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Analysis of the Effects of Bevacizumab Combined with Chemoradiotherapy on VEGF, bFGF, and Let-7 Levels in Non-Small Cell Lung Cancer and the Factors Influencing Therapeutic Efficacy: A Retrospective Cohort Study

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Objective: To explore the influence of bevacizumab combined with chemoradiotherapy on VEGF, bFGF, and Let-7 in patients with non-small cell lung cancer (NSCLC), and to analyze the factors affecting its efficacy.

Methods: Totally 150 patients with non-small cell lung cancer (NSCLC) treated in our hospital from November 2018 to November 2023 were retrospectively analyzed. The serum levels of VEGF, bFGF, and Let-7 were collected and compared. Patients were divided into good efficacy and poor efficacy groups based on short-term efficacy, and logistic regression analysis was used to analyze the factors affecting efficacy.

Results: Before treatment, there was no significant difference in the levels of VEGF, bFGF, and Let-7 between the two groups ($P>0.05$). After treatment, the levels of VEGF, bFGF, and Let-7 in both groups improved compared to before treatment, and compared with the control group, the study group had lower levels of VEGF and bFGF, and higher levels of Let-7, with statistically significant differences (all $P<0.05$). Multifactorial logistic regression analysis revealed that the course of disease, tumor diameter, and treatment regimen were independent factors influencing the therapeutic efficacy of NSCLC (all $P<0.05$).

Conclusion: For patients with NSCLC, the treatment regimen of bevacizumab combined with chemoradiotherapy can achieve better efficacy, with a higher objective response rate, effectively reduce the level of vascular endothelial growth factor, increase Let-7 level, and ensure safety. In addition, disease course, tumor diameter, and treatment regimen are independent factors affecting the efficacy of NSCLC. Therefore, these factors should be comprehensively considered when formulating treatment plans to ensure the best therapeutic effect.

Keywords: bevacizumab, non-small cell lung cancer, efficacy, adverse reactions, influencing factors

Introduction

Lung cancer stands as a formidable health challenge, characterized by a substantial incidence rate and an alarming mortality rate. Indeed, it has emerged as the leading cause of cancer-associated deaths worldwide. Among the diverse subtypes, non-small cell lung cancer (NSCLC) predominates, accounting for more than 80% of diagnosed cases.[1] NSCLC, characterized by its aggressive invasiveness and proclivity for metastasis, poses significant challenges due to the development of resistance mechanisms. These complexities have a profound impact on patient prognosis and necessitate innovative approaches to enhance treatment outcomes.[2]

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Concurrent chemoradiotherapy is a standard treatment regimen for NSCLC, particularly indicated for locally advanced stage III disease. It has been shown to inhibit tumor growth and extend patient survival by controlling locoregional disease progression.[3] VEGF is the most important pro-angiogenic factor in the angiogenesis process in lung cancer patients. VEGF is expressed in both small cell lung cancer and NSCLC, and overexpression of VEGF is associated with poor prognosis of lung cancer.[4] Bevacizumab is the first molecular targeted drug used in the treatment of NSCLC.[5] By binding to VEGF, bevacizumab can block tumor angiogenesis, inhibit tumor blood supply, and restrict tumor nutrition and oxygen supply, thereby inhibiting tumor growth and spread.[6] Studies have indicated that bevacizumab can improve the delivery of chemotherapy drugs to tumor tissues, enhancing the efficacy of chemotherapy.[7,8] Therefore, bevacizumab is often used in combination with chemotherapy drugs, and compared to traditional chemotherapy drugs, the adverse reactions and side effects of bevacizumab combined with chemotherapy drugs are relatively minimal.[9] B-fibroblast growth factor (b-FGF) is a growth factor that plays an important role in cell proliferation, differentiation, and angiogenesis. Studies have shown that b-FGF also plays a key role in the invasion and metastasis of NSCLC. MicroRNAs (miRNAs) are a class of non-coding small RNA molecules consisting of 18–25 nucleotides. It is generally believed that miRNAs play a crucial regulatory role in the post-transcriptional translation process. Approximately 50% of miRNAs in the human genome are located in chromosomal regions associated with tumors, suggesting their significant role in tumorigenesis.[10] Let-7, a member of the miRNA family, has been identified by Takamizawa et al as being downregulated in some lung cancer tissues and is considered a tumor suppressor gene. It negatively regulates multiple oncogenes, such as KRAS, cMYC, CDK6, HOXA9, TGFBR1, BCLXL, and MAP4K31, which are involved in promoting tumor development.[11] However, there is limited research on the effects of bevacizumab combined with concurrent chemoradiotherapy on the levels of VEGF, bFGF, and Let-7 in NSCLC patients, as well as the factors affecting efficacy.

