Evaluation of Glaucoma Progression in Large-Scale Clinical Data: The Japanese Archive of Multicentral Databases in Glaucoma (JAMDIG)


1Department of Ophthalmology, The University of Tokyo, Tokyo, Japan
2Department of Ophthalmology, Osaka University Graduate School of Medicine, Osaka, Japan
3Department of Ophthalmology, Shimane University Faculty of Medicine, Shimane, Japan
4Division of Ophthalmology, Matsue Red Cross Hospital, Shimane, Japan
5Department of Ophthalmology, Ehime University Graduate School of Medicine, Ehime, Japan
6Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan
7Department of Ophthalmology, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan
8Department of Ophthalmology, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan
9Department of Ophthalmology, University of Yamanashi Faculty of Medicine, Yamanashi, Japan
10Orthoptics and Visual Science, Department of Rehabilitation, School of Allied Health Sciences, Kitasato University, Kanagawa, Japan

Correspondence: Ryo Asaoka, Department of Ophthalmology, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655 Japan; rasaoa-tykim@umin.ac.jp.

Accepted: February 19, 2016
Submitted: December 29, 2015

PURPOSE. To develop a large-scale real clinical database of glaucoma (Japanese Archive of Multicentral Databases in Glaucoma: JAMDIG) and to investigate the effect of treatment.

METHODS. The study included a total of 1348 eyes of 805 primary open-angle glaucoma patients with 10 visual fields (VFs) measured with 24-2 or 30-2 Humphrey Field Analyzer (HFA) and intraocular pressure (IOP) records in 10 institutes in Japan. Those with 10 reliable VFs were further identified (638 eyes of 417 patients). Mean total deviation (mTD) of the 52 test points in the 24-2 HFA VF was calculated, and the relationship between mTD progression rate and seven variables (age, mTD of baseline VF, average IOP, standard deviation (SD) of IOP, previous argon/selective laser trabeculoplasties (ALT/SLT), previous trabeculectomy, and previous trabeculotomy) was analyzed.

RESULTS. The mTD in the initial VF was $-6.9 \pm 6.2$ dB and the mTD progression rate was $-0.26 \pm 0.46$ dB/year. Mean IOP during the follow-up period was $13.5 \pm 2.2$ mm Hg. Age and SD of IOP were related to mTD progression rate. However, in eyes with average IOP below 15 and also 13 mm Hg, only age and baseline VF mTD were related to mTD progression rate.

CONCLUSIONS. Age and the degree of VF damage were related to future progression. Average IOP was not related to the progression rate; however, fluctuation of IOP was associated with faster progression, although this was not the case when average IOP was below 15 mm Hg.

Keywords: glaucoma, visual field, progression, intraocular pressure

Glaucoma is one of the leading causes of blindness in the world. The disease is a progressive and irreversible optic neuropathy that can result in irrevocable visual field (VF) damage. Primary open-angle glaucoma (POAG) is the most common type, affecting more than 45 million people, with prevalence rates ranging from 0.5% to 8.8%.3–22 That increase with age.23 Previous studies have revealed different outcomes in preventing glaucomatous VF progression, in particular related with race.27,38 Hence, it is clinically very important to also investigate the efficacy of IOP reduction treatment in a real and large-scale clinical dataset. This has become achievable
Evaluation of Glaucoma Progression in JAMDIG Data

Thanks to the growing usage of the electronic medical record systems in Japan. Thus, the first purpose of the current study was to develop a large-scale real clinical database of glaucoma outcomes in Japanese patients (Japanese Archive of Multicentral Databases in Glaucoma: JAMDIG), and the second purpose of the current study was to investigate the effect of treatment in the dataset.

Subjects and Methods
The review board of each institute reviewed and approved all protocols. The studies complied with the tenets of the Declaration of Helsinki. Written consent was given by patients for their information to be stored in the hospital database and used for research; otherwise, based on the regulations of the Japanese Guidelines for Epidemiologic Study 2008 issued by the Japanese Government, the study protocols did not require that each patient provide written informed consent. Instead the protocol was posted at the outpatient clinic to notify participants of the study.

