REVIEW

Diagnostic imaging in patients with retinitis pigmentosa

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Abstract : Retinitis pigmentosa (RP) is a progressive inherited retinal disease, and patients with RP have reduced visual function caused by a degeneration of the photoreceptors and retinal pigment epithelium (RPE). At the end stage of RP, the degeneration of the photoreceptors in the fovea reduces central vision, and RP is one of the main causes of acquired blindness in developed countries. Therefore, morphological and functional assessments of the photoreceptors in the macula area can be useful in estimating the residual retinal function in RP patients. Optical coherence tomography (OCT) is a well-established method of examining the retinal architecture *in situ*. The photoreceptor inner/outer segment (IS/OS) junction is observed as a distinct, highly reflective line by OCT. The presence of the IS/OS junction in the OCT images is essential for normal visual function. Fundus autofluorescence (FAF) results from the accumulation of lipofuscin in the RPE cells and has been used to investigate RPE and retinal function. More than one-half of RP patients have an abnormally high density parafoveal FAF ring (AF ring). The AF ring represents the border between functional and dysfunctional retina. In this review, we shall summarize recent progress on diagnostic imaging in eyes with RP. J. Med. Invest. 59 : 1-11, February, 2012

Keywords **:** *diagnostic imaging, fundus autofluorescence, optical coherence tomography, retinal photoreceptor cell, retinitis pigmentosa*

INTRODUCTION

Retinitis pigmentosa (RP) is a slowly progressive inherited retinal disease, and patients with RP have reduced visual function mainly because of degeneration of the rod and cone photoreceptors and retinal pigment epithelium (RPE) (1-3). A clinical diagnosis of RP is made based on the family history, presence of nyctalopia, visual field constriction, characteristic pigmentary retinal changes, bone spicule pigmentation in the periphery, and reduction of the standard full-field electroretinograms (ERGs) consistent with rod-cone dystrophy (4). Currently, there is no treatment that can lead to a recovery of the decreased vision or halt the progression of the disease process. RP is one of the main causes of acquired blindness in developed countries.

Abnormal ERGs are already present in the first decade of life (5), and the amplitudes of the ERGs and size of the visual fields decrease exponential during the course of RP. These changes are presumably due to a degeneration of the photoreceptors (6). The early decrease in the ERG taken with the histopathologic abnormalities found in postmortem human RP retinas (3) indicates that the retinas of eyes with RP are abnormal from early life and progresses to greater severity. Several genetic mutations have been found to cause RP, e.g., X-linked,

autosomal dominant, and autosomal recessive conditions. However, RP without a known family history can also occur (1). In spite of genetic diversity, many RP patients have similar symptoms, signs, and retinal histopathology (1-3).

In RP patient, the retinal degeneration usually starts with degeneration of the rod photoreceptors which leads to nyctalopia. With advancement, the retinal degeneration gives rise to a characteristic ring-shaped scotoma in the mid-periphery. The scotoma can then expand to the periphery and macula. The earliest histopathologic change in all forms of RP is a shortening of the rod outer segments (3). As the disease progresses, the cone photoreceptors also degenerate which then reduces central vision (2, 3). Therefore, morphological and functional assessment of the photoreceptors in the macular area can be useful in estimating the remaining retinal function in advanced RP patients.

Optical coherence tomography (OCT) is a well-established method of examining the retinal architecture *in situ*. Another method used to study the retina and RPE is by examining fundus autofluorescence (FAF) which results from an accumulation of lipofuscin in the RPE cells. In this review, we shall summarize the recent findings on diagnostic imaging in eyes with RP.

OPTICAL COHERENCE TOMOGRAPHY (OCT)

OCT was introduced to ophthalmology over a decade ago, and it has been used to obtain *in situ* images of the retina of eyes with various types of retinal diseases. The ease of obtaining informative images by OCT has changed the diagnostic strategy used by ophthalmologists.

OCT is an optical analog of ultrasound imaging (7). Light can replace ultrasound because of the clear optical media of the eye. Using light instead of ultrasound is advantageous because shorter wavelengths permit higher resolution images. Moreover, no contact medium is required, as the difference in optical impedance, i.e., the difference in the refractive index between air and tissue, is not as large as the acoustic impedance. Unfortunately, the speed of light exceeds that of sound by a factor 15×10^4, which means that the optical echoes cannot be measured directly in contrast to ultrasonic echoes. To detect light echoes, OCT relies on a classical optical technique known as low coherence

interferometry, in which the signal-carrying light returning from the eye interferes with light that has travelled a known path length.