Therefore, this study included 102 NSCLC patients treated in our hospital, analyzed the effects of bevacizumab combined with concurrent chemoradiotherapy on the levels of VEGF, bFGF, and Let-7 in NSCLC patients, and explored the factors affecting efficacy. It is hoped that this study can provide new insights into the treatment of NSCLC patients and provide scientific basis for subsequent treatment plans.

Materials and Methods

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Haikou Third People's Hospital. Informed consent was obtained from all study participants. All the methods were carried out in accordance with the Declaration of Helsinki.

Sample Source

After approval from the Medical Ethics Committee of our hospital, clinical data of 150 patients with non-small cell lung cancer (NSCLC) who were treated in our hospital from November 2018 to November 2023 were retrospectively analyzed. A total of 102 patients were selected based on the inclusion and exclusion criteria. Forty-nine patients who received conventional chemotherapy were included in the control group, while fifty-three patients who received bevacizumab combined with chemotherapy were included in the study group.

Inclusion criteria: confirmed stage III/IV NSCLC; eligibility for chemoradiotherapy based on ECOG performance status (≤2); absence of metastases before treatment; no severe liver or kidney diseases; no contraindications to chemotherapy or radiotherapy; availability of complete clinical data and related follow-up information; and no significant comorbidities (eg, cardiovascular disease, diabetes, or chronic obstructive pulmonary disease).

Exclusion criteria: Patients with concomitant other tumors; patients with severe complications such as serious infections; patients with diseases of the hematopoietic system, cardiovascular system, or nervous system; patients with other pulmonary diseases; patients transferred to other hospitals during treatment; active bleeding disorders, or a history of gastrointestinal perforation.

Treatment Regimen

Radiotherapy plus TP (docetaxel + cisplatin) in control group and radiotherapy, TP plus Bevacizumab in study group.

Radiotherapy: Three-dimensional conformal or intensity-modulated radiotherapy was selected. Patients were placed in the supine position, and radiation was delivered at a dose of 2 Gy per fraction, once daily, five times per week, with a total radiation dose of 60–70 Gy in 30 fractions over a period of 6–7 weeks.

TP scheme: Concurrent chemotherapy with docetaxel (Jiangsu Hengrui Medicine Co., Ltd.; National Drug Approval No. H20020543) and cisplatin (Jiangsu Hansoh Pharmaceutical Group Co., Ltd.; National Drug Approval No. H20040812) was initiated at the beginning of radiotherapy. The chemotherapy regimen consisted of docetaxel 75 mg/m2 on day 1 and cisplatin 70 mg/m2 on days 1–3, administered every 3 weeks for 2 cycles. After completion of radiotherapy, patients had a one-month rest period (to allow recovery from the acute toxicities of chemoradiotherapy and to assess the response to the initial treatment) before receiving 4 cycles of consolidation chemotherapy with the TP regimen. Before initiating consolidation chemotherapy, all patients underwent a restaging computed tomography (CT) scan to evaluate tumor response, confirm the absence of disease progression, and plan subsequent treatment.

Bevacizumab: On the first day of chemotherapy, bevacizumab (Nanjing Sunshine Pharmaceutical Co., Ltd.; National Drug Approval No. S20233105) was administered at a dose of 7.5 mg/m2 in 250 mL of 0.9% NaCl solution via intravenous infusion, repeated every 3 weeks. The infusion duration for the first administration of bevacizumab was 90 minutes. If the patient tolerated the infusion well, the duration for subsequent administrations could be reduced to 60 minutes, and further reduced to 30 minutes if tolerated well. Patients in the study group received a total of 6 cycles of bevacizumab therapy, initiated concurrently with chemotherapy at the start of radiotherapy and continued during consolidation chemotherapy. Bevacizumab administration was stopped upon completion of the planned chemotherapy cycles.

