European Journal of Ophthalmology / Vol. 16 no. 2, 2006 / pp. 287-294

Preoperative factors influencing visual outcome following surgical excision of subfoveal choroidal neovascularization in age-related macular degeneration

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PURPOSE. *To evaluate long-term visual acuity outcomes and the influences of various preoperative factors on visual outcome in patients undergoing surgical removal of choroidal neovascular neovascularization (CNV) caused by age-related macular degeneration (ARMD).*

METHODS. *The authors studied 146 eyes of 146 patients who were followed for at least 1 year after surgical excision of CNV associated with ARMD. Surgical indications included subfoveal active CNV localized mainly above the retinal pigment epithelium (RPE) and a standard Japanese decimal visual acuity of 0.3 or worse. CNV above the RPE was diagnosed by fluorescein angiography, indocyanine green angiography, and optical coherence tomography. CNVs were divided into completely classic CNV or mainly classic CNV. The relationships of the postoperative logarithm of the minimum angle of resolution (logMAR) visual acuity with preoperative logMAR visual acuity, the shortest distance from the center of the foveal avascular zone to the CNV margin, CNV size, and age were analyzed.*

RESULTS. *Final logMAR visual acuity was improved (defined as a logMAR visual acuity increase of 0.2 or more) in 78 eyes (54%), stable in 47 (32%), and worsened in 21 (14%). Stepwise regression identified CNV size as a significant factor influencing final logMAR visual acuity (R^2 = 0.213, p<0.0001), while preoperative logMAR visual acuity, shortest distance from the center of the foveal avascular zone to the CNV margin, and age showed no significant correlation with final logMAR visual acuity. Surgical complications included retinal detachment in six eyes (4%), subretinal hematoma in four eyes (2%), macular hole in three (2%), and proliferative vitreoretinopathy in two (1%). CNV recurred postoperatively in 18 eyes (12%). In 92 eyes with completely classic CNV, visual acuity was improved in 57 (62%), stable in 27 (29%), and worsened in 8 (9%). In 54 eyes with mainly classic CNV, visual acuity was improved in 21(39%), stable in 20 (37%), and worsened in 13 (24%).*

CONCLUSIONS. *Surgical excision of CNV for ARMD was effective for completely classic CNV, and better postoperative visual acuity was achieved in cases of small CNV. Given the fact that photodynamic therapy (PDT) has only been used in Japan since 2004, future study should compare PDT and surgical excision in Japanese subjects for relative merits against surgical risk and postoperative complications, to define indications for PDT and surgical excision. (Eur J Ophthalmol 2006; 16: 287-94)*

KEY WORDS. *Age-related macular degeneration, Choroidal neovascularization, Long-term visual outcome, Preoperative factors, Surgical excision*

Accepted: October 20, 2005

Presented at the 107th Meeting of the Japanese Ophthalmological Society; Fukuoka City, Japan, April 2003.

1120-6721/287-08$15.00/0

INTRODUCTION

In patients with age-related macular degeneration (ARMD), various modalities have been used to treat subfoveal choroidal neovascularization (CNV), including surgical CNV excision (1-6), macular translocation, photodynamic therapy (PDT), intravitreal triamcinolone, intravitreal antivascular endothelial growth factor, and transpupillary thermotherapy (7-10). Surgical CNV excision causes some degree of defect in the retinal pigment epithelium (RPE), and formation of central scotoma as well as difficulty in achieving significant visual improvement are problems associated with this procedure (1, 4).

Based on histopathologic findings of ARMD, Green and Enger (11) reported 19.7% of eyes to have a sub-RPE component, 32.2% a subretinal component, and 48.1% subretinal and sub-RPE components. Grossniklaus and Gass (12) reported better postoperative outcomes after CNV excision in type 2 (subretinal neovascular membranes located between the sensory retina and RPE) cases than in type 1 (subretinal neovascular membranes located beneath the RPE) and type 1+2 cases based on clinical and histopathologic findings, but they also described preoperative detection of the type 1 component as being difficult.

