

# The Subclassification and Long-term Prognosis of Preproliferative Diabetic Retinopathy

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**Purpose:** We followed up 54 patients (95 eyes) with preproliferative diabetic retinopathy (PPDR) for at least 2 years, and then evaluated the proportion developing proliferative diabetic retinopathy (PDR), and the period from diagnosis of PPDR until the development of PDR.

**Methods:** We divided the 95 eyes affected by PPDR into 75 eyes with mild-type and 20 eyes with moderate-type based on our previously proposed subclassification, and evaluated long-term (2 or more years) prognosis.

**Results:** The proportion developing PDR was 24% in mild-type and 60% in moderate-type. The average period from diagnosis of PPDR until the development of PDR was 6 years and 5 months in mild-type, 2 years in moderate-type. The cumulative occurrence rates of PDR at 2, 5, and 10 years were estimated to be 0%, 14%, and 39% in mild-type and 35%, 58%, and 79% in moderate-type, respectively. The proportion developing PDR was significantly higher and the average period until PDR development significantly shorter in moderate than in mild-type. In mild-type eyes, the rate of progression to moderate-type was 56% and further progression from moderate-type to PDR occurred in 43%.

**Conclusion:** The above results again confirm the usefulness of our subclassification, and also provide valuable information about the long-term prognosis of PPDR. **Jpn J Ophthalmol 2002;46:323–329** © 2002 Japanese Ophthalmological Society

**Key Words:** Development of proliferative retinopathy, diabetic retinopathy, long-term prognosis, preproliferative diabetic retinopathy, subclassification of preproliferative diabetic retinopathy.

## Introduction

No studies on the long-term course of preproliferative diabetic retinopathy (PPDR) have evaluated in detail the incidence of proliferative diabetic retinopathy (PDR) or the duration of the period from the diagnosis of PPDR until the development of PDR. We previously subclassified PPDR into the following three types and observed the course for 1 year<sup>1</sup>: (1) mild-type in which ophthalmoscopy shows scattered soft exudates, and fluorescein angiography reveals only corresponding filling defects, but no definite nonperfused areas (Figure 1A); (2) moderate-type showing soft exudates and definite nonperfused ar-

reas (Figure 1B); and (3) severe-type showing soft exudates, nonperfused areas, and venous beading (Figure 1C). In this study, the incidence of PDR and the time until the development of PDR were evaluated in cases that could be followed up for at least 2 years.