Detection Method

Real-time quantitative PCR (rt-PCR) was used to determine the expression of Let-7 in lung cancer tissues, and total RNA was extracted using the kit, reverse transcription and synthesis of cDNA, and β-actin was used as the internal reference. Let-7 primer sequence: 5'-GCCGCTGAGGTAGTAG GTTGTA-3' (sense strand); 5'-GTGCAGGGTCCGAGGT-3' (antisense chain); 5'-ATAGCACAGCCTGGATAG CAACGTAC-3' (sense chain); 5'-CACCTTCTACAATGAGCT GCGTGTG-3' (antisense chain). The reaction system used included 12.5 μL of SYBR PremixExTap, 1 μL of primers, 2 μL of DNA template, 0.5 μL of ROX Reference Dye (50×), and 8 μL of dH2O. The reaction conditions were 95°C, 5 s; 60 °C, 30 sec; 40 cycles. The relative expression of let-7 was calculated by 2-ΔΔCT method.

Evaluation Indicators

1. Four weeks following chemotherapy, the recent therapeutic efficacy of both patient groups was assessed using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), established in 2009. The evaluation criteria included: Complete Response (CR), defined as the complete disappearance of all lesions sustained for at least 4 weeks; Partial Response (PR), defined as a minimum 30% reduction in the sum of the longest diameters of target lesions sustained for at least 4 weeks; Stable Disease (SD), indicating insufficient shrinkage to qualify for PR and no significant increase to meet the criteria for Progressive Disease (PD); and Progressive Disease (PD), characterized by the appearance of new lesions or significant progression of existing lesions. The total response rate (RR), defined as the sum of CR and PR, was calculated based on RECIST 1.1 criteria. Additionally, adverse reactions, including pulmonary, esophageal, bone marrow, and skin-related effects, were assessed.

2. Adverse reactions, including pulmonary, esophageal, bone marrow, and skin-related effects, were assessed.

Statistical Analysis

Count data were expressed as n (%) and compared between groups using the chi-square test. Measurement data were expressed as ($x \pm sd$) and compared using the *t*-test between groups. Statistical analyses were conducted using SPSS 20.0, and graphs were generated using GraphPad Prism 8. Based on the patient's recent treatment results, the patients were divided into groups with good and poor treatment effects, and regression analysis was performed. Logistic regression analysis was performed to identify independent predictors of treatment efficacy. Variables with statistical significance in univariate analysis ($P < 0.1$) were included in the multivariate logistic regression model using a stepwise backward

elimination method. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated to quantify the strength of associations. A two-tailed P-value < 0.05 was considered statistically significant.

Results

Baseline Data

In the control group, there were 27 males and 22 females, with an age range of 55–77 years and a mean age of (68.96 ±2.85) years. Histological types included 26 cases of adenocarcinoma, 19 cases of squamous cell carcinoma, and 4 cases of large cell carcinoma. TNM staging showed 36 cases in stage III and 13 cases in stage IV. There were 20 smokers and 19 drinkers. In the study group, there were 34 males and 19 females, with a mean age of (68.74±2.69) years. Histological types included 30 cases of adenocarcinoma, 17 cases of squamous cell carcinoma, and 6 cases of large cell carcinoma. TNM staging showed 38 cases in stage III and 15 cases in stage IV. There were 28 smokers and 23 drinkers. There were no significant differences in baseline characteristics between the two groups (P>0.05), indicating comparability (Table 1).

Levels of VEGF, bFGF, and Let-7

Comparative analysis revealed no significant differences in the levels of VEGF, bFGF, and Let-7 between the two groups before treatment (P > 0.05). After treatment, both groups showed improvement in VEGF, bFGF, and Let-7 levels compared to before treatment. Moreover, the study group exhibited lower levels of VEGF and bFGF and higher levels of Let-7 compared to the control group, with statistically significant differences (P < 0.05), as shown in Figure 1.

Recent Therapeutic Efficacy

Comparative analysis revealed that the total response rate in the study group (86.79%) was significantly higher than that in the control group (55.10%), as detailed in Table 2.

Occurrence of Adverse Reactions

Analysis of adverse reactions in both groups showed no significant difference in the occurrence rate of adverse reactions (P = 0.0535), as detailed in Table 3.