In 1994, Thomas et al (1) conducted CNV excision in 41 eyes with ARMD and reported no change in visual acuity in 73%. In 2000, we proposed that if cases with CNV located mainly above the RPE are selected, CNV excision will result in minimal RPE defects and greater improvement of visual acuity (4).

Although many cases undergoing CNV excision have been described, none of the reports to date has included multiple regression, on a large number of cases, aimed at examining the preoperative factors affecting long-term visual acuity. In this study, we evaluated the postoperative results of CNV judged to be mainly above the RPE and analyzed the influences of various preoperative factors on long-term visual outcome in these patients.

METHODS

Subjects and surgery

We studied 146 eyes of 146 patients with subfoveal CNV associated with ARMD, who underwent surgical excision of CNV at Nihon University Surugadai Hospital from March 1995 through March 2001, and were followed for at least 1 year (14 months to 8 years and 3 months). There were 105 men and 41 women, 66.9±8.6 years of age (50 to 90 years). Surgical indications included subfoveal active CNV located mainly above the RPE, fluorescent dye leakage from the CNV in late-phase fluorescein angiography, and a visual acuity of 0.3 or worse (4).

CNV above the RPE was diagnosed by fluorescein angiography, indocyanine green angiography, and optical coherence tomography; CNV was divided into completely classic CNV or mainly classic CNV. In completely classic CNV, fluorescein angiography depicted a neovascular network in the early phase and fluorescence leakage from the CNV in the late phase. Furthermore, indocyanine green angiography revealed fluorescence leakage consistent with CNV. Optical coherence tomography also showed that CNV was above the high reflection layer indicating the RPE. Mainly classic CNV cases showed most, but not all, of the above findings.

Combined surgery was performed. Vitreous surgery was done following cataract surgery. A posterior vitreous detachment (PVD) was produced in cases without PVD. A retinotomy was performed; the CNV was separated from the sensory retina and RPE using a spatula (Dorc, VN Zuidland, The Netherlands) under high perfusion pressure. Then, the CNV was excised using subretinal horizontal forceps (Dorc), and fluid–air exchange was conducted (1, 4).

Diagnostic methods

Visual acuity was measured with a standard Japanese decimal visual acuity chart and the logarithm of the minimum angle of resolution (logMAR = log 1/decimal visual acuity) was used for the analyses. “Improved” was defined as a logMAR visual acuity increase of 0.2 or more, “worse” as a logMAR visual acuity decrease of 0.2 or more, and “stable” as a logMAR visual acuity change of less than 0.2 (4). The relationships of postoperative logMAR visual acuity with preoperative logMAR visual acuity, the shortest distance between the center of the foveal avascular zone and the CNV margin, CNV size, and age were analyzed.

For optical coherence tomography (Humphrey Instruments, division of Carl Zeiss, San Leandro, CA, USA), the macular region was scanned horizontally and vertically by 3.0 mm or 5 mm through the fovea. Fluorescein angiographic and indocyanine green examinations were performed with a fundus camera (Topcon, Tokyo, Japan) and a scanning laser ophthalmoscope (Rodenstock Instruments, Munich, Germany), respectively.

CNV size was determined on fluorescein angiographic images as the greatest diameter measured with a micrometer caliper, and calculated taking the optic disc diameter as 1500 μm. The shortest distance from the center of the foveal avascular zone to the CNV margin was also determined on fluorescein angiographic images in the early phase using a micrometer caliper (Fig. 1).

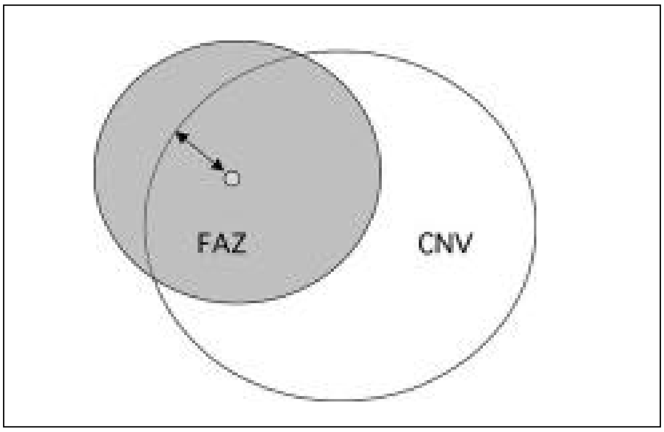


Fig. 1 - *The shortest distance from the center of the foveal avascular zone (FAZ) to the choroidal neovascularization (CNV) margin is determined on early phase fluorescein angiographic images using a micrometer caliper.*

Statistical analysis

Statistical analyses were conducted using stepwise regression, Fisher exact probability test, and the paired t-test. A p value less than 0.05 was considered significant.

