

Retinal Microvascular and Microstructural Alterations in Lung Cancer Patients Treated with Albumin-Bound Paclitaxel: A Novel OCTA Approach

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Abstract

Background: Lung cancer is one of the most prevalent malignant tumors worldwide and one of the leading causes of cancer-related deaths. In the early stages, most lung cancer patients have no specific clinical signs or symptoms, which often leads to delayed diagnosis. By the time obvious symptoms appear, the disease has usually progressed to intermediate or advanced stages.

Objective: This study aimed to conduct a comprehensive investigation into the retinal microvascular and microstructural alterations, particularly retinal thickness and vascular density, in lung cancer (LC) patients treated with albumin-bound paclitaxel (ABP), and to explore their potential as biomarkers for disease monitoring and treatment evaluation.

Methods: A total of 20 healthy controls (HCs group, 40 eyes), 20 untreated LC patients (LC group, 40 eyes), and 20 LC patients treated with ABP (ABP group, 40 eyes) were enrolled in this study. Retinal thickness and superficial vessel density (SVD) were analyzed by optical coherence tomography angiography (OCTA) in nine subregions defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Statistical analyses included one-way ANOVA and Bonferroni correction for multiple comparisons as well as receiver operating characteristic curve analyses to compare groups and assess the diagnostic accuracy of measured parameters.

Results: Retinal microvessel density was significantly lower in LC patients compared to HCs ($p < 0.001$), and further lower in patients in the ABP group ($p < 0.001$). ROC analysis demonstrated high diagnostic accuracy in differentiating groups based on retinal thickness and SVD (area under the curve, $AUC > 0.7$). Dry eye parameters, including tear break-up time (tBUT), Schirmer test (SIT), and tear meniscus height (TMH), were significantly impaired in both the LC and ABP groups compared to HCs ($p < 0.001$), with no significant improvement observed after ABP treatment.

Conclusions: OCTA is effective in detecting retinal microvascular changes in LC patients that are exacerbated by ABP treatment. These findings suggest that retinal changes can be used as an adjunctive biomarker to monitor disease progression and treatment-related toxicity in patients with LC.

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Original Manuscript

Retinal Microvascular and Microstructural Alterations in Lung Cancer Patients Treated with Albumin-Bound Paclitaxel: A Novel OCTA Approach

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Abstract

Purpose: This study aimed to conduct a comprehensive investigation into the retinal microvascular and microstructural alterations, particularly retinal thickness and vascular density, in lung cancer (LC) patients treated with albumin-bound paclitaxel (ABP), and to explore their potential as biomarkers for disease monitoring and treatment evaluation.

Methods: A total of 20 healthy controls (HCs group, 40 eyes), 20 untreated LC patients (LC group, 40 eyes), and 20 LC patients treated with ABP (ABP group, 40 eyes) were enrolled in this study. Retinal thickness and superficial vessel density (SVD) were analyzed by optical coherence tomography angiography (OCTA) in nine subregions defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Statistical analyses included one-way ANOVA and Bonferroni correction for multiple comparisons as well as receiver operating characteristic curve analyses to compare groups and assess the diagnostic accuracy of measured parameters.

Results: Retinal microvessel density was significantly lower in LC patients compared to HCs ($p < 0.001$), and further lower in patients in the ABP group ($p < 0.001$). ROC analysis demonstrated high diagnostic accuracy in differentiating groups based on retinal thickness and SVD (area under the curve, $AUC > 0.7$). Dry eye parameters, including tear break-up time (tBUT), Schirmer test (SIT), and tear meniscus height (TMH), were significantly impaired in both the LC and ABP groups compared to HCs ($p < 0.001$), with no significant improvement observed after ABP treatment.

Conclusion: OCTA is effective in detecting retinal microvascular changes in LC patients that are exacerbated by ABP treatment. These findings suggest that retinal changes can be used as an adjunctive biomarker to monitor disease progression and treatment-related toxicity in patients with LC.

Keywords: Albumin-bound paclitaxel (ABP); optical coherence tomography angiography (OCTA); retinal thickness; vessel density; lung cancer (LC)

1.Introduction

Lung cancer is one of the most prevalent malignant tumors worldwide and one of the leading causes of cancer-related deaths[1]. In the early stages, most lung cancer patients have no specific clinical signs or symptoms, which often leads to delayed diagnosis. By the time obvious symptoms appear, the disease has usually progressed to intermediate or advanced stages[2]. This not only increases the difficulty of treatment, but also creates a huge economic burden and leads to a poor prognosis [3]. Lung cancer with ocular lesions is very rare and such cases usually portend a poor prognosis [4]. Lung cancer has been identified as one of the leading causes of retinal metastases, and patients with this disease suffer from up to 54% of cancer-related deaths per year [5]. Early detection and appropriate treatment can significantly improve or delay the deterioration of vision and thus improve the prognosis of patients.