Univariate Analysis of Factors Influencing Therapeutic Efficacy

Based on the assessment of therapeutic efficacy, patients who achieved complete or partial remission were divided into the good efficacy group (n = 73), while those who did not respond as favorably were categorized into the poor efficacy

Table 1 Baseline Data

	Control Group	Study Group	χ2/t	P
n	49	53		
Gender (male/female)	27/22	34/19	0.867	0.352
Age (years old)	68.96±2.85	68.74±2.69	0.401	0.689
Histological type			0.641	0.726
Adenocarcinoma	26	30		
Squamous cell carcinoma	19	17		
Large cell carcinoma	4	6		
Differentiation degree			0.953	0.329
High	23	30		
Low-medium	26	23		
TNM staging			0.629	0.318
III	36	38		
IV	13	15		
Smoker (Yes/no)	20/29	28/25	1.475	0.225
Drinker (Yes/no)	19/30	23/30	0.224	0.636

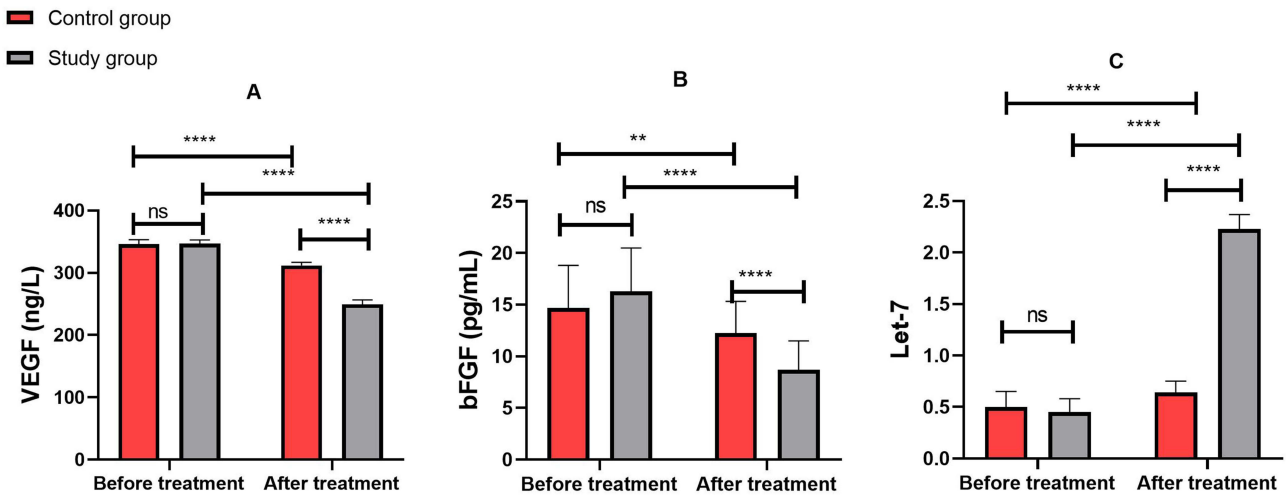

Figure 1 Comparison of VEGF, bFGF, and Let-7 levels in both groups. (**A**): Comparison of VEGF levels before and after treatment in both groups; (**B**): Comparison of bFGF levels before and after treatment in both groups; (**C**): Comparison of Let-7 levels before and after treatment in both groups.
Notes: nsP > 0.05; **P<0.01;****P<0.0001.

group (n = 29). Comparison of baseline characteristics between these two groups revealed no significant differences in terms of gender, tumor location, smoking history, or alcohol consumption (P > 0.05). However, notable distinctions were observed in age, duration of the disease, tumor diameter, KPS score, and treatment regimen. These factors have been identified as influential in determining the therapeutic efficacy of non-small cell lung cancer, as outlined in Table 4.

Multifactorial Logistic Regression Analysis

Values were assigned to the variables identified in Table 3, and logistic regression analysis was performed with efficacy as the dependent variable and age, course of disease, tumor diameter, KPS score, and treatment regimen as covariates, as shown in Table 5. Multifactorial logistic regression analysis was conducted to identify independent factors influencing therapeutic efficacy. The results demonstrated that disease duration (≥10 months), tumor diameter (≥5 cm), and treatment regimen (bevacizumab combined with chemotherapy) were statistically significant independent predictors of treatment outcomes. Patients with a shorter disease duration, smaller tumor diameter, and those treated with bevacizumab showed better therapeutic efficacy. The details are presented in Table 6.