RESULTS

All patients

In total, we assessed the outcomes of 105 men and 41 women whose mean ± SD CNV size was 1.2±0.6 (range: 0.3-2.8) disc diameters, and mean shortest distance between the center of the foveal avascular zone and the CNV margin was 0.3±0.2 (0-1.1) disc diameters. Compared to preoperative logMAR visual acuity, the postoperative logMAR final visual acuity showed significant improvement ($p<0.0001$, paired t-test).

The preoperative decimal visual acuity was 0.09 or worse in 76 eyes (52%), and 0.1-0.3 in 70 (48%). The final decimal visual acuity was 0.09 or worse in 41 eyes (28%), 0.1-0.3 in 83 (57%), and 0.4 or better in 22 (15%) (Fig. 2). The final logMAR visual acuity was improved in 78 eyes (54%), unchanged in 47 (32%), and worsened in 21 (14%) (Fig. 3).

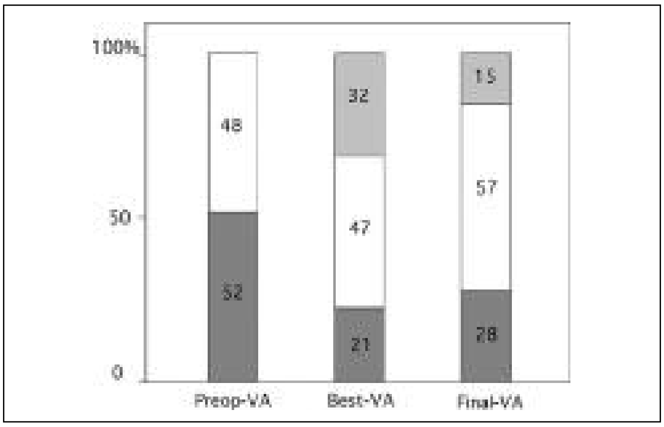


Fig. 2 - *Bar graph showing pre- and postoperative standard Japanese decimal visual acuity (VA) in all patients. Light gray = ≥0.4; white = 0.1-0.3; dark gray = ≤0.09.*

Stepwise regression identified CNV size as a significant factor influencing logMAR final visual acuity (R^2= 0.213, $p<0.0001$), while preoperative logMAR visual acuity, shortest distance between the center of the foveal avascular zone and the CNV margin, and age had no significant correlation with final logMAR visual acuity.