Data Collection
All of the data collected in the current study (JAMDIG) were obtained from ten institutes in Japan as listed in the appendix. Using the electronic records of each institute, all patients with POAG, including NTG, who satisfied the following criteria were identified retrospectively: (1) Glaucoma was the only disease causing VF damage; (2) each patient had at least 11 VF measurements with 24-2 or 30-2 Humphrey Field Analyzer II (HFA) (Carl Zeiss Meditec, Inc., Dublin, CA, USA) and at least 10 IOP measurements with Goldmann applanation tonometry. Primary open-angle glaucoma was defined as (1) presence of typical glaucomatous changes in the optic nerve head such as a rim notch with a rim width < 0.1 disc diameters or a vertical cup-to-disc ratio of >0.7 and/or a retinal nerve fiber layer defect with its edge at the optic nerve head margin greater than a major retinal vessel, diverging in an arcuate or wedge shape; and (2) gonioscopically wide open angles of grade 3 or 4 based on the Shaffer classification. Exclusion criterion were age below 20 years and possible secondary ocular hypertension in either eye.

From the medical record, a history of surgical/laser treatments was collected. Surgical treatment was categorized into two groups: surgeries associated with the creation of bleb using mitomycin-C (trabeculectomy and nonpenetrating trabeculectomy; trabeculectomy group) and other procedures (trabeculotomy and viscocanalostomy; trabeculotomy group). Each of these categories included both glaucoma surgery alone and combined glaucoma and cataract surgery. Laser treatment consisted of argon and selective laser trabeculoplasties (ALT/SLT group).

Data Filtering
Reliable VFs were defined as fixation loss (FL) rate < 20% and also false-positive (FP) rate < 15% following the criteria used by the HFA software; false negative (FN) was not used as an exclusion criterion. Reliable VFs were identified, and eyes with at least 11 reliable VFs were collected. Eyes that experienced any surgical procedure, including needling bleb revision and neodymium: yttrium aluminum garnet (YAG) capsulotomy, during this period were carefully excluded. Removing the baseline VF, the remaining 10 VFs for each eye were used to measure progression. We chose a minimum of 10 VFs because it has recently been reported that this volume is needed to precisely analyze VF progression.59 In the data collection phase, other clinical information such as central corneal thickness (CCT), general medical past history, history of smoking, and significant family history was also collected but not used in the current analysis due to a large proportion of missing values. Data from eyes with exfoliation glaucoma were initially collected but were excluded from the current analysis because of the very small number of eyes (13 in total).

Statistical Analysis
First, mean total deviation (mTD) of the 52 test points in the 24-2 HFA VF was calculated. Then, the progression rate of mTD was calculated using the 10 VFs collected from each eye with linear regression against time, similarly to the MD trend analysis employed in the HFA. As both eyes of a patient tend to progress similarly, a mixed linear regression model was employed to investigate mTD progression; in this model the eyes of a patient are nested within the patient. The average and standard deviation (SD) of IOP measurements were also calculated. These summary statistics, as well as mTD progression rate, were compared between eyes with previous trabeculectomy and other procedures.

The relationship between mTD progression rate and seven variables (age at the baseline VF measurement, mTD value of the baseline VF, average IOP SD of IOP previous ALT/SLT, previous trabeculectomy, and previous trabeculotomy) was analyzed using linear mixed modeling, whereby patients were treated as a random effect. The optimal linear model was selected using the second-order bias corrected Akaike Information Criterion (AICc) index. The AIC is a well-known statistical measure used in model selection, and the AICc is a corrected version of the statistic, which provides an accurate estimation even when the sample size is small.40 In a multivariate regression model, the degrees of freedom decreases with a large number of variables, and it is therefore recommended to use model selection methods to improve the model fit by removing redundant variables.41,42 In the current study, model selection was performed from seven variables, which corresponds to 27 choices of linear model. This calculation was performed using all eyes and also in two subgroups of patients whose average IOP fell below 15 and 13 mm Hg.

All analyses were performed using the statistical programing language R (R version 3.1.3; Foundation for Statistical Computing, Vienna, Austria).