Table 2 Comparison of Recent Therapeutic Efficacy [n(%)]

Group	n	Complete Remission	Partial Remission	Stable	Progression	The Total Response Rate (RR)
Control group	49	2 (4.08%)	25 (51.02%)	20 (40.82%)	2 (4.08)	27 (55.10%)
Study group	53	10 (18.87%)	36(67.92%)	6 (11.32%)	1 (1.89)	46 (86.79%)
$\chi 2$						12.571
P						<0.001

Table 3 Occurrence of Adverse Reactions

Group	n	Lung	Esophagus	Bone Marrow	Skin	Total
Control group	49	9 (18.37%)	5 (10.20%)	6 (12.24%)	15 (30.61%)	35 (71.42%)
Study group	53	6 (11.32%)	4 (7.55%)	6 (11.32%)	12 (22.64%)	28 (52.83%)
χ^2		–	–	–	–	3.7291
P		–	–	–	–	0.0535

Table 4 Univariate Analysis of Factors Influencing Patient Efficacy

Factors	Total	Good Efficacy	Poor Efficacy	χ2	P
n	102	73	29		
Age				4.9591	0.0260
≥68 years old	49	30	19		
< 68 years old	53	43	10		
Gender				0.3616	0.5476
Male	61	45	16		
Female	41	28	13		
Course of Disease				6.2601	0.0123
≥10 months	37	21	16		
< 10 months	65	52	13		
Tumor Diameter				9.3213	0.0023
≥5 cm	46	26	20		
< 5 cm	56	47	9		
Tumor Location				0.2941	0.5876
Central	47	35	12		
Peripheral	56	39	17		
KPS Score				6.4011	0.0114
≥80 points	62	50	12		
<80 points	40	23	17		
Treatment Regimen				12.571	0.0004
Bevacizumab plus TP	53	46	7		
TP	49	27	22		

Table 5 Assignment Table

Assignments	1	0
Covariates		
Age	≥68 years old	< 68 years old
Duration of disease	≥10 months	< 10 months
Tumor diameter	≥5 cm	< 5 cm
KPS score	<80 points	≥80 points
Treatment regimen	Chemotherapy	Bevacizumab combined with chemotherapy

Table 6 Multifactorial Logistic Regression Analysis

Factors	B	S.E	Wald	P	Exp (B)	EXP(B) 95% C.I.	
						Lower Limit	Upper Limit
Age	0.714	0.540	1.749	0.186	2.043	0.709	5.886
Disease duration	1.144	0.521	4.815	0.028	3.139	1.130	8.722
Tumor diameter	1.179	0.518	5.184	0.023	3.250	1.178	8.964
KPS score	0.943	0.515	3.352	0.067	2.569	0.936	7.053
Treatment regimen	1.447	0.544	7.076	0.008	4.250	1.464	12.345

Discussion

NSCLC is the most common type of lung cancer in clinical practice, and treatment typically involves combination regimens with chemotherapy as the mainstay.[12] Combination therapy can increase the toxicity of chemotherapy to tumors, improve tumor control rates, and thus prolong patient survival.[13] This study explored the effects of bevacizumab

combined with concurrent chemoradiotherapy on VEGF, bFGF, and Let-7 levels in NSCLC patients and analyzed the factors influencing its efficacy.