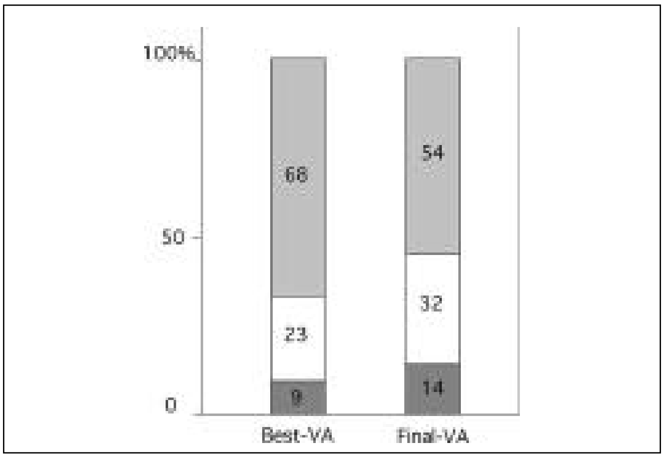
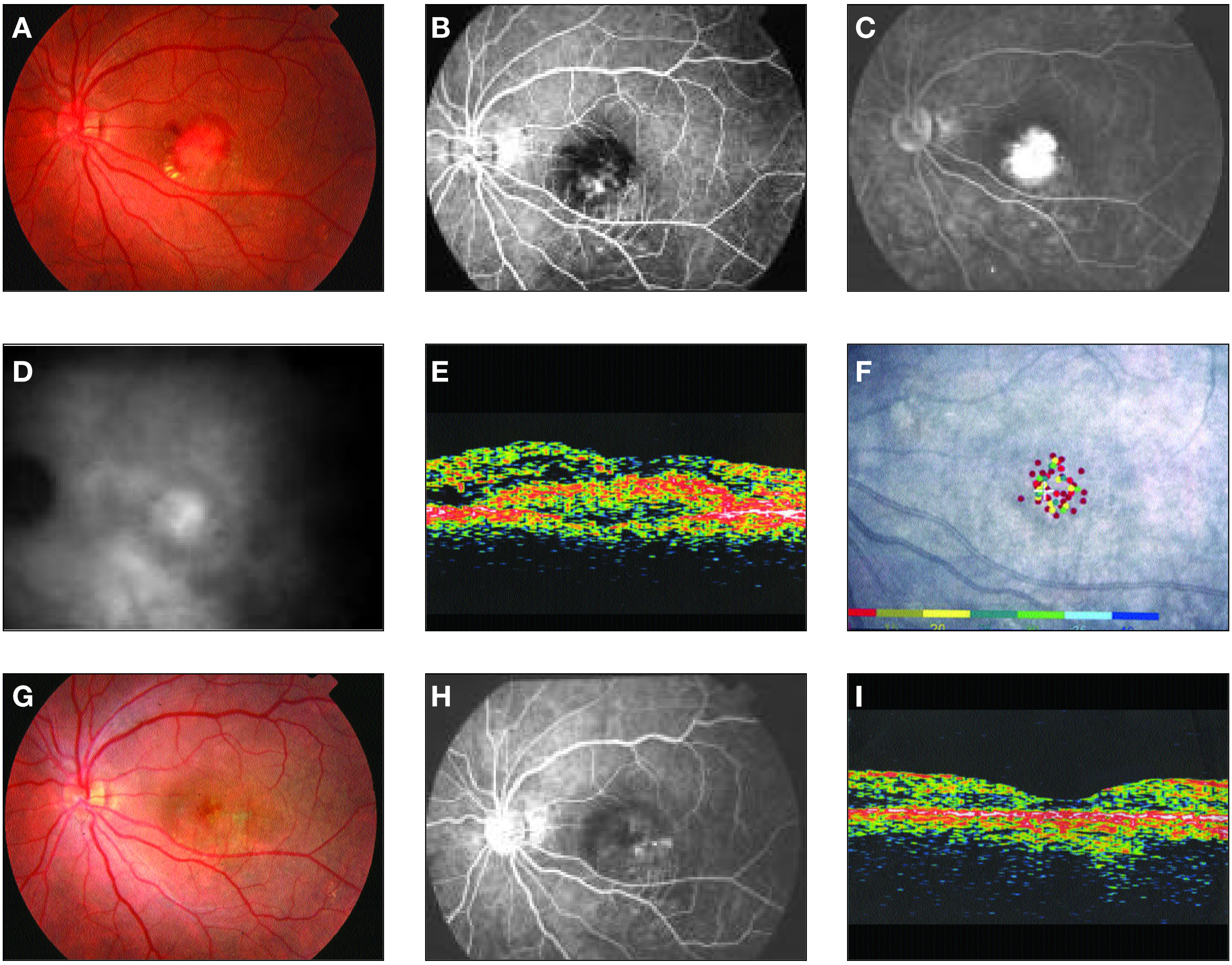


Fig. 3 - *Bar graph showing proportions of eyes in three categories of visual outcome for best and final visual acuity (VA) in all patients. Light gray = improved; white = stable; dark gray = worse.*