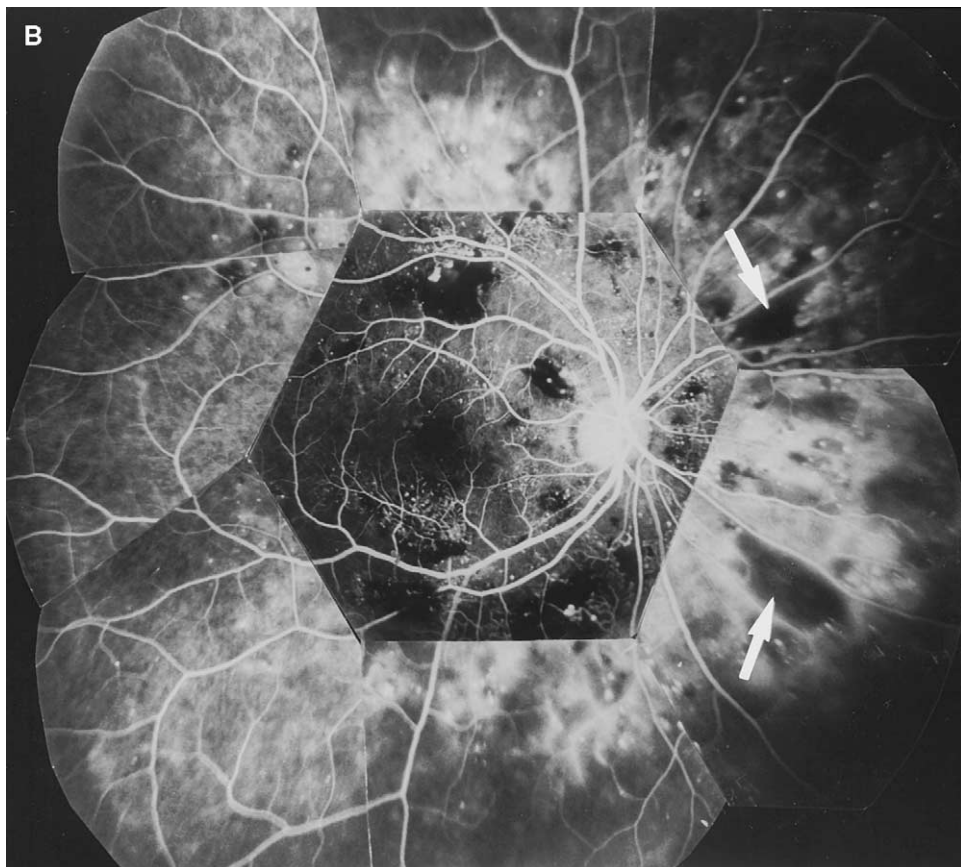
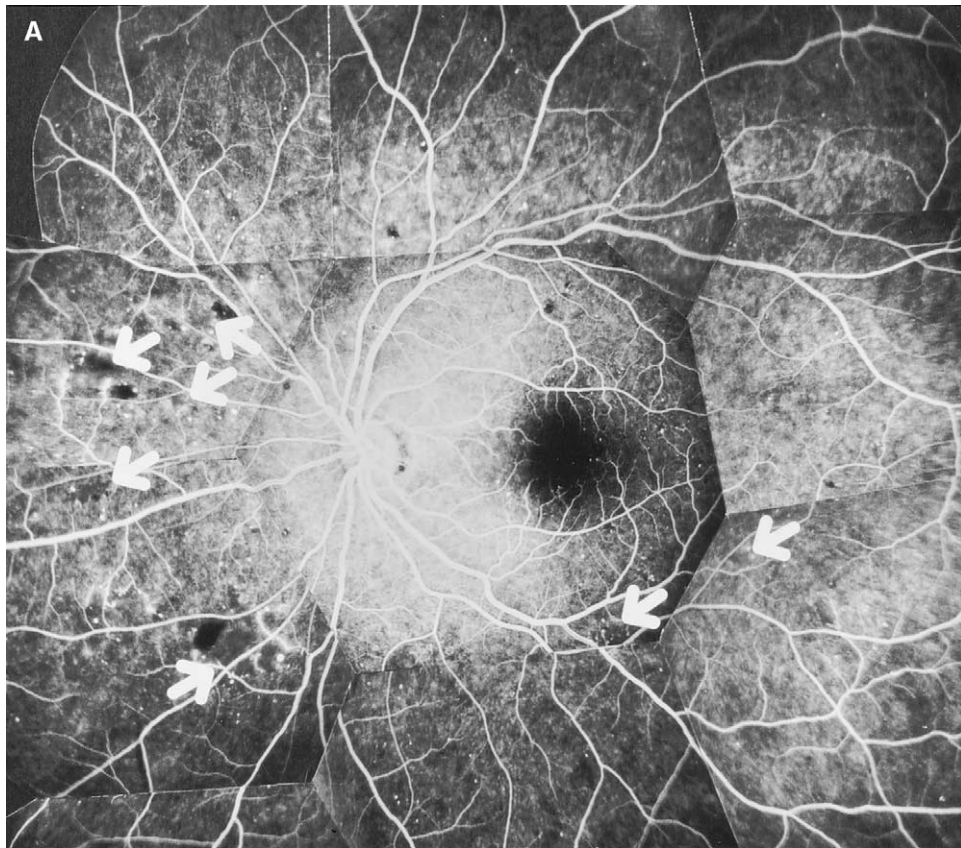
## Materials and Methods