Results
In the initial collecting phase, 1348 eyes of 805 POAG patients were identified between January 1997 and January 2015. Following the filtering process, 710 eyes of 490 patients were removed for the following reasons: 448 eyes had fewer than 11 reliable VFs; 78 eyes had fewer than 10 IOP measurements during the follow-up period, and 184 eyes underwent surgical treatment or YAG laser capsulotomy during the follow-up period. As a result, 638 eyes of 417 patients remained in the analysis. As shown in Table 1, the mean (±SD) age of patients was 54.8 ± 11.8 years, ranging from 21 to 84 years. The 10 VFs analyzed were obtained over 5.4 ± 1.1 [range, 2.1–9.4] years and IOP measurements were carried out 23.6 ± 6.0 [10–43] times per eye. The VFs were measured over an interval of 198.0 ± 42.6 [74.7–544.2] days while IOP was measured over an interval of 89.5 ± 31.3 [27.9–248.7] days. The mTD value in the initial VF was −6.9 ± 6.2 [−26.8 to 2.8] dB, and the mTD progression rate was −0.26 ± 0.46 [−2.6 to 1.4] dB/year (Fig. 1). Mean IOP during the follow-up period was 13.5 ± 2.2 [5.6–21.8] mm Hg (Fig. 2). Among the 638 eyes, 37 eyes of 34 patients had trabeculectomy prior to the
baseline VF; and 12 eyes of 10 patients had trabeculotomy prior to the baseline VF. Among these 12 eyes, all patients had trabeculectomy following trabeculotomy and prior to the baseline VF (see Table 2). Fifty-one eyes of 48 patients had ALT/SLT treatment prior to the baseline VF; forty-two eyes of 38 patients had ALT/SLT treatment during the follow-up period.

Mean IOP was significantly lower in eyes with previous trabeculectomy than in others (11.7 ± 3.2 [5.6–18.9] and 13.6 ± 2.1 [8.4–21.8] mm Hg, respectively, P < 0.001, linear mixed model). In contrast, there was not a significant difference between the SD of IOP in these eyes (1.7 ± 0.6 [0.8–4.4] and 1.6 ± 0.6 [0.70–6.9], respectively, P = 0.70, linear mixed model).

As shown in Figure 3, there was not a significant difference between the mTD progression rates in these eyes (−0.31 ± 0.50 [−2.3 to 0.56] and −0.26 ± 0.46 [−2.6 to 1.4] dB/year, respectively, P = 0.71, linear mixed model).

Figure 4 illustrates the relationship between mTD progression rate and age. There was a significant relationship between these parameters (mTD progression rate = 0.051 – 0.0058*age, P = 0.0014 for age, linear mixed model). There was not a significant relationship between mTD progression rate and mTD in the baseline VF (P = 0.16, linear mixed model; Fig. 5). The mTD progression rate was not significantly related to average IOP (P = 0.32, linear mixed model; Fig. 6), but significantly related to the SD of IOP (mTD progression rate = −0.13 – 0.084*SD of IOP, P = 0.011 for SD of IOP, linear mixed model; Fig. 7).

As a result of model selection using AICc, the optimal linear model for mTD progression rate was given by: mTD progression rate = −0.16 – 0.0055*age at the baseline VF measurement −0.077*SD of IOP, thus mTD of the baseline VF, average IOP, previous trabeculectomy, previous trabeculotomy, and previous ALT/SLT were not included (see Table 3).

Among the 638 eyes, 485 eyes of 320 patients had an average IOP below 15 mm Hg, whereby 33 eyes of 30 patients had previous trabeculectomy, 10 eyes of 9 patients had previous trabeculotomy, and 36 eyes of 28 patients had previous ALT/SLT. In this average IOP < 15 mm Hg group, the mTD progression rate was −0.26 ± 0.45 [−2.6 to 1.1] (mean ± SD [range]) dB/year and the optimal linear model for the mTD progression rate was: mTD progression rate = 0.039 − 0.0046*age at the baseline VF measurement + 0.0057*mTD of the baseline VF; average IOP SD of IOP, previous trabeculectomy, previous trabeculotomy, and previous ALT/SLT were not included (see Table 3). Similarly, 271 eyes of 187 patients had an average IOP below 13 mm Hg, whereby 22 eyes of 20 patients had previous trabeculectomy, 5 eyes of 5 patients had previous trabeculotomy, and 16 eyes of 15 patients had previous ALT/SLT. In this average IOP < 13 mm Hg group, the mTD progression rate was −0.25 ± 0.42 [−1.8 to 0.81] (mean ± SD [range]) dB/year and the optimal linear model for the mTD progression rate was: mTD progression rate = 0.10 – 0.0052*age at the baseline VF measurement + 0.0073*mTD of the baseline VF; average IOP SD of IOP, previous trabeculectomy, previous trabeculotomy, and previous ALT/SLT were not included (see Table 3).