Surgical complications included retinal detachment in six eyes (4%), subretinal hematoma in four eyes (2%), macular hole in three (2%), and proliferative vitreoretinopathy in two (1%) (including cases with multiple complications). Retinal detachment and proliferative vitreoretinopathy subsided upon reoperation in all cases. Subretinal hematoma was removed



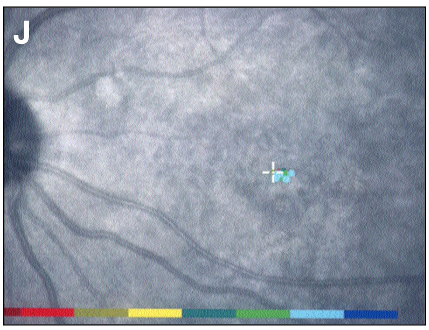


Fig. 4 - *A case of completely classic choroidal neovascularization (CNV) (55-year-old woman, preoperative visual acuity 0.3).* **(A- F)** *Before surgical excision of CNV;* **(G- J)** *1 year after surgery.* **(A)** *Fundus photograph showing a subfoveal CNV.* **(B)** *Early phase fluorescein angiography showing a 1.3 disc diameter neovascular network. The shortest distance from the center of the foveal avascular zone to the CNV margin is 0.3 disc diameters.* **(C)** *Late phase fluorescein angiography showing fluorescent dye leakage from the CNV.* **(D)** *Indocyanine green angiography did not reveal dye leakage consistent with occult CNV.* **(E)** *Vertical plane optical coherence tomography confirming the CNV to be located above the retinal pigment epithelium (RPE).* **(F)** *Scanning laser ophthalmoscopic perimetry showing fixation within the fovea.* **(G)** *Fundus photograph 1 year after CNV excision showing minimal RPE defect.* **(H)** *Fluorescein angiography showing minimal RPE defect.* **(I)** *Vertical plane optical coherence tomography showing slightly thinned sensory retina.* **(J)** *Scanning laser ophthalmoscopic perimetry showing fixation within the fovea.*

by reoperation. Three macular hole cases had no retinal detachment and were followed without further treatment. CNV recurred postoperatively in 18 eyes (12%), and twice in 3 eyes. Recurrence was detected between 1 and 6 months in 61%, 7 and 12 months in 22%, and 13 and 36 months in 17% of the cases. Among 18 eyes with recurrent CNV, 11 had repeat surgery to remove CNV, 4 were treated with retinal photocoagulation, and 3 with recurrence at sites not affecting vision were observed. The final visual acuity was lower than the highest visual acuity in 15 of 18 eyes with recurrent CNV.

