining to age, sex, performance status (PS), body mass index (BMI), operability, smoking history (current or past vs never smoker), the presence of diabetes mellitus (DM), the presence of pathological or cytological confirmation, tumor diameter, irradiation method (respiratory gated or not), and pretreatment Hb levels were obtained.

The World Health Organization defines BMI < 18.5 as underweight[21] Base on the BMI (kg/m^2) (calculated as follows: body weight (kg)/[height (m)]^2), the patients were classified into two groups (BMI < 18.5 and ≥18.5).

The survival periods were calculated from the completion of the SBRT.

The associations between Hb levels and other categorical variables were tested using Mann–Whitney *U*-test and the correlation with continuous variables was tested by Spearman's rank correlation coefficient. Local control (LC) and overall survival (OS) rates were calculated using the

Kaplan–Meier method, and group comparisons were made using the Log rank test. Univariate and multivariate Cox proportional hazard regression models were used to estimate the LC and OS rates. Variables for which the *p*-values were <0.10 in the univariate analysis were included in the multivariate analysis. Receiver-operating characteristic (ROC) analysis was performed to determine the optimal cut-off values for the pretreatment Hb level. A p-value <0.05 was considered to indicate a statistically significant difference.

Results

The patient characteristics are shown in Table 1. The median age of the 77 participants (56 men, 21 women) was 80 (range, 50–90) years. Most of the patients presented with a PS of 0 or 1 (n = 71, 92.2%). The median BMI was 21.5 (range, 13.1–37.3) kg/m^2. The median diameter of the tumor was 19 (range, 7–40) mm. More than half of the patients had a history of smoking (n = 57, 74.0%). The number of patients with a pathological confirmation of the diagnosis of NSCLC was 35 (45.4%). The number of patients with diabetes was 17 (22.1%). The reason for choosing SBRT was either inoperability (n = 56, 72.7%) or refusal of surgery (n = 21, 27.3%). The median Hb level was 12.8 (range, 7.8–18.3) g/dL.

The association between Hb levels and other parameters is shown in Table 2. The Hb levels were significantly lower in patients with lower BMI than in patients with a higher BMI. There was a weak positive correlation between Hb level and BMI. Also, the Hb levels were significantly higher in patients with a smoking history than in those without a smoking history. There was no significant correlation observed between Hb levels and the other parameters.

Table 1 Patients' Characteristics (N = 77)

Parameters	Median (Range)
Age (years)	80 (50–90)
Sex (male/ female)	56 (72.7%)/21 (27.3%)
PS (0/1/2/3)	41 (53.2%)/30 (39.0%)/ 5 (6.5%) /1 (1.3%)
BMI (kg/m^2)	21.5 (13.1–37.3)
(<18.5/≥18.5)	23 (29.9%)/54 (70.1%)
Operability (yes/no)	21 (27.3%)/51 (66.2%)
Smoking history (yes/no)	57 (74.0%)/20 (26.0%)
DM (yes/no)	17 (22.1%)/60 (77.9%)
Pathology (confirmed/unknown)	35 (45.5%)/ 42 (54.5%)
Tumor diameter (mm)	19 (7–40)
Irradiation (gating/non-gating)	58 (75.3%)/19 (24.7%)
Pretreatment Hb (g/dL)	12.8 (7.8–18.3)
Prescribed dose	
48 Gy in 4 fractions	50 (64.9%)
50 Gy in 5 fractions	23 (29.9%)
60 Gy in 8 fractions	4 (5.2%)
Follow-up periods (months)	24 (1–87)

Abbreviations: PS, performance status; BMI, body mass index; DM, diabetes mellitus; Hb, hemoglobin.

The median follow-up period was 24 (range, 1–87) months. Local recurrence was observed in 8 (10.4%) cases during the follow-up period. The 1- and 2-year LC rates were 94.8% and 86.4%, respectively. In univariate analysis, there was no significant prognostic value of the LC rate (Table 3).

Seventeen (22.1%) patients died during the follow-up period with 7 of them dying from lung cancer. The 1- and 2-year OS rates were 93.1% and 85.2%, respectively. Univariate analysis found anemia and BMI as significant factors for predicting the OS rates. Multivariate analysis confirmed anemia as the only significant independent prognostic factor (p = 0.02469) (Table 4). The optimal cut-off value of Hb level, as determined by ROC analysis, was 11.6 g/dL. The OS rates with lower Hb level were significantly poor than those with higher Hb level (p = 0.00767) (Figure 1). The 1- and 2-year OS rates for higher and lower Hb groups were 96.1% and 88.3%, and 84.4% and 76.0%, respectively.