**DISCUSSION**

Large-scale real clinical data were collected from ten centers in Japan. Data from 1348 eyes of 805 patients with open-angle glaucoma were collected. Among this dataset, 638 eyes from 417 patients with POAG were analyzed in the current study. It was observed that IOP was significantly lower in eyes with.
previous trabeculectomy; however, the SD of IOP measurements was not significantly different between groups. Similarly, mTD progression rate was not significantly different between eyes with and without previous trabeculectomy. Among the clinical parameters of age, mTD value in the baseline VF, ALT/SLT, previous trabeculectomy, previous trabeculotomy, and average IOP and SD of IOP, it was suggested that only age and SD of IOP were related to the mTD progression rate. A subgroup analysis using only eyes with an average IOP below 15 or 13 mm Hg revealed that only age and mTD value in the baseline VF were related to mTD progression rate.

The mean VF progression rate in the current study was −0.26 dB/year with a mean IOP of 13.5 mm Hg. Some recent comparable studies have reported the rates of VF progression using data obtained at real clinics. Heijl et al. reported a VF progression rate of −0.80 dB/year with a mean IOP between 18.1 and 20.2 mm Hg, obtained from 583 patients with open-angle glaucoma. De Moraes et al. reported a −0.45 dB/year VF progression rate with a mean IOP of 15.2 mm Hg, obtained from 587 patients with glaucoma. Our results suggest slower VF progression rates with lower IOP levels than observed in other reports.

It is of interest to compare the current results with a previous RCT in normal-tension glaucomatous eyes that provides natural history progression rate: The Collaborative Normal-Tension Glaucoma Study Group reported mean rates of approximately −0.4 dB/year. The VF progression rate in the current study is very similar to that in a previous observational study (−0.25 dB/year) based on 34 posttrabeculectomy patients with a maximum IOP of 12 mm Hg (mean: 10.3 mm Hg) and a follow-up of at least 3 years.

Age is an established risk factor for the progression of glaucoma. In agreement with this, age was selected in the optimal model with a negative coefficient (the older the patient, the faster progression). It is worth noting, however, that clinicians would tend to choose less aggressive treatments in elderly patients. Thus, the significant effect of age on the progression rate could be attributed, at least partially, to this treatment selection bias. Nevertheless, these two parameters were also selected in the subanalyses with eyes in which IOP was controlled at a low level; hence it is suggested that age is still a risk factor for progression, beyond any treatment selection bias.

Many previous studies have suggested that VF damage at baseline is a risk factor for progression. In agreement with this, the mTD at baseline parameter was selected in the

| Table 2. Demographic Data of Initial Data, Exclusion Reasons, and Treatment History in the Final Data Analyzed |
|--------------------------------------------------------|-----------------|
| **Data** | **Number** | **mTD, Mean ± SD [Range]** |
| Initial data | 1348 eyes of 805 patients | |
| Exclusion | | |
| Less than 11 reliable VFs: 448 eyes | | |
| Less than 10 IOP measurements between 2nd and 10th VFs: 78 eyes | | |
| Surgical treatment or YAG laser capsulotomy between 2nd and 10th VFs: 184 eyes | | |
| Final data | 638 eyes of 417 patients | |
| Trabeculectomy prior to the baseline VF: 37 eyes of 34 patients | −6.9 ± 6.2 [−26.8 to 2.8] |
| Trabeculotomy prior to the baseline VF: 12 eyes of 10 patients | −10.7 ± 7.1 [−26.8 to −1.4] |
| ALT/SLT treatment prior to the baseline VF: 51 eyes of 48 patients | −9.7 ± 8.4 [−25.6 to 0.6] |
| ALT/SLT treatment during the follow-up period: 42 eyes of 38 patients | −9.3 ± 5.7 [−24.7 to −0.8] |

---

Figure 3. Comparison of mTD progression rates with and without previous trabeculectomy. There was not a significant difference between the mTD progression rate with and without previous trabeculectomy. The box represents first and third quartile with median value, and error bars represent outside 1.5 times the interquartile range above the upper quartile and below the lower quartile mTD: mean of 52 total deviation values corresponding to 24-2 Humphrey visual field.