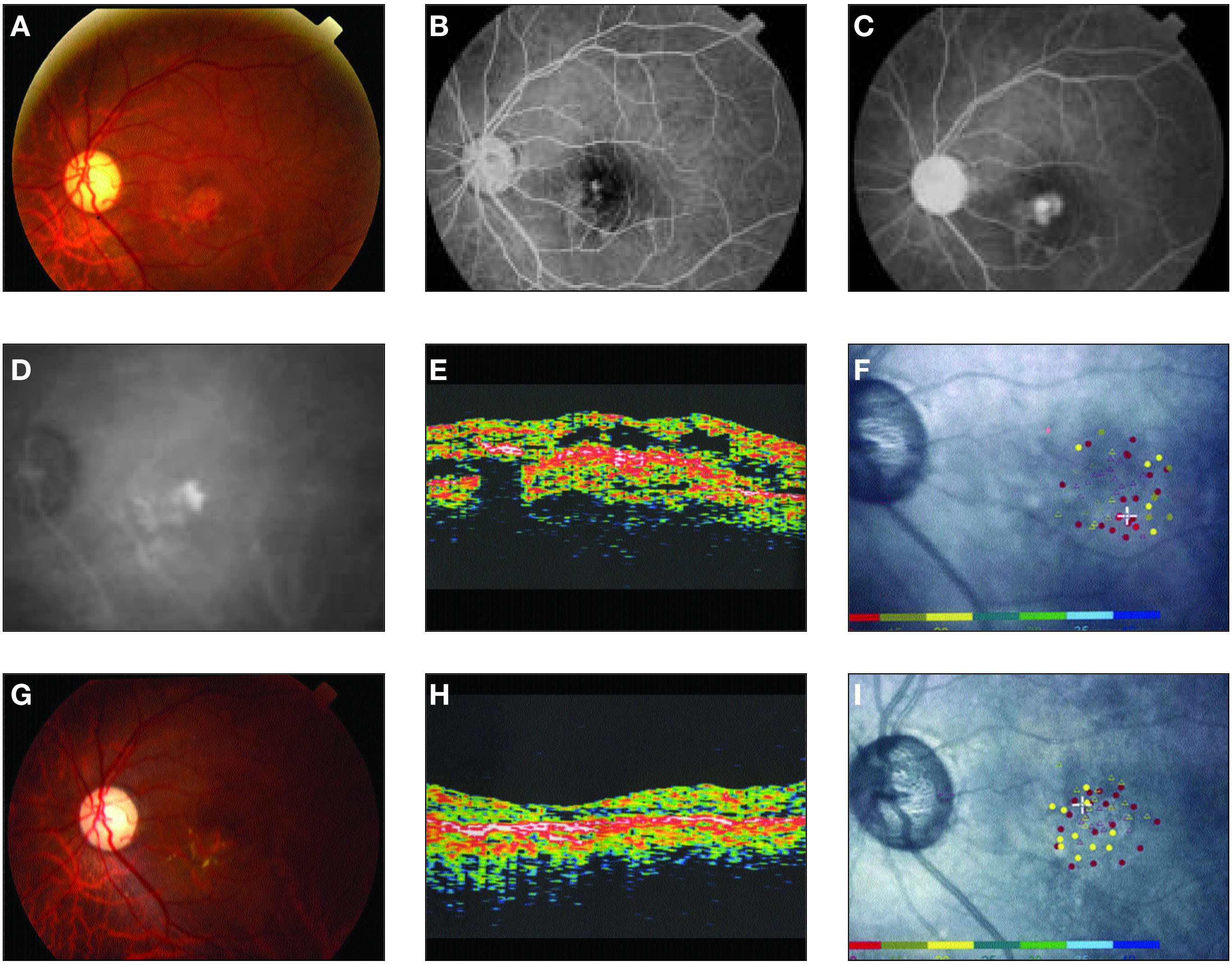


Fig. 5 - *A case with mainly classic choroidal neovascularization (CNV) (73-year-old man, preoperative visual acuity 0.09).* **(A- F)** *Before surgical excision of CNV;* **(G- J)** *1 year after surgery.* **(A)** *Fundus photograph showing subfoveal CNV.* **(B)** *Early phase fluorescein angiography depicts neovascular network measuring 0.2 disc diameters. The shortest distance from the center of the foveal avascular zone to the CNV margin is 0.1 disc diameter.* **(C)** *Late phase fluorescein angiography shows hyperfluorescence, 0.6 disc diameters, around the classic CNV.* **(D)** *Indocyanine green angiography revealed dye leakage consistent with occult CNV.* **(E)** *Vertical plane optical coherence tomography identifying the CNV as being located mainly above the retinal pigment epithelium (RPE).* **(E)** *Scanning laser ophthalmoscopic perimetry showing fixation inferotemporal to the CNV.* **(G)** *Fundus photograph 1 year after CNV excision showing the presence of a defect involving the RPE and choriocapillaris.* **(H)** *Optical coherence tomography showing a thinned sensory retina.* **(I)** *Scanning laser ophthalmoscopic perimetry showing fixation superonasal to the surgically disturbed aea.*

When the intraoperative status of PVD was compared with the frequency of retinal detachment, the frequency was significantly higher ($p<0.03$, Fisher exact probability test) in eyes without PVD (6/78) than in eyes with PVD (0/51).

Completely classic CNV and case presentation

Ninety-two patients (64 men and 28 women) had angiographically showed completely classic CNV. The mean ± SD CNV size was 1.0±0.5 (range: 0.3-2.6) disc diameters and the mean shortest distance from the center of the foveal avascular zone to the CNV margin was 0.3±0.2 (0-1.1) disc diameters.