Discussion

There was a weak positive correlation between Hb level and BMI. Hb levels in patients with lower BMI were significantly lower than in the group with higher BMI. This is explained by the fact that Hb level is correlated with nutritional status. That is, patients with poor nutrition had low Hb levels and low BMI. Hb levels were significantly higher in patients with smoking history than in those without smoking history. This was because most smokers were men. In fact, men (92.5%) had a significantly higher smoking history than women (40.0%) (Fisher's exact test, p = 0.00000735). Median pretreatment Hb levels in men and women were 13.1 (range, 8.9–18.3) and 11.4 (range, 7.8–14.6) g/dL, respectively. Because men had significantly higher Hb levels than women (p = 0.0187), and most smokers were men, smoking history could not be directly correlated with elevation of Hb levels.

In the recent years, there have been many reports indicating that pretreatment Hb levels significantly correlate with the outcomes in several types of cancer.[5–10] These reports include various treatment modalities, such as surgery, chemotherapy, radiation therapy, and combination of them. Though various

Table 2 Association Between Hb and Other Parameters

Categorical Variables		***p*-value**	
	Age (<80 vs ≥80) (years)	0.363	
	Sex (male vs female)	0.0187	
	PS (0 vs ≥1)	0.527	
	BMI (<18.5 vs ≥18.5) (kg/m2)	0.00974	
	Operability (yes vs no)	0.655	
	Smoking history (yes vs no)	0.00000735	
	DM (yes vs no)	0.854	
	Pathology (confirmed or unknown)	0.0677	
	Tumor diameter (<20 vs ≥20) (mm)	0.347	
	Irradiation (gating vs non-gating)	0.0752	
Continuous Variables		***p*-value**	***ρ***
	Age (years)	0.124	−0.177
	BMI (kg/m2)	0.046	0.228
	Tumor diameter (mm)	0.476	−0.0824

Abbreviations: Hb, hemoglobin; PS, performance status; BMI, body mass index; DM, diabetes mellitus.

Table 3 The Results of Univariate Analysis for Local Control Rate

Variables		**Local Control Rate**	
		Univariate	
		Hazard Ratio (95% CI)	**p value**
Age (years)	Continuous	0.9994 (0.9132–1.094)	0.9891
Sex	Male vs female	1.883 (0.2306–15.38)	0.5547
PS	0 vs ≥1	1.700 (0.4053–7.134)	0.4681
BMI (kg/m^2)	18.5< vs ≥18.5	2.974 (0.7009–12.48)	0.1363
Operability	Yes vs No	0.9538 (0.1917–4.745)	0.9539
Smoking history	Yes vs No	1.413 (0.1721–11.61)	0.7474
DM	Yes vs No	1.166 (0.3765–3.610)	0.7902
Pathology	Confirmed vs unknown	0.4003 (0.09509–1.685)	0.2219
Tumor diameter (mm)	Continuous	1.035 (0.9517–1.126)	0.4218
Irradiation	Gating vs non-gating	1.971 (0.2397–16.21)	0.5278
Pretreatment Hb (g/dL)	Continuous	0.8074 (0.5282–1.234)	0.3230

Abbreviations: CI, confidence interval; PS, performance status; BMI, body mass index; DM, diabetes mellitus; Hb, hemoglobin.

Table 4 The Results of Univariate and Multivariate Analysis for Overall Survival Rate

Variables		**Overall Survival Rate**			
		Univariate		**Multivariate**	
		Hazard Ratio (95% CI)	**p value**	**Hazard Ratio (95% CI)**	**p value**
Age (years)	Continuous	1.032 (0.9680–1.100)	0.3371		
Sex	Male vs female	1.743 (0.3875–7.843)	0.4689		
PS	0 vs ≥1	1.430 (0.5281–3.873)	0.4815		
BMI (kg/m^2)	18.5< vs ≥18.5	4.412 (1.515–12.85)	0.006483	2.6130 (0.8546–7.9900)	0.092100
Operability	Yes vs No	0.8752 (0.2817–2.719)	0.8177		
Smoking history	Yes vs No	0.5077 (0.1569–1.642)	0.2577		
DM	Yes vs No	1.166 (0.3765–3.610)	0.7902		
Pathology	Confirmed vs unknown	0.4064 (0.1519–1.087)	0.07297	0.8924 (0.3054–2.6080)	0.835200
Tumor diameter (mm)	Continuous	1.029 (0.9684–1.093)	0.3553		
Irradiation	Gating vs non-gating	0.5751 (0.1775–1.863)	0.3563		
Pretreatment Hb (g/dL)	Continuous	0.5647 (0.4037–0.7900)	0.0008476	0.5897 (0.4047–0.8593)	0.005974

Abbreviations: CI, confidence interval; PS, performance status; BMI, body mass index; DM, diabetes mellitus; Hb, hemoglobin.