Recently, a distinct, highly reflective line was detected just above the RPE layer in the images obtained by OCT (8, 9). This line has been identified as the photoreceptor inner/outer segment (IS/OS) junction (Figure 1). The integrity of this line is important because a distinct and continuous line indicates a normal alignment of membranous discs in the photoreceptor outer segments (10). Because the alignment of the discs is necessary for the normal functioning of the photoreceptors, the presence of a normal IS/OS line in the OCT images most likely indicates normally functioning photoreceptors. We have reported that the presence of a distinct and continuous IS/OS line in the OCT images is correlated with the recovery of good vision after intraocular surgery for macular hole or epiretinal membrane (11-13). An intact IS/OS line was highly correlated with normal visual function.
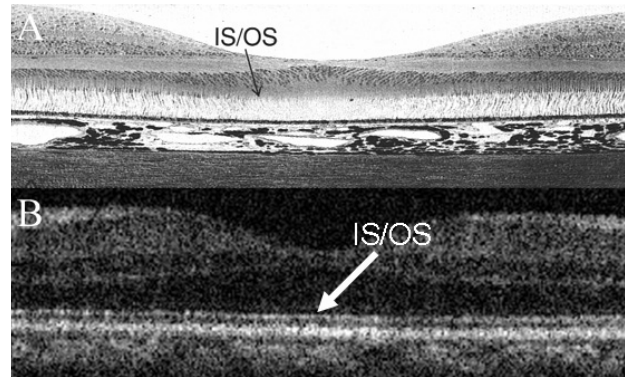

Figure 1.   Histology of normal retina (A) and optical coherence tomographic (OCT) image (B) from a normal subject. Photoreceptor inner/outer segment (IS/OS) junction line is clearly seen in the OCT image.

Several OCT studies have been conducted on RP patients to determine whether there is a significant correlation between the retinal microstructures and visual function (14-16). Sandberg *et al.* (15) examined the IS/OS line in RP patients, and they reported that an intact IS/OS line was significantly correlated with the visual acuity. However, they examined the IS/OS in only the central 1 mm area and examined the IS/OS using false-color images in which the IS/OS line is sometimes difficult to differentiate from the RPE layer especially in the high-signal areas of the OCT images (17). Witkin *et al.* (14) reported that the central foveal thickness and foveal outer segments lengths were significantly

associated with the visual acuity. They suggested that the foveal thinning was primarily due to photoreceptor loss.

We have examined whether a significant correlation is present between the visual acuity or the central foveal thickness and the integrity of the IS/OS line observed in the OCT grayscale images in 300 eyes of 163 patients with RP patients (18). Grayscale OCT images were used because they provide a more accurate identification and measurement of the length of the IS/OS line (17). The appearance of the IS/OS line in the OCT images at the fovea was graded from 1 to 3 : Grade 1, IS/OS line not visible ; Grade 2, disrupted IS/OS line ; and Grade 3, normal continuous IS/OS line (Figure 2). To grade the cases, we measured the length of the IS/OS which extended from just beneath the fovea, and defined eyes as Grade 3 when the length of the continuous IS/OS line was > 0.5 mm. The central foveal thickness was measured manually using the internal program on the OCT images at the thinnest point of the fovea.

Our analyses showed that the IS/OS line was not detected (Grade 1) in 31.0% of the eyes, an abnormal IS/OS (Grade 2) was detected in 22.3%, and the IS/OS was normal (Grade 3) in 46.7% of the eyes in patients with RP. The correlation between the IS/OS grade and age was not significant ($P=$ 0.5536), but the IS/OS grade was significantly correlated with the visual acuity (Figure 3) and the central foveal thickness (both $P < 0.0001$). The visual acuity was significantly better in Grade 3 eyes than Grades 1 and 2 (both $P < 0.0001$). The central foveal thickness was significantly thinner in Grade 1 eyes than in Grades 2 and 3 (both $P < 0.0001$). In Grade 3 eyes, the mean length of the IS/OS line was 2.51 ± 1.42 mm ($\pm$ SD), and the length of the IS/OS line was significantly correlated with the visual acuity ($r=0.375$, $P < 0.0001$).
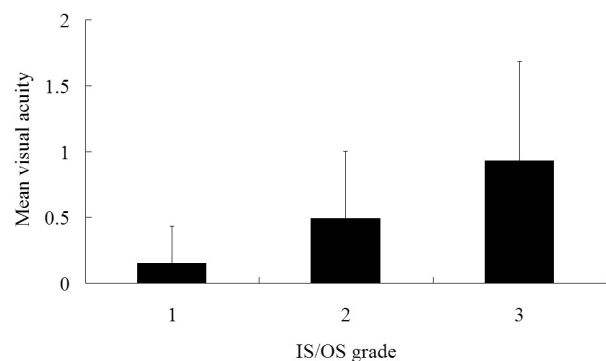
Figure 3 : Mean visual acuity in decimal units as a function of the grade of the photoreceptor inner/outer segment (IS/OS) junction. The difference in the mean visual acuity among the three groups is statistically significant ($P < 0.0001$).