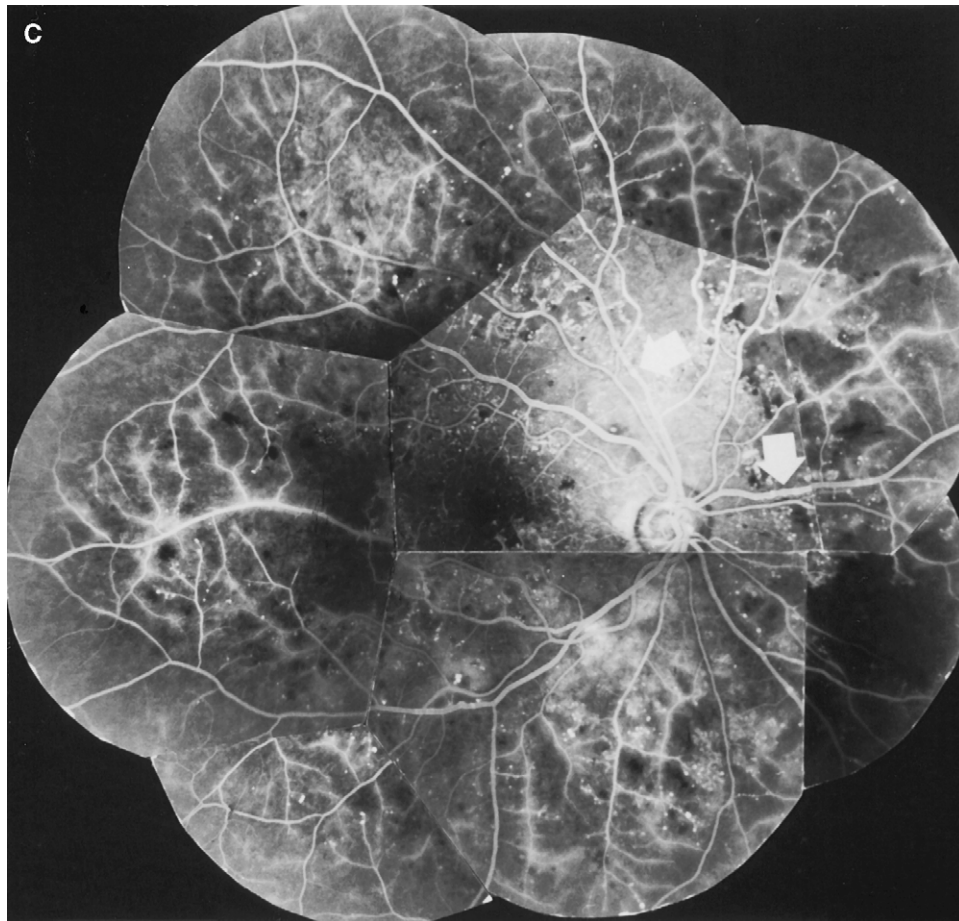
The subjects were 54 patients (95 eyes) followed up for 2 to 12 years (mean  $\pm$  SD = 6 years and 3 months  $\pm$  3 years and 8 months) at our department by fluorescein angiography at 6-month intervals, in principle.

The ages of patients at the initiation of this investigation ranged from 37 to 75 years (mean  $\pm$  SD = 55.6  $\pm$  7.5 years), and the estimated duration of diabetes mellitus was 1 to 28 years (mean  $\pm$  SD = 9.4  $\pm$  6.2 years).

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**Figure 1.** Subclassification of preproliferative diabetic retinopathy (findings of fluorescein angiography). (A) Mild-type: The arrows indicate filling defects corresponding to soft exudates. Neither nonperfused areas nor venous beading are present. (B) Moderate-type: The arrows indicate areas of nonperfusion. This perfusion state was regarded as the lower limit of nonperfusion. (C) Severe-type: The arrows indicate venous beading.

At the time of the initial examination, mild-type PPDR was observed in 75 eyes and moderate-type PPDR, in 20. Because there were only a few patients with the severe-type, only the mild- and moderate-types were evaluated in this study.

The progression rate of retinopathy was estimated by the Kaplan-Meier method. For statistical analysis, the  $\chi^2$  test, log-rank test, and Student *t*-test were used.  $P < .05$  was considered significant.