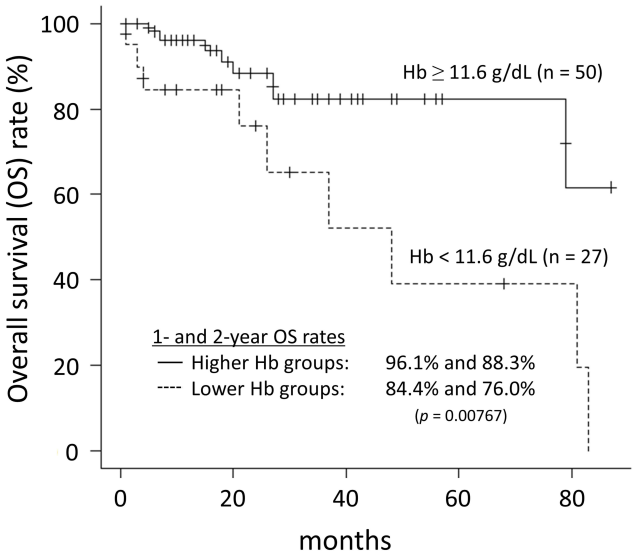

Figure 1 Overall survival rates for high and low hemoglobin groups.

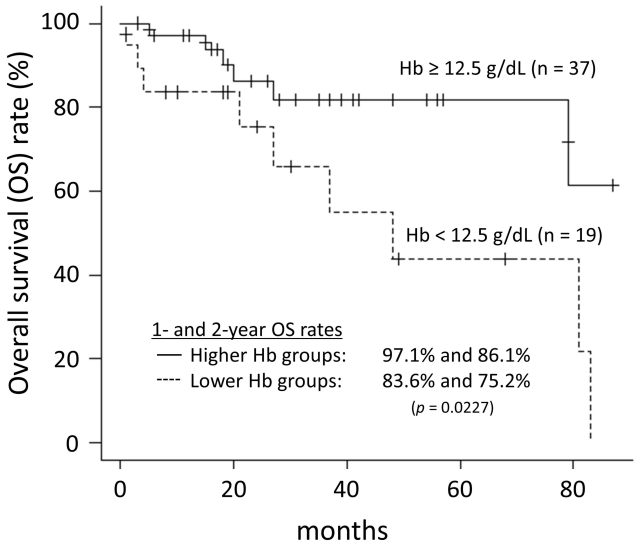

Figure 2 Overall survival rates of male patients for high and low hemoglobin groups.

outcome measures were reported, OS rates were most commonly reported. In patients with NSCLC, pretreatment Hb level was a significant predictor of prognosis in patients with treated by surgery or chemoradiotherapy.[11–17] However, literature about correlation between anemia and outcome in patients of NSCLC undergoing SBRT is lacking.[18,19] Shaverdian et al reported that pretreatment Hb levels correlated significantly with OS rate and non-local disease progression, but not with LC rate.[18] Their results were comparable to our results, where we found pretreatment Hb levels to correlate significantly with OS rate but not with the LC rate. As mentioned above, there is a significant difference in the Hb levels between males and females. However, since there were only 21 female enrolled patients, the relationship between Hb values and OS was analyzed for male patients only. The cutoff value for Hb was determined by ROC analysis, as in the case of the overall evaluation. The cutoff value for Hb in male patients was 12.5 g/dL. The OS in the lower Hb (<12.5 g/dL) group was significantly worse than that in the higher Hb (≥12.5 g/dL) group (p = 0.0227, Log rank test) (Figure 2).

Anemia is considered to cause intratumor hypoxia.[22] Because tumor hypoxia is one of the causes of radioresistance, patients with anemia are expected to have a lower LC rate post radiation therapy. However, in our results, pretreatment Hb levels correlated significantly with OS rate but not with the LC rate. There are a few hypotheses to explain this result. Hypoxia inducible factor (HIF) was discovered from hepatocellular carcinoma cell lines as a factor that could induce hypoxia-dependent erythropoietin.[23] HIF-1 induced the vascular endothelial growth factor, platelet-derived growth factor B, and basic fibroblast growth factor, and improved hypoxia.[24] In tumors, HIF-1 gets activated in response to hypoxia.[25] Therefore, it cannot be concluded that the oxygen concentration in the tumor of patients with a low serum Hb level will be lower than that of patients with a high serum Hb level. Additionally, HIF causes epithelial-mesenchymal transition and also promotes metastasis.[26] Hypoxia promotes tumor growth and progression to more aggressive character due to neo-angiogenesis, gene mutation, apoptosis inhibition, and free radical generation.[22,27–29]

SBRT is a relatively new treatment method. Many prognostic factors have been recently reported in patients with NSCLC who undergo SBRT, such as tumor size and standardized uptake value on 18F-fluorodeoxyglucose positron emission tomography.[30,31] Pretreatment Hb level is an easily derived and cost-effective blood parameter. Therefore, the utility of pretreatment Hb as a predictive prognostic indicator is high in the clinical setting.

Conclusion

Our data suggest that anemia is correlated with OS rates in patients with early-stage NSCLC who are treated with SBRT.

Disclosure

The authors report no conflicts of interest in this work.

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