We concluded that the presence of the IS/OS line was associated with better visual acuity and thicker fovea in RP patients. Our findings showed that OCT can be used to assess the integrity of the photoreceptor cells *in situ*, and the significant correlation between the visual acuity and presence or length of the IS/OS line indicated that the IS/OS line might be an important parameter that can be used to monitor RP patients.

The visual function of patients is usually assessed by the conventional visual acuity. However, the visual acuity represents only the visual function at the foveal center. The retinal sensitivity is a better indicator of the quality of macular function because it represents the sensitivity of a larger retinal area than the conventional distant visual acuity (19, 20). The ability to perform daily tasks is strongly dependent on an intact central visual field, therefore the retinal sensitivity could be a better indicator of practical visual capabilities of patients.

We examined whether a significant correlation was present between the retinal sensitivity and the length of the IS/OS line in RP patients (21).

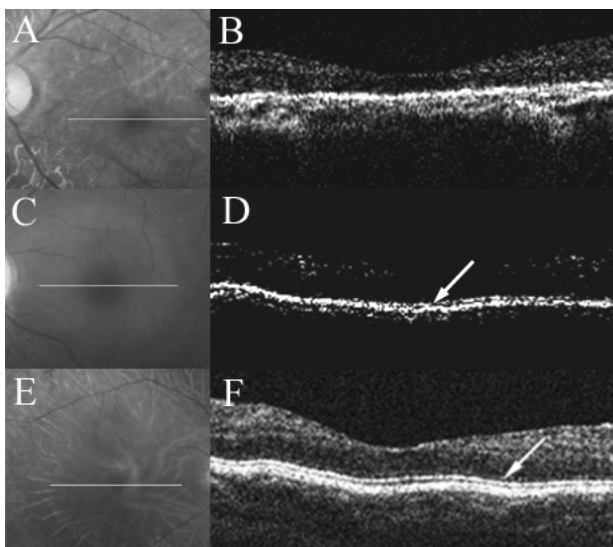Sixty-seven eyes of 36 consecutive patients with

Figure 2.   Grading of photoreceptor inner/outer segment (IS/OS) junction.
The left column shows fundus photographs, and the right column shows optical coherence tomographic (OCT) images. In the fundus photographs, the white lines indicate the direction of the OCT scan. (A, B) An eye classified as Grade 1 without an IS/OS line. (C, D) An eye classified as Grade 2 with an abnormal IS/OS line. White arrow indicates a disrupted IS/OS line. (E, F) An eye classified as Grade 3 with a normal IS/OS line. White arrow points to the continuous IS/OS line.

RP were examined. The recently introduced fundus-related microperimeter, Micro Perimeter-1 (MP-1) (Nidek, Gamagori, Japan) was used to determine the mean retinal sensitivity at 24 locations covering the central 10° (Figure 4). MP1 can be used to obtain quantitative and reliable measurements of the retinal sensitivity by tracking eye movements while
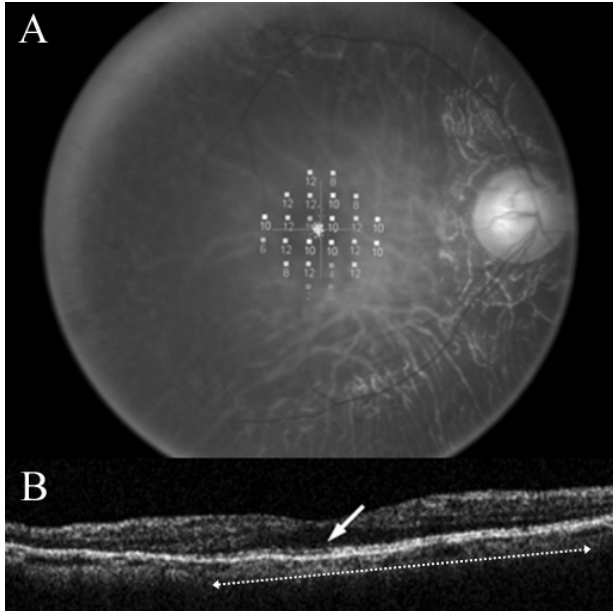

Figure 4.   Microperimetric map and optical coherence tomographic (OCT) images from an eye in which a continuous photoreceptor inner/outer segment (IS/OS) junction was detected. (A) Microperimetric map image of a 60-year-old man with retinitis pigmentosa. Twenty-four stimulus locations covering the central 10° field were tested. The mean retinal sensitivity at the 24 locations is 9.6 dB. (B) OCT image of a 5-mm horizontal scan. The IS/OS line can be observed as a distinct highly reflective line (white arrow). The length of the IS/OS was computed to be 3.6 mm (white dotted arrow).

the patient is focused on a fixation target (19, 20). The length of the IS/OS line in the fovea was measured using the internal program of the OCT. Our findings showed that the length of the IS/OS line was significantly correlated with the mean retinal sensitivity (r=0.614, $P < 0.0001$; Figure 5).