## Results

### *Incidence of PDR in All Eyes*

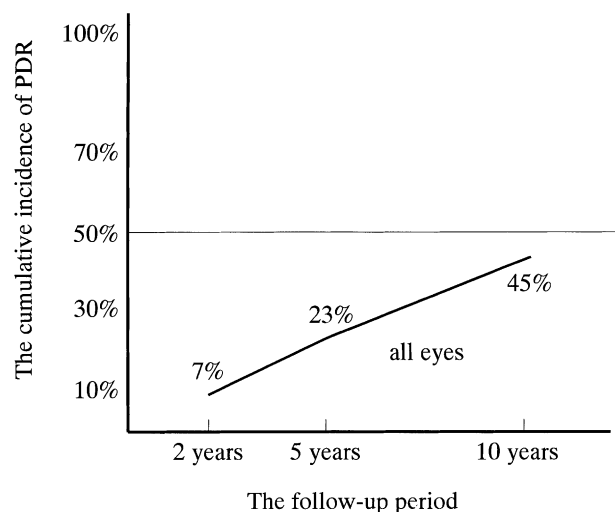
Of the 95 eyes, 31 (32%) developed PDR. The cumulative incidence of PDR estimated by the Kaplan-Meier method (Figure 2) was 7% at 2 years, 23% at 5 years, and 45% at 10 years. The patient ages ranged from 37 to 69 years (mean  $\pm$  SD = 55.0  $\pm$  7.7 years) in cases that developed PDR and from 42 to

75 years (mean  $\pm$  SD = 56.0  $\pm$  7.2 years) in those that did not develop PDR.

There was no significant difference between the two groups (Student *t*-test,  $P = .64$ ).

### *Incidence of PDR in the Mild- and Moderate-types*

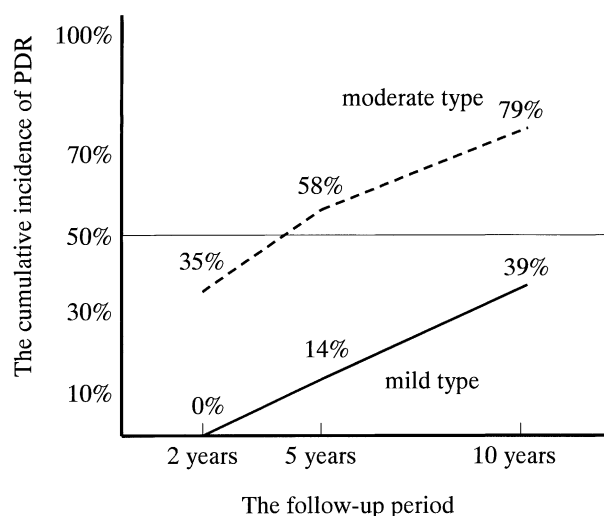
PDR developed in 18 (24%) of the 75 eyes with mild-type at the initial examination and in 12 (60%) of the 20 eyes with moderate-type. The incidence of PDR was significantly higher for the moderate than the mild-type ( $\chi^2$  test,  $P < .005$ ). In cases with mild-type, the patient age ranged from 37 to 69 years (mean  $\pm$  SD = 56.1  $\pm$  9.3 years) in those who developed PDR, and from 42 to 75 years (mean  $\pm$  SD = 55.6  $\pm$  7.5 years) in those who did not develop PDR. There was no significant difference between the two groups (Student *t*-test,  $P = .86$ ). On the other hand,



**Figure 2.** Cumulative incidence of proliferative diabetic retinopathy in all eyes.

in cases with moderate-type, the patient age ranged from 45 to 62 years (mean  $\pm$  SD = 53.5  $\pm$  5.1 years) in cases that developed PDR and from 54 to 65 years (mean  $\pm$  SD = 58.8  $\pm$  4.6 years) in cases that did not develop PDR. There was no significant difference between the two groups (Student *t*-test, *P* = .11).