Figure 4. The relationship between mTD progression rate and age at the baseline VF. There was a significant relationship between these parameters (mTD progression rate = 0.051 − 0.0058*age, P = 0.0014 for age, linear mixed model). Figure plotted as a smoothed scatter plot. VF, visual field; mTD, mean of 52 total deviation values corresponding to 24-2 Humphrey visual field.
optimal model with a positive coefficient (the worse the mTD values, the faster progression) in eyes with low IOP (mean < 15 mm Hg); however, this parameter was not related to progression in the analysis using all eyes and instead, SD of IOP was related. Thus VF damage at baseline was related to progression rate only when mean IOP was below 15 mm Hg.

Many previous studies have made it known, beyond doubt, that high IOP is a risk factor for the progression of glaucoma. Interestingly, in the current study, average IOP was not significantly related to mTD progression rate (Fig. 6), and it was not included in any of the optimal linear models. This result should be attributed to the difference in the study designs. In the current study, all data were collected in a retrospective manner. As a result, eyes deemed to be at high risk of progression tended to be treated with intensive treatments such as trabeculotomy, ALT/SLT, or even trabeculectomy. Thus, the current results do not deny the efficacy of these treatments, in particular for eyes with a high risk of progression. In turn, it could be suggested that current treatment strategies (in the Japanese institutes contributing data to this study) are successfully preventing the progression of glaucoma associated with average IOP.

The effect of variation in IOP on the progression of glaucoma is controversial. In the current study, SD of IOP was significantly related to progression rate in the analysis using all eyes. As discussed above, the current data are “biased” by the treatment selection of clinicians. As a result, IOP reduction was generally well controlled in our data, as is often seen in clinical settings, in terms of the average value. Nonetheless, our results suggest that VF progression is associated with high variation in IOP. Clinicians should advise patients regarding the importance of treatment compliance because there is no doubt that this is directly related to the variance of IOP. The importance of IOP variation was not observed when average IOP was lower than 15 mm Hg.

It has been reported that trabeculectomy is associated with a reduction in IOP fluctuation between visits or postural change, which could reduce the progression of VF damage. Nonetheless, our current results suggest that IOP fluctuation/variation following trabeculectomy was no different from values in nonoperated eyes. The reason for these contradictory results is unclear, but again could be attributed to a difference in study design; previous studies estimated IOP

### Table 3. Results of Optimal Linear Model Obtained by AICc Model Selection

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All Eyes, N = 638</th>
<th>Average IOP &lt; 15 mm Hg, N = 485</th>
<th>Average IOP &lt; 13 mm Hg, N = 271</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at the baseline VF</td>
<td>−0.0055</td>
<td>0.0017</td>
<td>0.00097</td>
</tr>
<tr>
<td>mTD value of the baseline VF</td>
<td>NS</td>
<td>0.0046</td>
<td>0.0018</td>
</tr>
<tr>
<td>Average IOP</td>
<td>NS</td>
<td>0.0057</td>
<td>0.0033</td>
</tr>
<tr>
<td>SD of IOP</td>
<td>−0.077</td>
<td>0.033</td>
<td>0.020</td>
</tr>
<tr>
<td>Previous ALT/SLT</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Previous trabeculectomy</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not selected in the optimal model.
fluctuation within a very short period, such as following postural change or over a 24-hour period, whereas the current study estimated fluctuation over a much longer follow-up period. On the other hand, SD of IOP was significantly related to the progression rate, so consideration should be given to the fluctuation of IOP, irrespective of the history of trabeculotomy, when clinicians make treatment decisions.

