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Clinical outcome and subjective quality of life after photodynamic therapy in patients with age-related macular degeneration

F. KRUMMENAUER[1], M. BRAUN[1], H.B. DICK[2]

[1]Department of Medical Biometry, Epidemiology and Informatics, Universität of Mainz, Mainz
[2]University Eye Hospital, University of Mainz Medical School, Mainz - Germany

PURPOSE. *Whereas the efficacy of photodynamic therapy (PDT) in preventing the progression of age-related macular degeneration (ARMD) is established, its effect on quality of life is under discussion.*
METHODS. *All patients who underwent PDT during 2000 and 2001 at the University Eye Hospital of Mainz were interviewed using a standardized 82-item questionnaire on quality of life and patient satisfaction in ophthalmologic patients. Information was assessed in terms of 82 questions; global scores ranging from 1.0 (optimum self-estimated quality of life) to 4.0 (worst) were derived. Cataract patients' scores were used to characterize the ARMD patients' subjective outcome; the latter were then related to clinical outcome parameters via logistic regressions.*
RESULTS. *A total of 84 patients (50% female, median age 77 years) were interviewed, who underwent a median of three PDT interventions. During the period of PDT treatment, their median decrease in visual acuity was 3 lines from 0.125 to 0.063. Patients who reported a subjective increase in visual function during this period showed a median private flexibility score of 1.86; patients with the subjective impression of visual function decrease, a median score of 2.71; the median scores for mobility were 2.00 versus 3.00, for flexibility in reading 1.91 versus 3.64, for psychological stress 1.56 versus 2.25, and for communicational flexibility 1.72 versus 2.25. The difference in reading flexibility was statistically significant (p=0.001) after correction for clinical cofactors.*
CONCLUSIONS. *The established clinical benefit of PDT treatment concerning its efficacy in ARMD progression prevention coincides with an at least slight subjective benefit in quality of life and patient satisfaction. However, the latter is associated with the patients' subjective impression of visual acuity progression rather than with clinically validated outcome after PDT treatment. (Eur J Ophthalmol 2005; 15: 74-80)*

KEY WORDS. *Quality of life, Photodynamic therapy, Age-related macular degeneration*

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INTRODUCTION

Photodynamic therapy (PDT) has become one of the most promising approaches to preventing the progression of age-related macular degeneration (ARMD).

However, in addition to its established interventional efficacy concerning ARMD progression, some patients report a subjective increase in vision clarity, which in some rare cases can be confirmed by an objectively measured increase of these patients' visual acuity during the PDT treatment period. These cases not only profit from progression inhibition, but also report a remarkable gain in

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subjective quality of life due to regained flexibility and mobility in their daily life.

A questionnaire-based cross-sectional study on quality of life and patient satisfaction in ARMD patients after PDT treatment was implemented at the University Eye Hospital of Mainz, which comprised daily life aspects as well as ARMD-specific determinants (e.g., reading flexibility) of quality of life.

PATIENTS AND METHODS

Quality of life assessment

The psychometrically standardized Mainz questionnaire on quality of life in ophthalmologic patients (1) was used to estimate ARMD patients' self reported quality of life and subjective gain attributable to the PDT treatment. This questionnaire was designed and evaluated (1) to assess the quality of life determinants private flexibility (e.g., daily life), mobility (driving, sports), flexibility in reading, psychological stress, and communication flexibility (watching news on TV, visiting friends) by means of 82 paraphrased items (Tab. I), which are all answered in terms of an identical four-staged scale.

Each item has to be assigned to one of the answer categories correct, merely correct, hardly correct, or incorrect (semantic translation from the original German questionnaire).

The answers to all those items belonging to one of the above aspects (dimensions) are then averaged to derive a total score for this aspect, which ranges between 1.0 (best rating for all items belonging to this aspect) to 4.0 (worst rating for each item).

Median results of these scores can then be used to, for example, contrast the quality of life ratings of ARMD patients with the ratings of patients with different ophthalmologic disorders to determine ARMD-specific quality of life determinants.

During evaluation of the Mainz questionnaire, which was first designed for application to cataract patients and probands without ophthalmologic disorders, median scores for the above quality of life dimensions were found to range about 2.5 for cataract patients before and about 1.5 or better after surgery (despite the psychological stress score).

Probands of comparable age showed median scores of about 1.4 or better.