In the eyes with the mild-type, the period until the development of PDR was 2 years and 3 months to 16 years and 2 months (mean  $\pm$  SD = 6 years and 5 months  $\pm$  3 years and 10 months; Table 1). The cumulative incidence of PDR for the mild-type was estimated to be 0% at 2 years, 14% at 5 years, and 39% at 10 years. In eyes with the moderate-type, the period until the development of PDR was 7 months to 5 years and 4 months (mean  $\pm$  SD = 2 years  $\pm$  1 year and 6 months). The cumulative incidence of PDR for the moderate-type was 35% at 2 years, 58% at 5 years, and 79% at 10 years (Figure 3). The period until the development of PDR was significantly shorter for



**Figure 3.** Cumulative incidence of proliferative diabetic retinopathy for mild and moderate-types. Solid line: mild-type, broken line: moderate-type.

the moderate-type than for the mild-type (log-rank test, *P* < .0001).

### Courses of 75 Eyes with Mild-type at the Initial Examination

The incidence of progression from mild- to moderate-type and that of further progression from moderate-type to PDR were evaluated. Of the 75 eyes with the mild-type at the initial examination, 42 (56%) showed progression to the moderate-type during the course of follow-up. The cumulative incidence of progression from mild to moderate-type was estimated to be 25% at 2 years, 52% at 5 years, and 63% at 10 years (Figure 4).

Of the 42 eyes that showed progression to the moderate-type, 18 (43%) showed further progression to PDR. The period from progression to the moderate-type until the development of PDR was 7 months to 5 years and 9 months (mean  $\pm$  SD = 2 years and 5 months  $\pm$  1 year and 5 months; Table 2). The cumulative incidence of PDR was estimated to be 28% at 2 years, 53% at 5 years, and 63% at 10 years (Figure 5). The cumulative incidence of progression from mild to moderate-type was similar to that of progression from moderate-type to PDR.

A few eyes with the mild-type at the time of the initial examination showed progression to the moderate-type and further progression to the severe-type.

However, statistical analysis was not possible because of the small number of severe cases. Therefore, these eyes were included among those that showed "progression to the moderate-type" in this study.

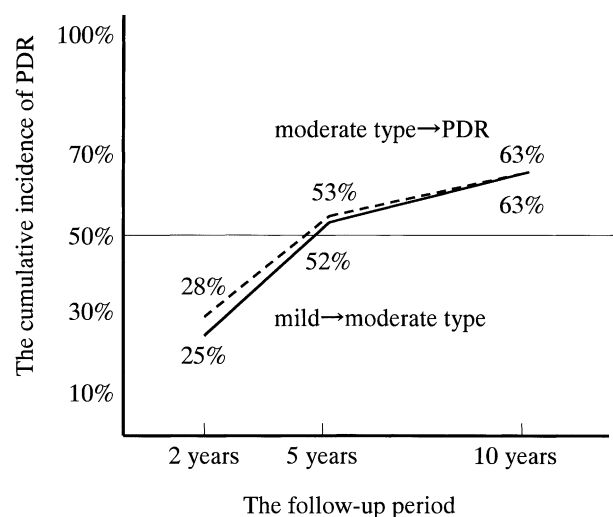
**Table 1.** Incidence and Duration Until Development of Proliferative Diabetic Retinopathy (PDR) for the Mild- and Moderate-types at Initial Examination

	Incidence of PDR Development*	Duration Until PDR Development†
Mild-type‡	18/75 eyes (24)	6 y and 5 mo $\pm$ 3 y and 10 mo
Moderate-type‡	12/20 eyes (60)	2 y $\pm$ 1 y and 6 mo
<i>P</i> value	<.005	<.0001

\*Values in parentheses are percentages.

†Values are mean  $\pm$  SD.

‡At initial examination.



**Figure 4.** Cumulative incidence of progression from mild to moderate-type and that of progression from moderate-type to proliferative diabetic retinopathy (PDR) in 75 eyes with mild-type at the initial examination. Solid line: progression from mild to moderate-type, broken line: progression from moderate-type to PDR.