The study found that after treatment, the levels of VEGF, bFGF, and Let-7 in both groups of patients improved compared to before treatment. Additionally, compared to the control group, the study group showed lower levels of VEGF and bFGF, and higher levels of Let-7. This indicates that both treatment modalities have a positive impact on tumor growth and progression, with the combined treatment showing a more significant effect. VEGF and bFGF are two proteins associated with angiogenesis, playing crucial roles in tumor growth and metastasis.[14] Reducing VEGF and bFGF levels after treatment helps inhibit tumor angiogenesis, reducing tumor nutrition supply and growth. VEGF, as a critical regulator of angiogenesis, is significantly influenced by hypoxic conditions in the tumor microenvironment. Hypoxia-inducible factor-1 alpha (HIF-1α) mediates VEGF expression under hypoxic conditions, promoting tumor vascularization and adaptive metabolic shifts. Additionally, HIF-1α activates pathways such as glycolysis and lactate metabolism to support tumor survival and progression. These findings emphasize the role of the VEGF-HIF axis in NSCLC and highlight its potential as a therapeutic target.[15] LET-7 inhibits the occurrence, progression, invasion and metastasis of lung cancer by inhibiting the expression of related oncogenes, tumor angiogenesis, and improving the sensitivity of chemoradiotherapy and targeted therapy.[16,17] A large number of studies have shown that Let-7 has a tumor suppressive effect in various types of cancer, and overexpression of Let-7 can effectively inhibit the proliferation of tumors, and in vitro and in vivo experiments have shown that recovery or overexpression of Let-7 can inhibit the growth and migration of lung cancer and induce cell cycle arrest of lung cancer cell lines in vitro, making it a potential therapeutic target.[18,19] The growth and metastasis of tumor cells depend on the formation of neo neovascular tumors. The latest research has proved that Let-7 can inhibit the formation of microvessels around tumors, create a hypoxic state in tumor tissues and the destruction of tumor microenvironment, thereby inhibiting the growth and metastasis of tumors.[20] The increase in Let-7 levels after treatment helps suppress tumor cell proliferation and metastasis, thereby improving treatment outcomes. Furthermore, Let-7 may exert its tumor-suppressive effects through interactions with hypoxia-related pathways. By downregulating HIF-1α, Let-7 indirectly inhibits VEGF expression, thereby restricting tumor adaptation to hypoxic conditions. This inhibition of hypoxia-induced angiogenesis and metabolic reprogramming disrupts the tumor microenvironment, further reducing tumor growth and invasiveness.[21] Furthermore, this study compared the clinical efficacy of concurrent chemoradiotherapy and bevacizumab combined with concurrent chemoradiotherapy in the treatment of NSCLC. It found that the combined treatment regimen had more pronounced advantages, demonstrating both efficacy and safety. The efficacy is reflected in the significantly higher effective rate (86.79%) in the combined treatment group compared to the control group (55.10%), while the safety is reflected in the similar occurrence rates of adverse reactions between the two groups (P=0.0535). This indicates that using bevacizumab combined with concurrent chemoradiotherapy can maintain the stability of patients' conditions, achieve a higher remission rate, and does not increase adverse reactions.

The study also conducted logistic regression analysis to examine factors that influenced the therapeutic efficacy of NSCLC treatment. The results indicated that the duration of the disease, tumor diameter, and treatment regimen were independent factors that significantly impacted the treatment efficacy in NSCLC patients. The rationale for this analysis is as follows:

1. Duration of the disease: A longer duration of the disease suggests that the tumor may have progressed to an advanced stage, leading to a greater tumor burden and invasiveness. Consequently, patients with a longer duration of the disease may exhibit a poorer response to treatment. Additionally, a longer duration of the disease may indicate a poorer overall health status, resulting in reduced tolerance to treatment.[22]
2. Tumor diameter: Tumor diameter refers to the measurement of the tumor at its maximum size. A larger tumor diameter often signifies a larger tumor volume, which may exhibit further growth and spread.[23] Larger tumors are generally more challenging to completely remove and tend to respond poorly to treatment. Moreover, larger tumors can cause increased invasion and damage to surrounding tissues and organs.[24]
3. Treatment regimen: Bevacizumab, a monoclonal antibody targeting VEGF, was used in combination with chemotherapy in this study.[25] Compared to chemotherapy alone, the addition of bevacizumab to chemotherapy

has been associated with improved treatment outcomes. Bevacizumab functions by targeting VEGF, thereby inhibiting tumor angiogenesis, a crucial process in tumor growth and metastasis.[26,27] By reducing tumor blood supply, bevacizumab can impede tumor growth and spread, ultimately enhancing the efficacy of chemotherapy.

However, it is important to acknowledge some limitations of this study. The retrospective nature of the study introduces the possibility of unknown or unrecorded factors that may influence the results, potentially introducing bias. Therefore, future studies are encouraged to expand the sample size and conduct more comprehensive prospective research to enhance the validity and reliability of the findings.

Conclusion

The integration of bevacizumab with concurrent chemoradiotherapy holds promise for improving outcomes in patients diagnosed with NSCLC. This therapeutic approach has been associated with higher efficacy rates, demonstrated efficacy in reducing VEGF levels, and shown to elevate Let-7 levels. Importantly, it has also exhibited a satisfactory safety profile. Furthermore, the duration of the disease, tumor diameter, and treatment regimen have been identified as independent factors significantly impacting the effectiveness of NSCLC treatment. Consequently, when formulating treatment plans, a comprehensive consideration of these factors is imperative to ensure optimal treatment outcomes.

Disclosure

The authors report no conflicts of interest in this work.

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