Consistent with our results, Fischer *et al.* (22) reported that the area of the visual field (Goldmann perimetry isopter I4e) was significantly correlated with the IS/OS length. It has also been reported that the photoreceptor outer segment length (distance between RPE to IS/OS line) decreases linearly with a reduction of local field sensitivity (6). Jacobson *et al.* (23) reported that the extent of normal laminar retinal architecture evaluated by OCT corresponded to the extent of normal visual function evaluated by static chromatic perimetry. These findings suggested that the length of the IS/OS line is most likely correlated with retinal function in RP patients.

FUNDUS AUTOFLUORESCENCE (FAF)

FAF imaging is another noninvasive method of assessing the retina and RPE. The autofluorescence of the fundus results from the accumulation of lipofuscin pigment in the RPE cells, and it has been used to investigate eyes with different types of retinal diseases (24-27). Lipofuscin accumulates in lysosomes as a by-product of the degradation of the photoreceptor outer segments (28). A normal
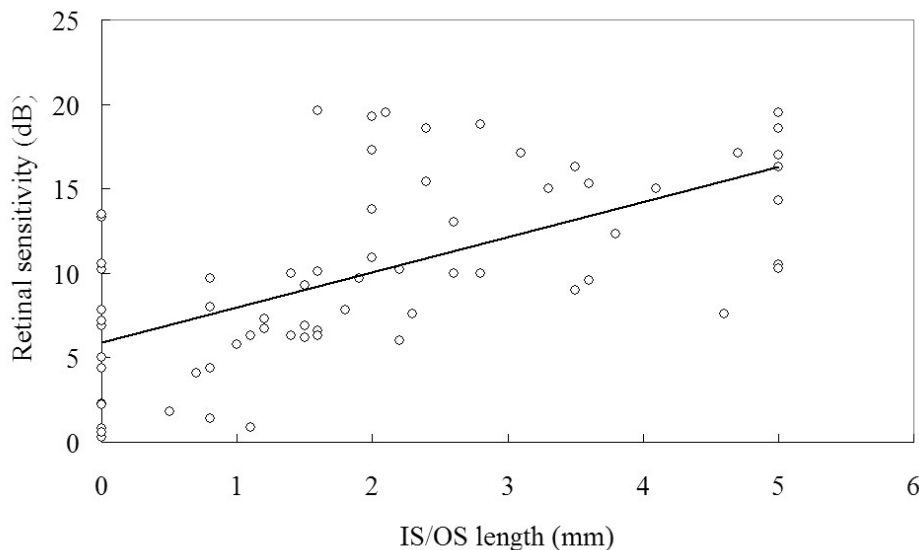
Figure 5.   Correlation between the length of the photoreceptor inner/outer segment (IS/OS) junction and the retinal sensitivity. There is a significant positive correlation between the length of the IS/OS line and the retinal sensitivity (r=0.614, $P < 0.0001$). The solid line represents the linear regression curve (y=5.898+2.088x).

or near-normal FAF pattern indicates that the photoreceptors are intact, and the integrity of the photoreceptor/RPE complex is normal (28). Normal photoreceptor function is dependent on normal RPE cell function, and its contribution to the visual cycle and the constant phagocytosis of shed distal outer segments, a process involved in the renewal of photoreceptor discs. Abnormally high levels of FAF indicate abnormal metabolism in the RPE cells ; viz., a high turnover of photoreceptor outer segments, disrupted phagocytosis, or an intrinsic defect in the ability of the RPE to recycle the phagosomes (29). Decreased or absent FAF indicates RPE atrophy, loss of photoreceptors, or the presence of materials between the RPE and camera that attenuate the FAF signal.

FAF images can be obtained with a confocal scanning laser ophthalmoscope or with a conventional fundus camera-based system. In the confocal scanning laser ophthalmoscope, the optically-pumped solid state laser (488 nm) is used for excitation, and a > 500 nm barrier filter is used to detected the FAF. FAF images of a rectangular 30-degree field of view are recorded through a dilated pupil. Using image analysis software, a series of images is summed to enhance the signal-to-noise ratio, and an averaged single image is analyzed. The fundus camera-based system used a conventional fundus camera with a band pass filter centered at 580 nm (bandwidth, 500-610 nm) for the excitation light and a matched barrier filter centered at 695 nm (bandwidth, 675-715 nm ; Spectrotech, Saugus, MA, USA) for the observation light (30, 31).