### The Incidence of PDR in the Moderate-type

As described above, 42 eyes that were considered mild-type at the initial examination progressed to the moderate-type: of these, 43% showed further progression to PDR. Of the 20 eyes with the moderate-type at the time of initial examination, 60% showed progression to PDR. The incidence of further progression to PDR was higher for the moderate than the mild-type at the initial examination, but the difference did not reach statistical significance ( $\chi^2$  test,  $P > .2$ ). The mean period until the development of PDR was 2 years and 5 months for the mild-type at the initial examination that progressed to the moderate-type and 2 years for the moderate-type at the initial

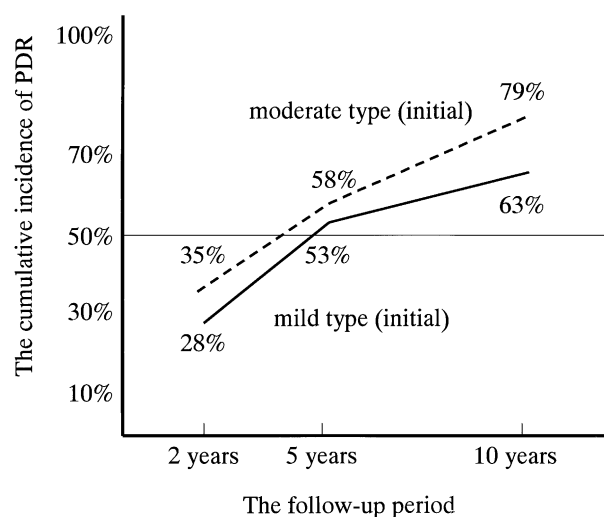
**Table 2.** Incidence and Duration Until Development of Proliferative Diabetic Retinopathy (PDR) for the Moderate Type

	Incidence of PDR Development*	Duration Until PDR Development†
Mild-type‡ → Moderate-type	18/42 eyes (43)	2 y and 5 mo ± 1 y and 5 mo
Moderate-type‡ (initial)	12/29 eyes (60)	2 y ± 1 y and 6 mo
P value	>.2	>.08

\*Values in parentheses are percentages.

†Values are mean ± SD.

‡At the initial examination.



**Figure 5.** Cumulative incidence of proliferative diabetic retinopathy (PDR) for the mild-type at the initial examination that progressed to the moderate-type and for the moderate-type at the initial examination. Solid line: progression from mild-type at the initial examination to PDR, broken line: progression from moderate-type at the initial examination to PDR, mild-type (initial): mild-type at the initial examination, moderate-type (initial): moderate-type at the initial examination.

examination (log-rank test,  $P > .08$ ); the cumulative incidence of PDR was also similar in the two types.

## Discussion

We previously followed up 155 eyes with PPDR for 1 year<sup>1</sup> and observed the development of PDR in 16% (0% for the mild-type, 17% for the moderate-type, and 46% for the severe-type at the initial examination). In this study, 75 eyes with the mild-type and 20 with the moderate-type at the initial examination (total, 95 eyes) were followed up for at least 2 years (mean = 6 years and 3 months), and the incidence of PDR was 32%. The cumulative incidence of PDR estimated by the Kaplan-Meier method was approximately 10% at 2 years, 20% at 5 years, and 50% at 10 years, showing a nearly linear increase as disease duration increased.

When PPDR was classified at the initial examination as mild or severe, 24% of the eyes with the mild-type showed progression to PDR during the course of follow-up. The interval between the diagnosis of the mild-type and the development of PDR varied from 2 years and 3 months to 16 years and 2 months (mean = 6 years and 5 months). However, the cumulative incidence of PDR was estimated to be 0% at 2

years, slightly higher than 10% at 5 years, and approximately 40% even after 10 years, indicating slow progression of the mild-type.

Of the eyes with mild-type at the initial examination, approximately 60% showed progression to the moderate-type, and nearly 40% of the eyes showing progression to the moderate-type showed further progression to PDR. The cumulative incidence of progression from mild to moderate-type was similar to that of progression from moderate-type to PDR.