Compared to preoperative visual acuity, the postoperative final logMAR visual acuity showed significant improvement ($p<0.0001$, paired t-test).

The preoperative visual acuity was 0.09 or worse in 42 eyes (46%), and 0.1-0.3 in 50 (54%). The final visual acuity was 0.09 or worse in 12 eyes (13%), 0.1 - 0.3 in 61 (66%), and 0.4 or better in 19 (21%). Final visual acuity was improved in 57 eyes (62%), unchanged in 27 (29%), and worsened in 8 (9%).

Case presentation

A 55-year-old woman with preoperative visual acuity of 0.3 had a subfoveal CNV 1.3 disc diameters in size (Fig. 4, A and B). The shortest distance from the center of the foveal avascular zone to the CNV margin was 0.3 disc diameters (Fig. 4B). Fluorescein angiography showed a neovascular network in the early phase (Fig. 4B) and fluorescent dye leakage from the CNV in the late phase (Fig. 4C). Indocyanine green angiography in the late phase (Fig. 4D) and optical coherence tomography in vertical cross-section (Fig. 4E) confirm the CNV to be located above the RPE. Scanning laser ophthalmoscopic perimetry showed fixation to be within the fovea (Fig. 4F).

One year after CNV excision, visual acuity recovered to 1.0 (Fig. 4G). The RPE defect was minimal on fluorescein angiography (Fig. 4H). Optical coherence tomography showed slight thinning of the sensory retina (Fig. 4I). Perimetry confirmed fixation to be within the fovea (Fig. 4J).

Mainly classic CNV and case presentation

Fifty-four patients (41 men and 13 women) angiographically showed mainly classic CNV. The mean ± SD CNV size was 1.5±0.6 (range: 0.6 - 2.8) disc diameters, and mean distance from the center of the foveal avascular zone to the CNV margin was 0.4±0.3 (0 - 1.1) disc diameters. Compared to preoperative visual acuity, the postoperative best logMAR visual acuity and final logMAR visual acuity both showed significant improvement ($p<0.001$ and $p=0.0082$, respectively; paired t-test).

The preoperative visual acuity was 0.09 or worse in 34 eyes (63%), and 0.1 - 0.3 in 20 eyes (37%). The final visual acuity was 0.09 or worse in 27 eyes (50%), 0.1 - 0.3 in 25 (46%), and 0.4 or better in 2 (4%). The final visual acuity was improved in 21 eyes (39%), unchanged in 20 (37%), and worse in 13 (34%).

Case presentation

A 73-year-old man with preoperative visual acuity of 0.09 was found to have a subfoveal CNV measuring 0.6 disc diameters (Fig, 5, A and B).

The shortest distance from the center of the foveal avascular zone to the CNV margin was 0.1 disc diameter (Fig. 5B).

Fluorescein angiography and indocyanine green angiography depicted hyperfluorescence, 0.2 disc diameters, in the early phase and hyperfluorescence, 0.6 disc diameters, around the CNV in the late phase (Fig. 5, B - D). Optical coherence tomography identified the CNV as being located mainly above the RPE (Fig. 5E). Scanning laser ophthalmoscopic perimetry showed fixation to be inferotemporal to the CNV (Fig. 5F).

One year after CNV excision, visual acuity had improved to 0.2. There was a defect involving the RPE and choriocapillaris (Fig. 5G).

Optical coherence tomography showed a thinned sensory retina (Fig. 5H). Perimetry showed fixation to be superonasal to the surgically disturbed area (Fig. 5I).

DISCUSSION

In 1994, Thomas and colleagues (1) surgically excised subfoveal CNV in ARMD cases, but achieved only preservation of preoperative visual acuity postoperatively. In 1999, Scheider et al (3) used fluorescein angiographic findings to classify 35 eyes with foveal ARMD into subfoveal well-defined CNV and subfoveal ill-defined CNV groups and compared their postoperative visual outcomes. They reported favorable visual outcomes in well-defined CNV cases (improvement of visual acuity by three grades or more in 40% and unchanged in 50%) while visual acuity was generally only preserved in ill-defined CNV cases (improvement of visual acuity by three grades or more in 22% and unchanged in 56%). Therefore, CNV excision for ARMD patients may be expected to achieve relatively good visual acuity, when applied to well-defined CNV.