Several FAF patterns have been observed in patients with RP, and more than half of the RP patients have an abnormally high density parafoveal FAF ring (AF ring ; Figure 6) (26). Murakami *et al.* (29) classified the eyes of RP patients according to three types of abnormal FAF pattern ; 1) those with an AF ring, 2) those with an abnormal central FAF, i.e., high density disciform FAF spreading centrifugally from the fovea, and 3) the absence of both patterns. They reported that an AF ring was detected in 59% of RP patients, an abnormal central FAF in 18%, and an absence of both patterns in 24% (29). We have found that the AF ring was present in 63 (57.8%) of 109 eyes with typical RP (32).

The AF ring is considered to represent the border between functional and dysfunctional retina, and the edge of the ring corresponds with the inner margin of the visual field defect (25-27, 33). Popovic *et al.* (26) found that the radius of the AF ring was
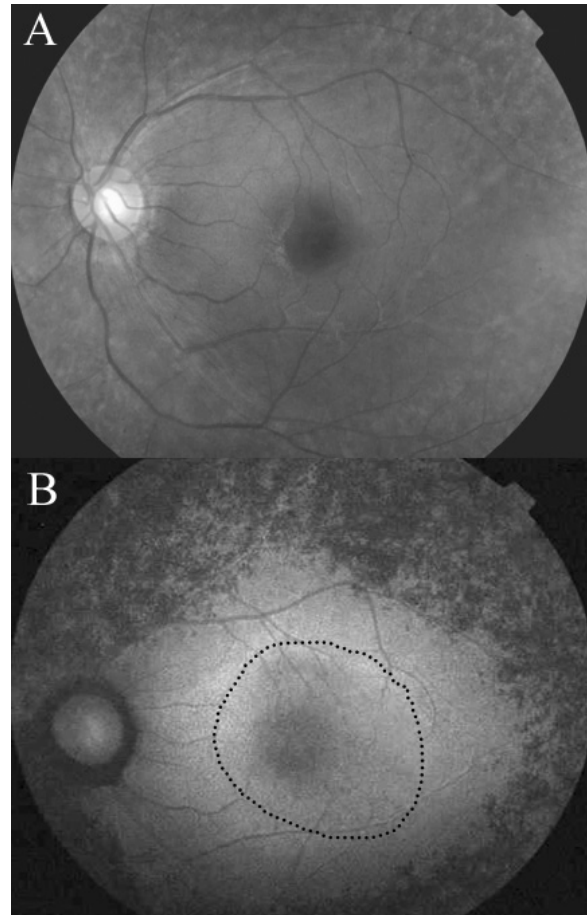

Figure 6.   Fundus photograph (A) and fundus autofluorescence (FAF) image (B) of an eye with retinitis pigmentosa (58-year-old man). An abnormal parafoveal ring of high density FAF (AF ring) can be seen in the FAF image (black dotted line).

strongly correlated with retinal sensitivity. We have also found that the diameter of the AF ring was significantly correlated with retinal sensitivity (32). Fleckenstein *et al.* (34) and Lima *et al.* (35) reported that a disruption of the IS/OS line and a decrease in the outer nuclear layer thickness were found across the AF ring using OCT. It has also been reported that the diameter of the AF ring was significantly correlated with the length of the IS/OS line in 20 patients with RP (29). We have reported that the diameter and area of the AF ring were significantly correlated with the length of the IS/OS line (32). Taken together, the AF ring is significantly associated with retinal function and the length of the IS/OS line.

Changes in RPE function in RP patients is considered to be a secondary process that can result from increased metabolic load on the RPE due to photoreceptor apoptosis (26, 36). Abnormal hyperfluorescence that is seen in the AF ring may indicate an abnormally high rate of phagocytosis of degenerated photoreceptors (29, 34, 35). Wakabayashi

et al. (37) reported that the AF ring might represent the regional distribution of active photoreceptor degeneration and a region of higher rate of phagocytosis of outer segments by the RPE. When the lipofuscin accumulation reached a critical level, which would cause an FAF signal close to the maximum intensity, the RPE cells die with a concomitant loss of lipofuscin granules. The death of photoreceptor cells with RPE atrophy leads to the absence of FAF (26) that can be seen in the peripheral area of RP eyes. Murakami *et al.* (29) also suggested that photoreceptor death may occur before the RPE degeneration in RP patients with an AF ring. However, clinicopathologic analysis is needed to determine whether a precise association exists between the AF ring and the photoreceptor status.

CHANGES OF IMAGING DURING THE DISEASE PROGRESSION

In RP patients, several OCT studies have shown a significant correlation between the presence and continuity of the IS/OS line and the visual function (14-16). On the other hand, the AF ring represents a transition between abnormal paracentral and normal central cone system function and corresponds to the inner margin of the visual field defect (25-27). However, the changes in IS/OS or AF ring during the progression of RP was undetermined.