Paclitaxel, a well - established antineoplastic agent, is formulated with various carriers to facilitate its delivery to the target tissue matrix due to its hydrophobic nature [6]. Derived from the bark of the Pacific yew (*Taxus brevifolia*), paclitaxel acts on microtubules and the microtubule system[7]. It promotes the polymerization of microtubule proteins into microtubules and inhibits microtubule depolymerization [8], ultimately blocking cell growth, inducing tumor cell atrophy, and potentially triggering apoptosis [9]. Clinically, paclitaxel is used to treat multiple cancers. Albumin - bound paclitaxel (ABP), also known as nab - paclitaxel or Abraxane, is a newer generation of paclitaxel formulation conjugated with human serum albumin (HSA) [10]. This conjugation enables more stable delivery of paclitaxel to tumor cells, leading to improved therapeutic efficacy and reduced side effects compared with traditional paclitaxel formulations [11]. The U.S. Food and Drug Administration (FDA) has approved the use of ABP for the treatment of a variety of cancers, including metastatic breast cancer, non-small cell lung cancer and pancreatic cancer[12]. In non - small cell lung cancer, ABP has been demonstrated to improve overall survival and progression - free survival compared with traditional paclitaxel formulations [13,14].

Optical coherence tomography angiography (OCTA) is an emerging noninvasive imaging technique.As a functional extension of optical coherence tomography (OCT), it can generate high - resolution angiographic images with volumetric blood flow information in a short period [15]. OCTA offers significant advantages in blood flow imaging, and its accurate and efficient imaging capabilities have been widely acknowledged. Currently, it is clinically used as a diagnostic tool [16]. There are numerous reports on the use of OCTA in various diseases such as thyroid-related eye disease, age-related macular degeneration and diabetes mellitus [17].

Previous studies have indicated that the use of ABP can cause a decrease in deep retinal vascular density, and this change becomes more pronounced after more than 5 years of drug use [18]. Some researchers consider this reduction in vascular density as a potential precursor of ABP toxicity; however, longitudinal studies are lacking [19]. The novelty of our study lies in using different partitioning methods to divide the OCTA fundus images into multiple areas, aiming to precisely locate the specific sites of altered microvascular density in patients' eyes. Moreover, we established three groups for comparison: patients who had used ABP, patients who had not used ABP, and healthy control subjects. This was to explore whether LC disease progression is involved in the process of ABP - induced reduction of fundus microvascular density.

2.Methods

2.1Subjects

This clinical controlled study was conducted from January 1, 2023 to December

31, 2023 in the Ophthalmology Department of the First Affiliated Hospital of Nanchang University. A total of 20 lung cancer patients (lung cancer group), 20 lung cancer patients treated with albumin-bound paclitaxel (ABP) for more than 6 months (ABP group), and 20 age- and sex-matched healthy controls (HC group) were recruited for the study. Ophthalmologists at the study center performed a thorough clinical examination of all subjects and optical coherence tomography angiography (OCTA) imaging to assess ocular abnormalities.

2.2 Inclusion Criteria

All patients were randomly selected from existing outpatient cases. The inclusion criteria were as follows: For the LC group, (1) newly diagnosed with LC; (2) no prior treatment with paclitaxel or its derivatives; (3) absence of immune system diseases such as Sjögren's syndrome and other corneal and ocular diseases. For the ABP group, (1) previously diagnosed with LC; (2) duration of paclitaxel treatment ≥ 6 months; (3) exclusion of immune system diseases such as dry eye syndrome and other corneal and ocular diseases. For the healthy controls (HCs), (1) no diagnosis of any physical disease; (2) no history of taking chemotherapy drugs such as paclitaxel and its derivatives or steroids.

2.3 Exclusion Criteria

Individuals meeting any of the following criteria were excluded: (1) systemic diseases, including neurological diseases that could affect the eyes and optic nerve; (2) metabolic diseases such as diabetes and hypertension; (3) retinal pathologies, such as glaucoma and arteriovenous diseases; (4) history of ophthalmic trauma or surgery; (5) other diseases that could affect fundus imaging; and (6) pregnant or breastfeeding women.

2.4 Ethical Statement

The study was conducted in strict accordance with the principles set out in the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (approval number: 2021039). Prior to enrollment, all participants received a comprehensive briefing on the study methods and potential risks and benefits. After being fully informed of these details, they submitted written informed consent to participate in the study.

2.5 Clinical Examinations

The patient underwent a series of clinical and ophthalmologic examinations: (1) pulmonary function tests and a CT scan of the lungs were used to confirm LC status; (2) the Hospital Anxiety and Depression Scale (HADS) was used to assess the patient's mental status; (3) a basic ocular examination included visual acuity (VA) measurements, intraocular pressure (IOP) measurements, ocular staining scores (OSS) (scores of 0 - 12), measurement of tear breakup using sodium fluorescein time (tBUT), tear meniscus height measurement, and Schirmer's test (SIT); (4) OCTA was performed to assess retinal microvascular and microstructural changes.