To reduce the progression of retinopathy, we photocoagulated nonperfused areas for the moderate but not the mild-type. Therefore, when progression from the moderate-type to PDR is evaluated, consideration should be given to the inhibitory effects of photocoagulation on progression to PDR.

For the mild-type at the initial examination, the cumulative incidence of progression from mild to moderate-type was similar to that of further progression from moderate-type to PDR, suggesting essentially constant and slow progression of the mild-type.

On the other hand, for the moderate-type at the initial examination, our previous 1-year follow up study<sup>1</sup> revealed a PDR incidence of 18%.

In this study, the incidence of PDR was 60% for the moderate-type at the initial examination, which was significantly higher than the PDR incidence for the mild-type (24%). The cumulative incidence of PDR at 5 years for the moderate-type was estimated to be 58%, which was more than three times that for the mild-type (14%). These results indicate rapid progression of the moderate-type as compared with the mild-type at the initial examination.

When ophthalmoscopy reveals soft exudates, we make a diagnosis of PPDR and perform fluorescein angiography.<sup>3</sup> For the mild-type showing only filling defects corresponding to soft exudates but no definite nonperfused areas on fluorescein angiograms at the initial examination, fluorescein angiography is repeated at 6-month intervals. When definite nonperfused areas are observed, progression to the moderate-type is diagnosed. When new blood vessels are confirmed, progression to PDR is diagnosed.

Therefore, in eyes with the mild-type at the initial examination, progression to the moderate-type or PDR may have been accurately diagnosed. However, in eyes with the moderate-type already showing nonperfused areas at the initial examination, the possibility that a long period has passed because progression to the moderate-type cannot be excluded. Therefore, the interval between diagnosis of the moderate-type and progression to PDR may not have been accurately determined. However, as described above, there were no

marked differences in the incidence of PDR or the period until the development of PDR between the mild-type at the initial examination that progressed to the moderate-type and the moderate-type at the initial examination, and the cumulative incidence of PDR was also similar in the two. Therefore, the progression rate appeared to have been fairly accurately estimated even for the moderate-type at the initial examination.

Niki et al<sup>2</sup> and Ando<sup>3</sup> proposed subclassifications of PPDR. Niki et al<sup>2</sup> evaluated in detail the distribution and extension rate of nonperfused areas in early stage retinopathy while Ando<sup>3</sup> carefully analyzed background factors in cases showing progression to PDR. However, there were no descriptions of the incidence of PDR developing from PPDR or the period until the development of PDR in their studies. To our knowledge, there has been only one such study, by Shimizu et al,<sup>4</sup> who observed the course for 3 years.

They reported the incidence of PDR to be 29% in the group treated by photocoagulation to inhibit the progression of retinopathy, 57% in the group who were only observed, and 38% in all cases.

In this study, though not described in the Results section, the incidence of PDR at 3 years was 22% in all eyes, being lower than that reported by Shimizu et al.<sup>4</sup> This lower incidence may be because only moderate to severe cases according to our classification, ie, no mild cases, were included in the study by Shimizu. Though also not shown in the results, the incidence of PDR at 3 years for the moderate-type at the initial examination was 45%, which was similar to the 38% reported by Shimizu et al.<sup>4</sup>

In eyes with the mild and moderate-types at the time of initial examination that could be observed for at least 2 years, the incidence of PDR and the interval between the diagnosis of PPDR and the development of PDR were evaluated.

The outcomes also differed between the mild and moderate-types after a long course, ie, 2 years or more. This result confirmed the usefulness of our subclassification. In our previous study, eyes with the mild or moderate-type accounted for about 90% of the 155 eyes with PPDR.<sup>1</sup> The results of this study on mild and moderate-types may provide useful information for evaluating the long-term prognosis of PPDR.

In the future, systemic factors such as control of blood glucose should be included among the items evaluated. In this study, when ophthalmoscopy revealed soft exudates, a diagnosis of PPDR was made, and fluorescein angiography was performed. Therefore, it is possible that this study did not include PPDR cases showing nonperfused areas without soft exudates.<sup>5</sup>

These problems require further study.

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