We had evaluated the changes of AF ring and IS/OS line in relation to visual function during the progression of RP (32). The AF ring was examined in 50 eyes of 26 patients with typical RP. In addition, OCT and microperimetry were performed on these patients. During the follow-up period of >2 years, the changes in the diameter and area of the AF ring, the length of the IS/OS line, visual acuity, and mean retinal sensitivity in the central $10°$ were determined (Figure 7). We found that the diameter and area of the AF ring, the length of the IS/OS line, visual acuity, and mean retinal sensitivity decreased significantly during the follow-up period (all, $P < 0.0001$). The decrease in the AF ring diameter was significantly correlated with the decrease in retinal sensitivity ($P=0.0105$), visual acuity ($P=0.0252$), and
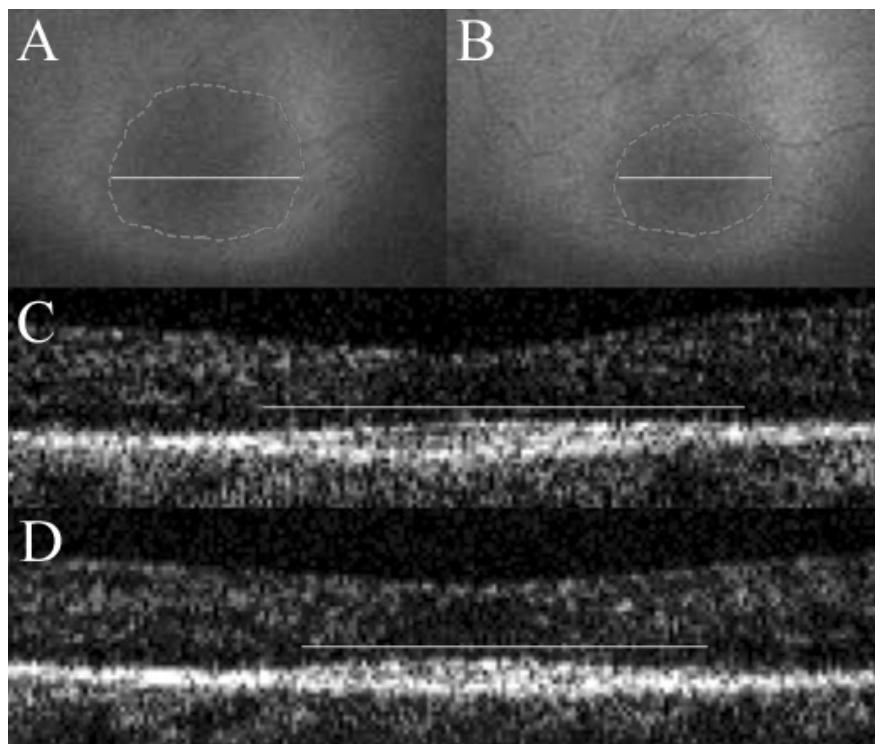
Figure 7.   Fundus autofluorescence (FAF) images and optical coherence tomographic (OCT) images of an eye with retinitis pigmentosa (59-year-old woman).
(A, B) FAF images at the baseline (A) and the final visit (B). A progressive constriction of an abnormal parafoveal ring of high density FAF (AF ring) can be seen. Gray dotted lines indicate the area of the AF ring and white lines indicate the diameter of the AF ring.
(C, D) OCT images of a horizontal scan at the baseline (C) and the final visit (D). The photoreceptor inner and outer segment (IS/OS) junction line can be observed as a distinct highly reflective line. A slight decrease in the length of the IS/OS line can be seen. White lines indicate the IS/OS lengths.

length of the IS/OS line (*P*=0.0015 ; Figure 8). The decrease in AF ring area was significantly correlated with the decrease in retinal sensitivity (*P*=0.0047 ; Figure 9), visual acuity (*P*=0.0026), and length of IS/OS line (*P*=0.0011). The decrease in the length of the IS/OS line was significantly correlated with the decrease in retinal sensitivity (*P*=0.0018), and visual acuity (*P*=0.0291).

Wakabayashi *et al.* (37) also reported that a progressive reduction in the size of the AF ring was accompanied by a decrease in the area where the