2.6 Ocular Surface Evaluation

Tear breakup time (BUT) was measured after uniformly applying sodium fluorescein to the ocular surface. The time from a blink until the initial tear film breakup was observed under cobalt - blue light. A BUT value < 10 s was considered positive. The ocular staining score (OSS) was evaluated by combining corneal fluorescein staining and conjunctival lysine green staining. An OSS score ≥ 3 was regarded as positive. For the Schirmer's test (SIT) without

anesthesia, one end of a 5 × 35 mm filter paper was folded at a right angle, sterilized, and placed in the conjunctival sac. An SIT value < 5 mm after 5 min was considered positive. For tear meniscus height (TMH) measurement, infrared light was used for focusing, and the patient was asked to blink. Subsequently, the TMH was measured and recorded with the Keratograph 5M under white - light exposure.

2.7 Optical coherence tomography angiography

The RTVue Avanti XR system (Optovue, Fremont, CA) was employed for OCTA imaging, which can display both retinal sections and microvasculature. In this study, the specific settings were as follows: The scanning speed is 70,000 A-scans per second with a center wavelength of 840 nm, a bandwidth of 45 nm, a horizontal resolution of 22 µm and an axial resolution of 5 µm. Five consecutive angiograms were obtained using the 6 × 6 mm scan pattern, with B - scans along the X - axis and 216 raster positions along the Y - axis, centered on the fovea. A total of 1080 B - scans (216y×5) were acquired at a frame rate of 270 frames per second. The entire scan duration was 3.9 s, and a three - dimensional 3 × 3 mm OCTA image of each eye was generated.

Classification of retinal subregions based on the Early Treatment Diabetic Retinopathy Study (ETDRS) (defined by three concentric circles with radii of 0.5, 1.5, and 3 mm), the retina was divided into nine regions for thickness analysis. These nine regions included the inner nasal (IN), outer nasal (ON), inner inferior (II), outer inferior (OI), inner temporal (IT), outer temporal (OT), inner superior (IS), outer superior (OS), and foveal center (C). Inner retinal thickness (inner RT) is the thickness from the inner limiting membrane (ILM) to the inner plexiform layer, and full retinal thickness (full RT) is the thickness from the ILM to the retinal pigment epithelium (RPE). Outer retinal thickness (outer RT) was calculated as the difference between the full layer RT and the inner layer RT. Vessel density was calculated from the center of the macula to the edge of the 3 mm × 3 mm brightness gradient image by constructing a model and measuring macular retinal thickness and superficial vessel density (SVD). Data were initially obtained from the right eye of all participants. For left - eye data, they were flipped, and then the two sets of data were averaged for analysis (shown in Figure 1).

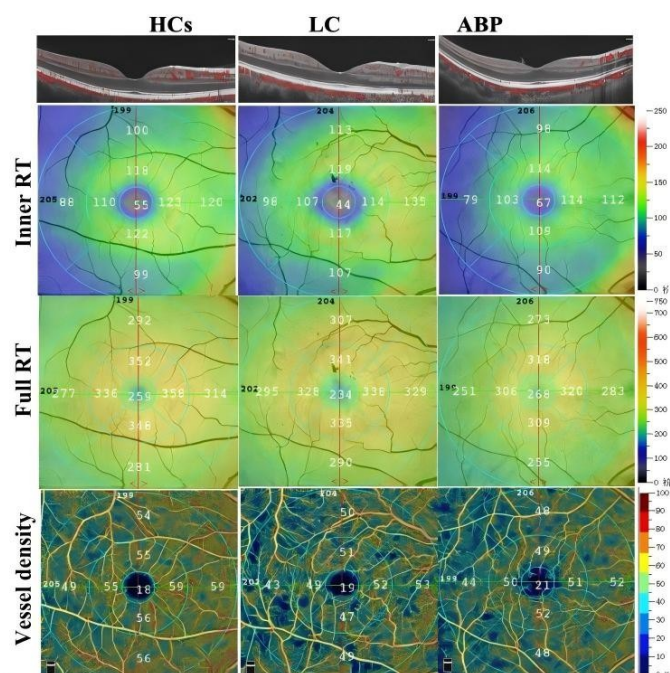


Figure1:RT in a cross-sectional OCTA study of LC,ABP and control group. ETDRS was used to evaluate the inner, full RT, and SVD. HCs, healthy controls; LC, lung cancer; ABP, albumin-bound paclitaxel;RT, retinal thickness; superficial vessel density.

2.8 Statistical Analysis

All statistical analyses were performed using GraphPad Prism 9.0 (GraphPad Software, San Diego, CA). Continuous variables are expressed as mean $\pm$ standard deviation (SD). To assess between-group differences, a one-way ANOVA with Bonferroni post hoc correction was used. Diagnostic accuracy of OCTA parameters was assessed by receiver operating characteristic curves (ROC). Linear regression was used to analyze the relationship between HADS score and disease duration. Statistical significance was determined when the P-value was less than 0.05.