In our present study, visual acuity was improved in 62% of completely classic CNV cases, stable in 29%, and worsened in 9%. On the other hand, visual acuity was improved in 39% of mainly classic CNV cases, stable in 37%, and worsened in 24%. Therefore, surgical excision of CNV caused by ARMD is clearly indicated for completely classic CNV, while surgery may be indicated for mainly classic CNV for the purpose of preserving preoperative visual acuity. Simultaneous cataract surgery was conducted because all the patients were 50 years of age or older. Although cataract surgery is expected to affect the visual outcome to some extent, surgical excision of CNV due to

ARMD may be indicated for the purpose of preserving and even improving preoperative visual acuity.

Various factors have been reported to affect the visual outcome of CNV excision in patients with ARMD: the preoperative factors included CNV classification, CNV size, time from CNV onset to surgery, age, preoperative visual acuity, distance between the center of the foveal avascular zone and the CNV margin, and CNV ingrowth site, while postoperative factors included CNV recurrence (4, 5). In the present study, we did not examine the period from onset to surgery because the time of onset was unclear in many cases.

We also did not examine CNV ingrowth site because multiple ingrowth sites were found in some cases and the sites could not be identified even by indocyanine green angiography in 57% of our patients (5).

Stepwise regression identified CNV size as a significant factor influencing final logMAR visual acuity. This result may be explained as follows. For small CNVs, the CNV margin is close to the center of the fovea; therefore, even if a scotoma is formed at the site of CNV excision, fixation remains possible near the fovea, which contributes to improved visual acuity.

Before the advent of PDT and transpupillary thermotherapy, laser photocoagulation was conducted for foveal CNV. While it is difficult to compare our results directly with the results of the Macular Photocoagulation Study (MPS) Group, the MPS conducted photocoagulation circumscribing the CNV and the absolute scotoma formed is thus larger than the CNV (13). In this context, surgical excision is superior to photocoagulation in producing a smaller scotoma, and consequently obtaining better visual outcome.

Previously we also compared the results of photocoagulation and surgical excision and reported better visual outcome for surgical excision (14). Because of tissue destruction, photocoagulation is now conducted only for CNV that are separated from the fovea by more than 200 μm (15). PDT has been reported to be especially effective for predominantly classic CNV (16, 17). Recently, therapeutic strategies combining PDT with intravitreal antivascular endothelial growth factor injection (7) or intravitreal triamcinolone injection (10) have been reported to improve visual acuity and reduce the number of treatment sessions. Our results are better than those of PDT obtained by the Treatment of Age-Related Macular Degeneration with PDT (TAP) Study Group (18, 19). However, the Japanese Age-Related Macular Degeneration Trial (JAT) Study Group that adopted the same indications as the TAP Study reported better results than the TAP Study (20). Thus, it is likely that results obtained in Japanese subjects are better than those in Western countries both for PDT and surgical excision, implying a need to compare PDT and surgical excision in Japanese subjects with the same CNV types. PDT has only been used in Japan since May 2004. Since we are currently conducting PDT on cases conventionally indicated for surgical CNV excision, we shall compare the results of PDT and surgical excision, weighing the relative merits against surgical risk and postoperative complications to clearly define the indications for PDT and surgical excision.

In 2004, the Submacular Surgery Trial (SST) Research Group followed the outcome of surgery for subfoveal CNV in ARMD for 2 years and reported no difference in postoperative visual acuity compared to the observation group (21).

However, the subjects in SST had predominantly classic CNV and minimally classic CNV, and were different from our subjects with completely classic CNV and mainly classic CNV.

To overcome the RPE defect resulting from CNV excision, autologous RPE transplantation during CNV excision is being attempted (22, 23). We also conducted autografting of the RPE during CNV excision, but RPE aggregation developed and fixation was not obtained at the RPE graft site (24). Therefore the usefulness of RPE grafting has not yet been established.

The authors have no commercial or proprietary interest in the product or the company.

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