IS/OS line was present during a mean follow-up period of 3.1 years. Most recently, Robson *et al.* (38) reported that the AF ring was progressively decreased in 17 patients after a mean follow-up period of 3.9 years. They also reported that the radius of the AF ring was reduced by up to 40% with a mean rate of decrease between 0.8%/year to 15.8%/year. In addition, they observed that a small AF ring was replaced by areas of RPE atrophy with a consequent decrease in the visual acuity during 6 years of follow-up. Taken together, the progressive constriction of
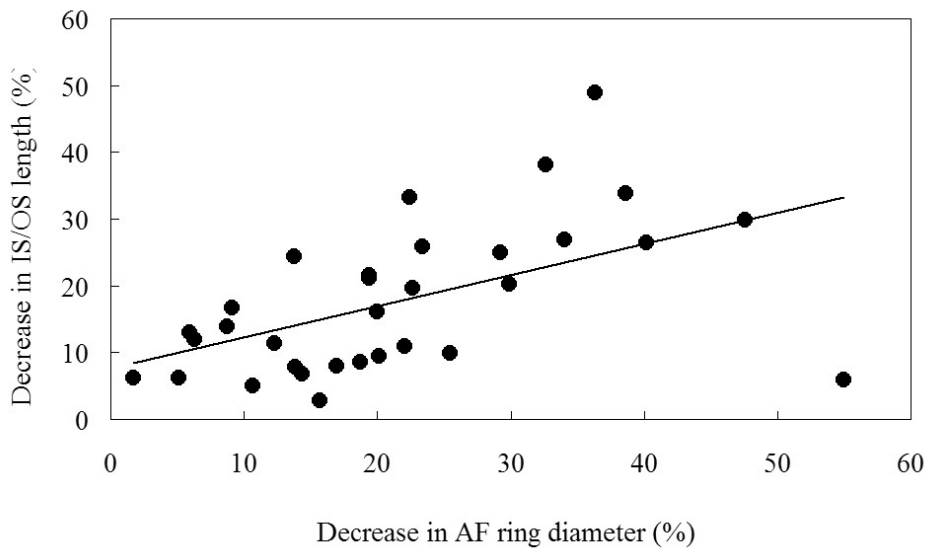

Figure 8.   Correlation between the decrease in the diameter of the autofluorescence ring (AF ring) and decrease in the length of the photoreceptor inner/outer segment (IS/OS) junction line. There is a significant positive correlation between decrease in the AF ring diameter and decrease in the IS/OS length (r=0.531, *P*=0.0015). The solid line represents the linear regression curve (y=7.594+ 0.467x). A decrease in the AF ring diameter and the IS/OS length are presented as a ratio of the decrease from the baseline divided by the value at the baseline.
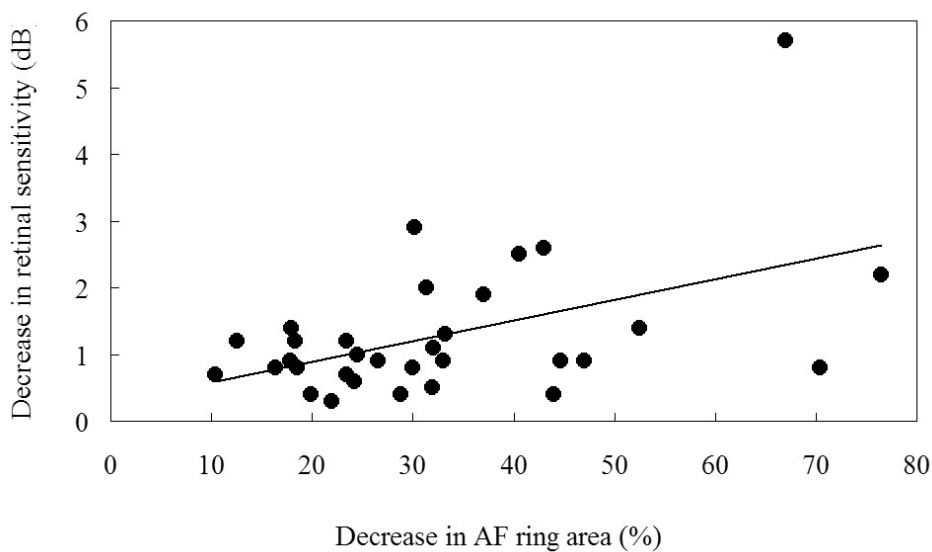

Figure 9.   Correlation between decrease in the area of the autofluorescence ring (AF ring) and decrease in the retinal sensitivity. There is a significant positive correlation between decrease in the AF ring area and decrease in the retinal sensitivity (r=0.482, *P*= 0.0047). The solid line represents the linear regression curve (y=0.278+0.031x). Decrease in the AF ring area was presented as a ratio of the decrease from the baseline divided by the value at the baseline.