3. Results

3.1 Subjects

A total of 60 participants were recruited for this study, including 20 lung cancer (LC) patients (40 eyes), 20 LC patients treated with albumin - bound paclitaxel (ABP) (40 eyes), and 20 healthy controls (HCs) (40 eyes). No significant differences in age, blood pressure, duration of ABP treatment, or intraocular pressure (IOP) among the three groups. However, the Hospital Anxiety and Depression Scale (HADS) scores (HCs: 2.60 ± 1.14 , LC: 6.40 ± 1.23 , ABP: 8.70 ± 2.25) and visual acuity (HCs: 0.84 ± 0.18 , LC: 0.68 ± 0.21 , ABP: 0.57 ± 0.16) of the LC and ABP groups were significantly higher than those of the HCs ($P < 0.001$). Significant differences were also observed in tear breakup time (tBUT) (HCs: 11.92 ± 3.70 s, LC: 4.85 ± 1.00 s, ABP: 4.97 ± 0.92 s), ocular staining score (OSS) (HCs: 0, LC: 3.45 ± 1.93 , ABP: 3.00 ± 1.13), Schirmer's test (SIT) result (HCs: 11.00 ± 4.05 mm, LC: 3.12 ± 1.26 mm, ABP: 3.15 ± 0.70 mm), and tear meniscus height (TMH) (HCs: 0.49 ± 0.20 mm, LC: 0.15 ± 0.04 mm, ABP: 0.15 ± 0.04 mm) between the LC and ABP groups compared to the HCs group ($p < 0.001$). Specifically, tBUT, SIT, and TMH decreased, while OSS increased in the LC and ABP groups compared with HCs. These data suggest that ABP treatment does not effectively improve the dry-eye condition in LC patients. Detailed data are shown in Table 1.

Table1. Basic characteristics of subjects.

	HCs	LC	ABP	P-value
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Age (years, mean $\pm$ SD)	61.35 $\pm$ 5.25	59.85 $\pm$ 6.0	60.85 $\pm$ 4.9	N/S
Duration (month)	/	/	16.45 $\pm$ 9.5	N/A
Diastolic blood pressure (mmHg)	126.80 $\pm$ 13.45	126.50 $\pm$ 5.95	120.95 $\pm$ 4.88	N/S
Systolic blood pressure (mmHg)	82.55 $\pm$ 5.86	82.40 $\pm$ 9.01	74.80 $\pm$ 10.18	N/S
Average visual acuity	0.84 $\pm$ 0.18	0.68 $\pm$ 0.21	0.57 $\pm$ 0.16	<0.001
Average IOP (mmHg)	15.25 $\pm$ 1.49	15.13 $\pm$ 1.60	15.20 $\pm$ 1.91	N/S
Average tBUT (s)	11.92 $\pm$ 3.70	4.85 $\pm$ 1.00	4.97 $\pm$ 0.92	<0.001
Average OSS	0	3.45 $\pm$ 1.93	3.00 $\pm$ 1.13	<0.001
Average SIT (mm)	11.00 $\pm$ 4.05	3.12 $\pm$ 1.26	3.15 $\pm$ 0.70	<0.001
Average TMH (mm)	0.49 $\pm$ 0.20	0.15 $\pm$ 0.04	0.15 $\pm$ 0.04	<0.001
Average HADS	2.60 $\pm$ 1.14	6.40 $\pm$ 1.23	8.70 $\pm$ 2.25	<0.001

Abbreviations: HCs, healthy controls; LC, lung cancer; ABP, albumin - bound paclitaxel; IOP, intraocular pressure; NA, not applicable; NS, not significant; OSS, ocular staining score; SIT, Schirmer's test; tBUT, tear breakup time; TMH, tear meniscus height. $p < 0.001$ for HCs versus LC and HCs versus ABP.

3.2 Macular Retinal Thickness

Through image segmentation (Figure 1), significant differences were identified between the HCs and LC groups: The full RT in the IS, OS, IT, and OT regions of LC patients was significantly lower than that of HCs ($P < 0.05$) (Figure 1A). No significant differences ($P > 0.05$) were found in inner RT. The outer RT in the IS, OS, ON, IT, II, OT, and C regions of LC patients was also significantly lower compared to HCs ($P < 0.05$) (Figure 1C). Significant differences were also observed between the ABP and LC groups: The full RT in the OI and II regions of ABP - treated patients was lower than that of LC patients ($P < 0.05$) (Figure 1E). Inner RT showed no significant differences ($P > 0.05$). The outer RT in the OI and II regions of ABP - treated patients was significantly lower than that of LC patients ($P < 0.001$). A comprehensive comparison of RT among the three groups is presented in Figures 1 and Table 2.

3.3 Superficial Macular Retinal Vascular Density

The superficial vessel density (SVD) of different retinal regions is presented in Figures 1 and Table 3. The SVD in the IT, OT, IS, OS, ON, and C regions of LC patients was significantly lower compared to that of HCs ($P < 0.05$). When comparing the ABP group with the LC group, significant differences in SVD were identified in the II, OI, IT, and C regions ($p < 0.05$; as shown in Figures 2 and Table 3). These results suggest that both LC and ABP treatment have distinct

[illegible]

TABLE 2 Comparison of macular retinal thickness at different locations among three groups .