In Japan, trabeculotomy is frequently performed in adults with glaucoma. This bleb-independent glaucoma surgery is often performed when glaucoma is not in an advanced stage and preoperative IOP is not too high (usually below 30 mm Hg); otherwise trabeculectomy tends to be performed. In the current analysis, previous trabeculotomy was not related to the progression rate. However, it is not appropriate to draw conclusions about the effect of trabeculotomy on future VF progression based on the current results because of the limited number of patients (n = 12). Furthermore, all among the 12 eyes had trabeculectomy after trabeculotomy, prior to the baseline VF; hence further study should be carried out to shed light on the effect of trabeculotomy on the progression of VF damage. The effect of another treatment option, ALT/SLT, on VF progression was also assessed, but a significant relationship was not observed. We included eyes with ALT/SLT during the observation period because ALT/SLT usually does not have a significant effect on the VF. In contrast, trabeculotomy and trabeculectomy often will affect patients’ VFs. We carried out model selection again in which eyes that had undergone ALT/SLT (42 eyes) were dropped from the data. Similarly, we also performed model selection again in which eyes that had undergone ALT/SLT were dropped from the data. Similarly, we also performed model selection in which eyes with average IOP below 15 mm Hg and also eyes with average IOP < 15 mm Hg. As a consequence, very similar results were obtained. The same parameters were selected with very similar coefficient values, with just one exception. The SD of IOP was selected instead of mTD of the baseline VF in eyes with IOP < 15 mm Hg (results not presented in this paper).

There are a number of limitations to the current study. A possible caveat is the exclusion of central corneal thickness.

**Acknowledgments**

Supported in part by Grant 26–i26279 (RA) from the Ministry of Education, Culture, Sports, Science and Technology of Japan and Japan Science and Technology Agency (JST) CREST (RA).

Disclosure: Y. Fujino, None; R. Asaoka, None; H. Murata, None; A. Miki, None; M. Tanito, None; S. Mizoue, None; K. Mori, None; K. Suzuki, None; T. Yamashita, None; K. Kashiwagi, None; N. Shoji, None.

**References**


APPENDIX

JAMDIG Centers and Investigators: Participating Institutions and Investigators

Study Co-Chairman: Nobuyuki Shoji, medical doctor [MD]

Clinical Centers

Department of Ophthalmology, The University of Tokyo, Tokyo, Japan: Ryo Asaoka, medical doctor; Yuri Fujino, orthoptist; Masato Matsuura, orthoptist; Michio Yanagisawa, orthoptist; Hiroyo Hirasawa, MD; Hiroshi Murata, MD; Chihiro Mayama, MD.

Department of Ophthalmology, Osaka University Graduate School of Medicine, Osaka, Japan: Atsuya Miki, MD; Shinichi Usui, MD; Kenji Matsushita, MD; Kohji Nishida, MD.

Department of Ophthalmology, Shimane University Faculty of Medicine, Shimane, Japan: Masaki Tanie, MD; Tetsuro Omura, orthoptist.

Department of Ophthalmology, Ehime University Graduate School of Medicine, Ehime, Japan: Shiro Mizoue, MD.

Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan: Kazuhiko Mori, MD; Yoko Ikeda, MD; Hiromi Yamada, administration staff.

Department of Ophthalmology, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan: Katsuyoshi Suzuki, MD; Shinichiro Teranishi, MD; Rie Shiraishi, MD; Masaaki Kobayashi, MD; Manami Ohta, MD; Tadahiko Ogata, MD.

Department of Ophthalmology, Kagoshima University, Graduate School of Medical and Dental Sciences, Kagoshima, Japan: Takehiro Yamashita, MD.

Department of Ophthalmology, University of Yamanashi Faculty of Medicine, Yamanashi, Japan: Kenji Kashiwagi, MD; Fumihiko Mabuchi, MD.

Orthoptics and Visual Science, Department of Rehabilitation, School of Allied Health Sciences, Kitasato University, Kanagawa, Japan: Nobuyuki Shoji, MD; Kazunori Hirasawa, orthoptist.

Operations and Steering Committee: Ryo Asaoka, MD; Atsuya Miki, MD; Masaki Tanito, MD; Shiro Mizoue, MD; Kazuhiko Mori, MD; Katsuyoshi Suzuki, MD; Kenji Kashiwagi, MD; Takehiro Yamashita, MD; Nobuyuki Shoji, MD.