the AF ring reflects the morphological changes of the photoreceptors during the progression of RP and is associated with a worsening of visual function.
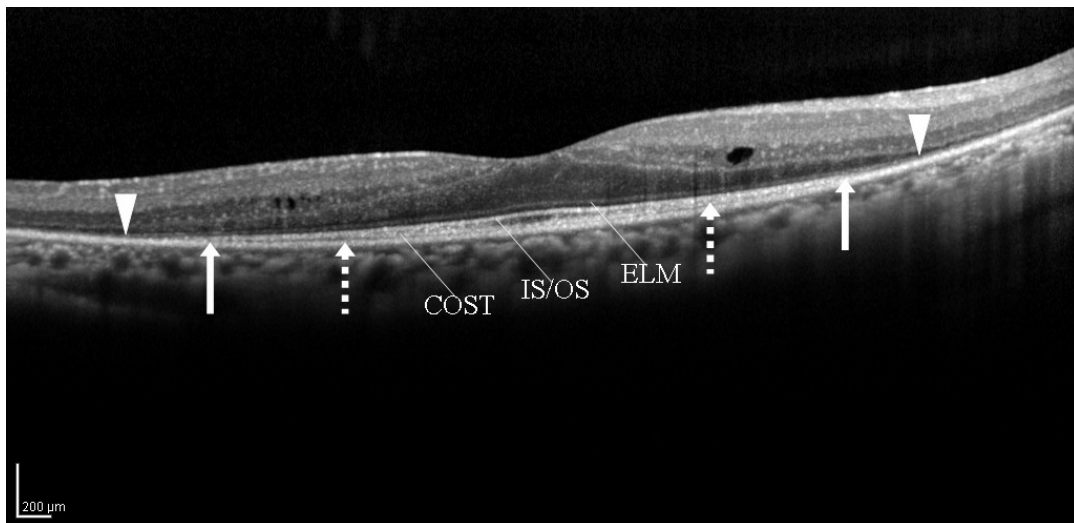
SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY (SD-OCT)

With the most recent improvements of OCT, the pathological changes of retina can be observed in much greater detail (13). Spectral-domain OCT (SD-OCT) uses low-coherence interferometry to detect light echoes, and uses a spectrometer and high-speed camera to obtain the images. The SD-OCT instrument is based on the mathematical basis of Fourier transformation (39). This eponym derives from the French mathematician Joseph Fourier, who described the decomposition of a periodic function into a sum of simple sinusoidal oscillating functions. Because the application of his formula has the effect of measuring all echoes of light simultaneously, as compared with sequentially in the case of conventional OCT, SD-OCT significantly increases the amount of data acquired in each session. This ability results in a significant reduction of motion artifacts and an increase in the signal-to-noise ratio compared with conventional OCTs.

The axial resolution of conventional OCT instrument, the time-domain OCT, was 10-20 μm while the SD-OCT has a 5 to 6 μm axial resolution. This has improved the ability to detect intraretinal microstructures and to identify pathologic changes in the retinal architecture in various diseases. The imaging speed of SD-OCT is up to 100 times the speed of conventional OCT. Therefore, SD-OCT can clearly delineate not only the IS/OS junction but also the external limiting membrane (ELM ; junction between the inner segments and the Müller cells) and the cone outer segment tips (COST) line (Figure 10).

Using SD-OCT, Wakabayashi *et al.* (37) reported that the diameter of the AF ring was correlated significantly with the length of the IS/OS line in eyes with RP. The area outside the AF ring corresponded with the area where the IS/OS junction and ELM were not detected. They reported that the border of the AF ring demarcated the border between the central retina with preservation of the IS/OS junction and ELM, and the more peripheral retina with a loss of these microstructures. They also reported that the transverse extent of the preserved ELM was significantly larger than that of the IS/OS line in eyes with RP. In our preliminary study, we also observed that the length of the ELM was significantly longer than that of the IS/OS line, and it was significantly correlated with the length of the IS/OS line. In addition, the length of the COST line was significantly shorter than that of IS/OS line. The lengths of the ELM, IS/OS, and COST lines were significantly associated with visual function. These results suggested that retinal layer may become disorganized first at the COST line, followed by the IS/OS line, and finally the ELM.

Figure 10.   Spectral-domain optical coherence tomographic (SD-OCT) image of an eye with retinitis pigmentosa (52-year-old man). In addition to photoreceptor inner/outer segment (IS/OS) junction line, the external limiting membrane (ELM) and cone outer segment tips (COST) line are clearly seen in the SD-OCT image. White dotted arrows indicate an end point of COST line. White arrows indicate an end point of IS/OS line, and white arrow heads an end point of ELM line.

CONCLUSIONS

In RP patients, the presence and continuity of the IS/OS line is associated with good visual function. In addition, the large AF ring is associated with good retinal function and the good preservation of the IS/OS line. During the progression of RP, the size of AF ring decreases, and this is accompanied by a shortening of the length of the IS/OS line, a decrease in retinal sensitivity, and a worsening of visual acuity. The decrease in the diameter of the AF ring is significantly correlated with the decrease in retinal sensitivity, visual acuity, and length of the IS/OS line. Moreover, the decrease in area of the AF ring is significantly correlated with the decrease in retinal sensitivity, visual acuity, and IS/OS length. Taken together, the AF ring and the IS/OS line may be important parameters to monitor RP patients. Further studies with high resolution images of SD-OCT should lead to better understanding of the relationship between the microstructure of the macular photoreceptor layer and visual function in RP patients.

CONFLICT OR COMMERCIAL INTEREST

None for each author

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