[unpublished, non-peer-reviewed preprint]

N	115.95±5.56	113.90±8.78	0.216	111.67±8.84	113.90±8.78	0.262
ON	124.03±4.36	121.25±6.61	0.030 *	118.63±5.69	121.25±6.61	0.061
	114.83±5.30	111.22±6.33	0.007 **	97.88±11.08	111.22±6.33	0.000 **
OI	103.47±6.56	101.72±8.53	0.307	92.53±5.29	101.72±8.53	0.000 **
IT	105.03±3.68	90.00±6.12	0.000 **	88.65±7.99	90.00±6.12	0.399
OT	94.38±5.13	85.55±7.18	0.000 **	82.78±5.31	85.55±7.18	0.053
C	52.42±5.19	48.40±5.49	0.001 **	46.70±5.58	48.40±5.49	0.174

Macular inner retinal thickness (μm, mean ± SD)

S	218.82±14.41	215.03±16.4 3	0.275	213.47±17.89	215.03±16.4 3	0.688
OS	186.45±14.92	180.95±22.4 9	0.202	178.88±24.77	180.95±22.4 9	0.696
N	207.60±13.94	208.43±15.2 3	0.801	206.68±27.71	208.43±15.2 3	0.727
ON	192.43±9.68	193.75±11.0 9	0.571	193.25±23.63	193.75±11.0 9	0.904
	209.15±13.67	210.88±21.7 0	0.672	211.95±22.60	210.88±21.7 0	0.829
OI	175.85±8.32	176.47±26.8 9	0.889	167.22±23.80	176.47±26.8 9	0.107
IT	210.10±14.62	212.75±11.9 0	0.377	209.85±21.84	212.75±11.9 0	0.464
OT	180.90±8.92	180.35±18.4 4	0.866	180.68±19.29	180.35±18.4 4	0.939
C	192.43±31.31	186.63±13.7 7	0.288	183.63±17.38	186.63±13.7 7	0.395

p<0.05 ** p<0.01

Independent-samples t-test. Bold indicates $P < 0.05$. C, center; II, inner inferior; IN, inner nasal; IS, inner superior; IT, inner temporal; OI, outer inferior; ON, outer nasal; OS, outer superior; OT, outer temporal. HCs, healthy controls; LC, lung cancer; ABP, albumin-bound paclitaxel

TABLE 3 Comparison of superficial vessel density at different locations among three groups .

Location	ABP group vs. LC group (μm, mean ± SD)		P-value ^a	HCs group vs. LC group (μm, mean ± SD)		P-value ^a
	ABP (n=20, 40e yes)	LC (n=20, 40e yes)		HCs (n=20, 40e yes)	LC (n=20, 40e yes)	
S	46.83±7.91	48.60±4.27	0.216	53.90±3.27	48.60±4.27	0.000 *
OS	44.55±6.17	45.63±6.13	0.437	51.55±2.65	45.63±6.13	0.000 *
N	49.05±4.07	50.65±4.23	0.089	51.30±3.44	50.65±4.23	0.453
ON	50.38±5.15	51.55±4.45	0.278	53.80±2.68	51.55±4.45	0.008 *
I	47.33±2.62	51.13±8.62	0.011 *	52.40±3.74	51.13±8.62	0.395

OI	47.08±7.20	51.30±5.09	0.003 **	52.30±2.79	51.30±5.09	0.281
IT	47.13±4.21	48.95±3.10	0.031 *	54.50±2.86	48.95±3.10	0.000* *
OT	45.95±3.05	46.58±3.26	0.379	50.80±2.78	46.58±3.26	0.000* *
C	19.80±2.29	21.73±3.65	0.006 **	24.93±4.17	21.73±3.65	0.000* *

p<0.05 ** p<0.01

^aIndependent-samples t-test. C, center; II, inner inferior; IN, inner nasal; IS, inner superior; IT, inner temporal; OI, outer inferior; ON, outer nasal; OS, outer superior; OT, outer temporal; LC, lung cancer; HCs, healthy controls; ABP, albumin-bound paclitaxel

3.4 ROC Curve Analysis of RT and SVD

The OCTA technique demonstrated high specificity and sensitivity in differentiating retinal density changes among the HCs, LC, and ABP groups. The results of the ROC analysis with the largest area under the curve (AUC) are reported (Figure 2). For the ROC curve analysis of retinal thickness and superficial vessel density between the LC and HCs groups (a - b): The AUCs for the RT ROC curves were as follows: full IS = 0.785 (95% CI: 68.67% - 88.27%); full OS = 0.763 (95% CI: 65.44% - 87.06%); full OT = 0.775 (95% CI: 67.05% - 88.01%); full IT = 0.768 (95% CI: 65.87% - 87.75%); outer IS = 0.924 (95% CI: 86.78% - 98.03%); outer OS = 0.861 (95% CI: 76.70% - 95.49%); outer OT = 0.820 (95% CI: 73.12% - 90.88%). The AUCs for the SVD ROC curves were as follows: OS = 0.802 (95% CI: 69.50% - 90.87%); IT = 0.902 (95% CI: 83.69% - 96.62%); OT = 0.857 (95% CI: 77.25% - 94.19%). Regarding the ROC curve analysis of retinal thickness and superficial vessel density between the ABP and LC groups (c - d): The AUCs for the RT ROC curves were as follows: full OI = 0.701 (95% CI: 58.75% - 81.44%); outer OI = 0.808 (95% CI: 71.42% - 90.27%); outer II = 0.838 (95% CI: 75.25% - 92.37%). The AUCs for the SVD ROC curves were as follows: OI = 0.695 (95% CI: 0.579 - 0.810); C = 0.695 (95% CI: 0.576 - 0.814) (Figure 3). These ROC curve results indicate that retinal thickness and SVD measured by OCTA have the potential to distinguish different groups, providing valuable diagnostic information.

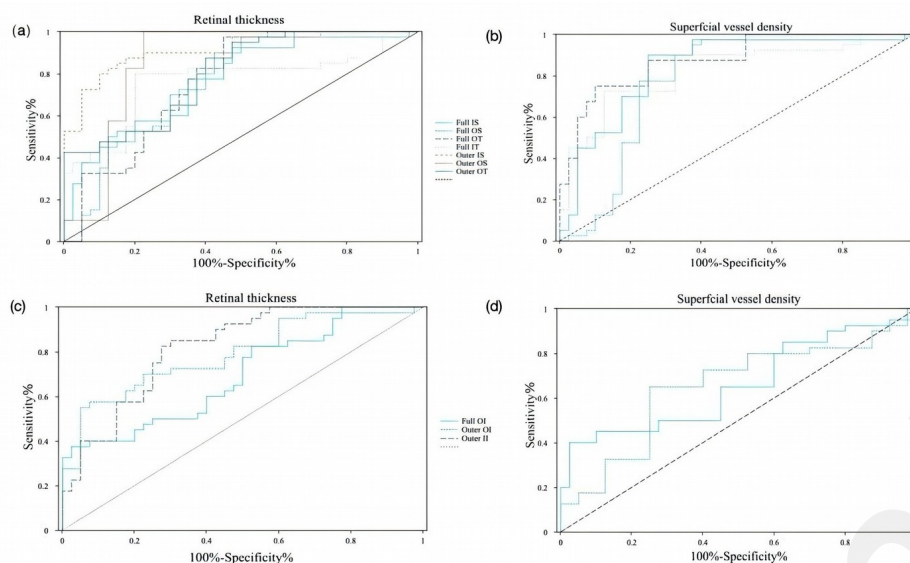


Figure 3 .ROC curve analysis of retinal thickness and superficial vessel density
ROC curve analysis of retinal thickness and superficial vessel density between the LC and HC groups (a - b). The area under the curve (AUCs) for RT ROC curves were as follows: full IS = 0.785 (95% CI: 68.67% - 88.27%); full OS = 0.763 (95% CI: 65.44% - 87.06%); full OT = 0.775 (95% CI: 67.05% - 88.01%); full IT = 0.768 (95% CI: 65.87% - 87.75%); outer IS = 0.924 (95% CI: 86.78% - 98.03%); outer OS = 0.861 (95% CI: 76.70% - 95.49%); outer OT = 0.820 (95% CI: 73.12% - 90.88%). The AUCs for SVD ROC curves were as follows: OS = 0.802 (95% CI: 69.50% - 90.87%); IT = 0.902 (95% CI: 83.69% - 96.62%); OT = 0.857 (95% CI: 77.25% - 94.19%). ROC curve analysis of retinal thickness and superficial vessel density between the ABP and LC groups (c - d). The area under the curve (AUCs) for RT ROC curves were as follows: full OI = 0.701 (95% CI: 58.75% - 81.44%); outer OI = 0.808 (95% CI: 71.42% - 90.27%); outer II = 0.838 (95% CI: 75.25% - 92.37%). The AUCs for SVD ROC curves were as follows: OI = 0.695 (95% CI: 0.579 - 0.810); C = 0.695 (95% CI: 0.576 - 0.814). C, center; CI, confidence interval; II, inner inferior; IN, inner nasal; IS, inner superior; OI, outer inferior; ON, outer nasal; ROC, receiver operating characteristic; RT, retinal thickness; SVD, superficial vessel density. HCs, healthy controls; LC, lung cancer; ABP, albumin - bound paclitaxel.

4. Discussion

This study demonstrated that lung cancer significantly reduces ocular vascular density, which is exacerbated by ABP treatment. In addition, ABP treatment was not effective in improving dry eye symptoms associated with lung cancer.

Lung cancer is a malignant tumor that originates in the bronchial mucosa or glands of the lungs. Its development is associated with multiple factors, such as family genetics, long - term dust inhalation, and frequent smoking [20]. As one of the malignancies with a relatively high incidence [21], the treatment of lung cancer mainly includes surgical resection, radiotherapy, chemotherapy, targeted therapy and immunotherapy [22]. Intraocular metastasis of lung cancer is mainly related to hematogenous dissemination of tumor cells. The specific site of tumor cell colonization in the eye is closely associated with the unique blood - supply characteristics of the eye. Specifically, due to its rich blood supply, the posterior pole of the choroid is the most common site of intraocular metastasis, while the retina and optic nerve glands, solely supplied by the central retinal artery, are rarely affected [23]. When the retina is involved, tumor cells first infiltrate the inner retina and may spread through the central retinal artery that nourishes the inner retina. [24].

OCTA, a non - invasive screening technique, has been proven effective in accurately and reliably detecting retinopathy in neurodegenerative and vascular diseases [25]. In this study, we utilized OCTA to examine the retinal vessel density in LC patients and those treated with ABP. The results showed that the retinal vessel density was significantly lower in LC patients compared to healthy controls and was further decreased in ABP - treated patients. Previous studies

have reported that reduced vascularity is common in LC patients, indicating that a decrease in fundus vascular density may be associated with LC and could potentially serve as a biomarker [26]. For instance, in unilateral retinal vein occlusions, the microvascular density in the ipsilateral eye decreases, and the thickness of the retinal nerve-fiber layer and ganglionic-intracellular-plexiform layer was positively correlated with vascular density and capillary-plexus perfusion pressure.[27]. In another study on a systemic disease, structural changes in the retina were found to be closely related to alterations in microvascular density, suggesting subclinical retinal ischemia accompanied by neurodegeneration [28]. It has also been reported that in LC, ischemic damage to the retina is related to perfusion pressure, and neuropathy and microvascular changes are highly correlated in the early stages of the disease [29].

The retina is one of the most vascularized tissues in the body and is highly susceptible to inflammation. The activation of the immune response can cause damage, triggering platelet activation and clotting pathways, which in turn form intravascular microthrombi, leading to tissue ischemia and chronic hypoxia [30]. The high sensitivity of the retina to subclinical changes allows it to reflect many pre - clinical symptoms, which is of great clinical significance in the context of ABP treatment for LC. Retinal vascular changes can provide a basis for the early differentiation of neurological disorders [31]. The decrease in vascular density in the ABP group may be attributed to the retinal toxicity of ABP. ABP inhibits the function of lysosomes and the endocytosis of retinal pigment epithelium (RPE) cells, preventing the degradation of old photoreceptor outer segments [32]. Additionally, the entrapment of ABP in the RPE leads to lipofuscin accumulation, resulting in photoreceptor damage and visual - acuity loss [33]. Overall, ABP accumulation in the RPE and retina can cause damage to these tissues. Therefore, we hypothesize that ABP accumulation in the retina leads to retinal ischemia and hypoxia, ultimately resulting in a decrease in vascular density.

Dry eyes are primarily associated with lid - gland dysfunction. Previous studies have reported decreased corneal sensory nerve fiber density and function and decreased tear production in keratoconus patients. In our study, both the LC and ABP groups exhibited signs of dry - eye symptoms (Table 1, according to the Dry Eye Workshop (DEWS) II criteria: tBUT < 10s, SIT < 10mm/5min, TMH < 0.15mm) [34]. However, in some cases, patients may present objective signs of ocular dryness but do not report it as their chief complaint. This may be due to a decrease in nerve - fiber density and function in the advanced stages of the disease, leading to reduced ocular sensation. In the LC group, SIT scores, tBUT, and TMH all decreased, while OSS increased, indicating dry - eye symptoms. After ABP treatment, although SIT scores, tBUT, and TMH increased to some extent in the ABP group, and OSS decreased relatively compared to the LC group, the improvement was not significant. These data support the above - mentioned theory.

The results of ROC curves show that the vessel density measured by OCTA has good discriminatory power. Lung cancer has a wide variety of symptoms, and atypical symptoms are difficult to detect at an early stage, which makes the diagnosis and treatment of the disease challenging. After ABP treatment, LC

patients may present with a variety of ocular manifestations that are difficult to assess using standardized tools. Currently, there is a lack of standardized tools for assessing ocular indications. In this study, we used OCTA to successfully differentiate between healthy controls, LC patients, and LC patients treated with ABP, suggesting that vascular density measured by OCTA has the potential to be a promising biomarker for the diagnosis of different disease progression.

In most cases, fluorescein angiography is considered the gold standard for diagnosing ocular disease. However, the invasive nature of fluorescein angiography limits its clinical use, especially in specific populations, such as patients with renal disease and severe hypertension, who are unable to undergo this test frequently during follow-up [35]. OCTA provides a more detailed visualization of retinal and choroidal blood flow compared to fluorescence angiography [36]. In some cases, the fundus changes detected by OCTA can indicate the early stage of the disease and be used to monitor disease progression [37].

Significant differences were found between the HCs and LC groups. The full RT in the IS, OS, IT, and OT regions of LC patients was significantly lower than that of HCs ($P < 0.05$). No significant differences ($P > 0.05$) existed in inner RT. The outer RT in the IS, OS, ON, IT, II, OT, and C regions of LC patients was also significantly lower compared to HCs ($P < 0.05$). Significant differences were found between the ABP and LC groups. The full RT in the OI and II regions of ABP - treated patients was lower than that of LC patients ($P < 0.05$). No significant differences ($P > 0.05$) existed in inner RT. The outer RT in the OI and II regions of ABP - treated patients was significantly lower than that of LC patients ($P < 0.001$). The superficial vessel density (SVD) of LC patients was significantly lower in the IT, OT, IS, OS, ON, and C regions compared to HCs ($P < 0.05$). Significant differences were found between the ABP group and LC groups in the II, OI, IT, and C regions ($p < 0.05$). In the future, longitudinal studies defining the stages of the disease may be more convincing, and the contrast would also be more meaningful.

Based on our research, changes in macular thickness and superficial vessel density (SVD) can be regarded as important indicators for evaluating the progression of lung cancer (LC). The progression of LC may lead to retinal arterial or venous occlusion and neurologic lesions manifesting as macular edema, subretinal fluid, hyperreflectivity of the retinal neuroepithelial layer, and thinning of the retinal nerve fiber layer [38]. OCTA technology can be employed to assess vessel density and even the severity of occlusion [39]. The significance of OCTA in early diagnosis and follow - up has been verified in monitoring ischemic - related irreversible visual loss [40]. In the early stages of many chronic diseases, vascular abnormalities, particularly microvascular changes, occur in affected organs but are hard to detect externally. The fundus retina is rich in blood vessels and is the only site where blood vessels can be directly visualized in real time without invasive procedures, makes it essential to evaluate the distribution and status of these vessels for the diagnosis and prediction of systemic microvascular lesions [42].

In addition to physical abnormalities, LC patients frequently experience psychological problems. Psychological disorders can interact with the tumor - related disease process, factors affecting disease progression and response to treatment [43]. It has been reported that anxiety and depression are prevalent in cancer patients [44]. However, relatively few investigations have been conducted on the mental health of lung cancer patients. In this study, the LC and ABP groups had significantly higher Hospital Anxiety and Depression Scale (HADS) scores compared to the healthy controls (HCs) (HCs: 2.60 ± 1.14 , LC: 6.40 ± 1.23 , ABP: 8.70 ± 2.25 ; $P < 0.001$). Moreover, HADS scores increased with the extension of disease duration ($r = 0.7670$, $P < 0.0001$) (Figure 4), further confirming the presence of psychological problems in LC patients.

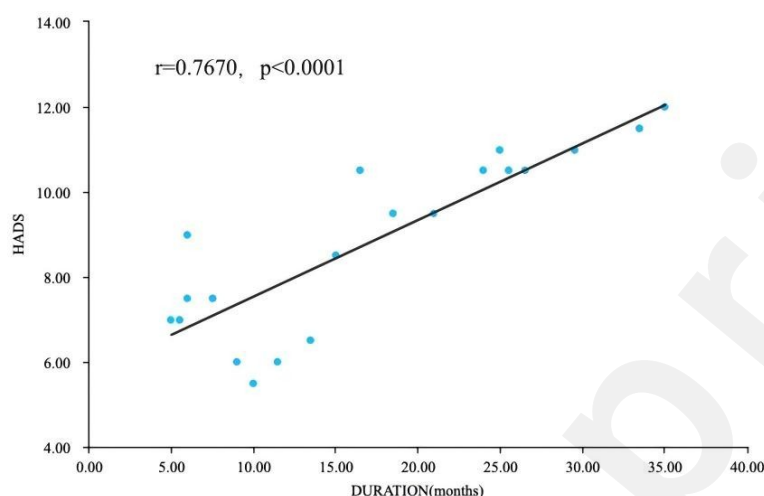


Figure 4: Relationship between disease duration and HADS.

A significant correlation was found between disease duration and HADS ($r=0.7670$, $p<0.0001$).

However, there are some limitations to this study. First, due to the relatively small sample size, the findings need to be further validated in future large-scale studies. Second, other factors that may affect retinal thickness (RT) and vessel density (VD) should also be considered. For example, this study did not differentiate between patients on different treatment regimens, so the effect of other drugs could not be excluded. In future studies, we plan to strengthen cooperation with other regional hospitals to expand the sample size, reduce bias, and collect more comprehensive data.

5. Conclusion

Our OCTA-based study found that both retinal thickness (RT) and superficial vascular density (SVD) decreased further after ABP treatment. This suggests that ABP may play a crucial role in promoting microvascular alterations in lung cancer (LC) patients. These microvascular alterations have the potential to be adjunctive biomarkers of diagnostic value. Abnormal visual acuity (VA), Schirmer's test (SIT) scores, tear meniscus height (TMH), and tear break-up time (BUT) values in patients with lung cancer contribute to the high incidence of dry eye disease (DED) in this patient population. This study provides a new perspective for understanding the relationship between LC treatment and ocular changes and provides a new direction for LC treatment.

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