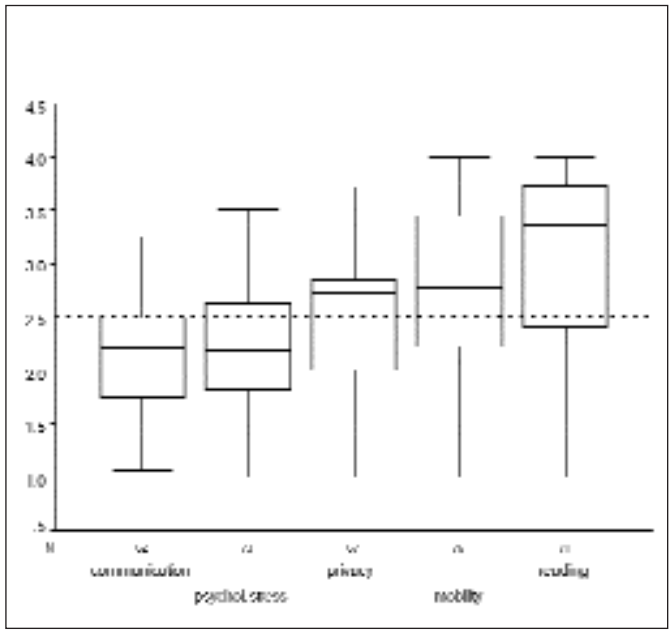

Fig. 1 - *Box plots for the quality of life scores personal communication, psychological stress, flexibility in privacy, mobility, and reading flexibility (horizontals denote medians and quartiles, verticals minimum and maximum observed values, circles and stars mark statistical outliers and extreme values).*

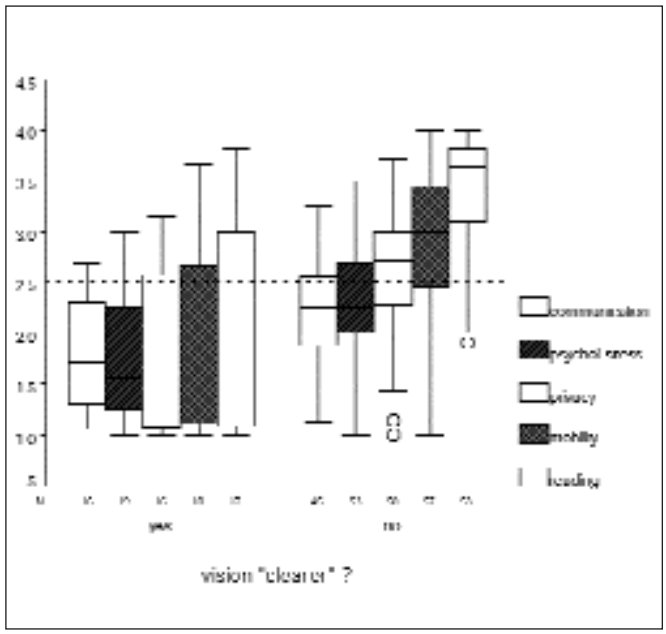

Fig. 2 - *Box plots for the quality of life scores personal communication, psychological stress, flexibility in privacy, mobility, and reading flexibility, stratified for the subjective impression of clearer vision since treatment started (horizontals denote medians and quartiles, verticals minimum and maximum observed values, circles and stars mark statistical outliers and extreme values).*

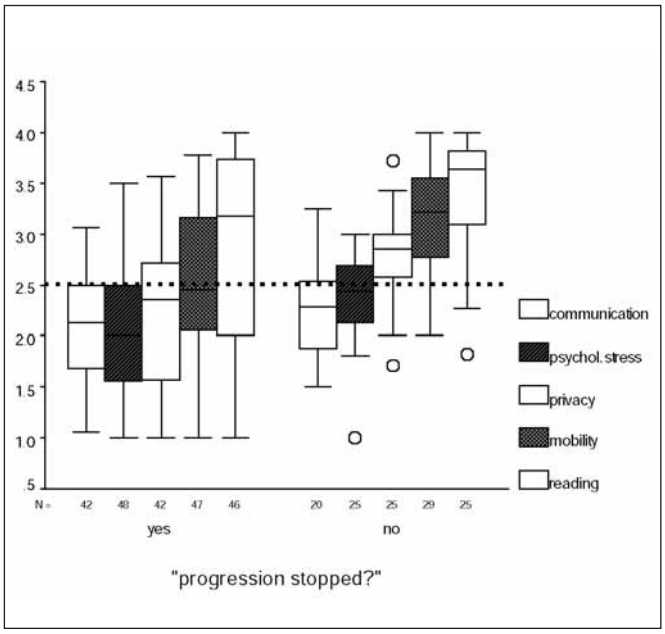

Fig. 3 - *Box plots for the quality of life scores personal communication, psychological stress, flexibility in privacy, mobility, and reading flexibility, stratified for the subjective impression of stopped progression since treatment started (horizontals denote medians and quartiles, verticals minimum and maximum observed values, circles and stars mark statistical outliers and extreme values).*

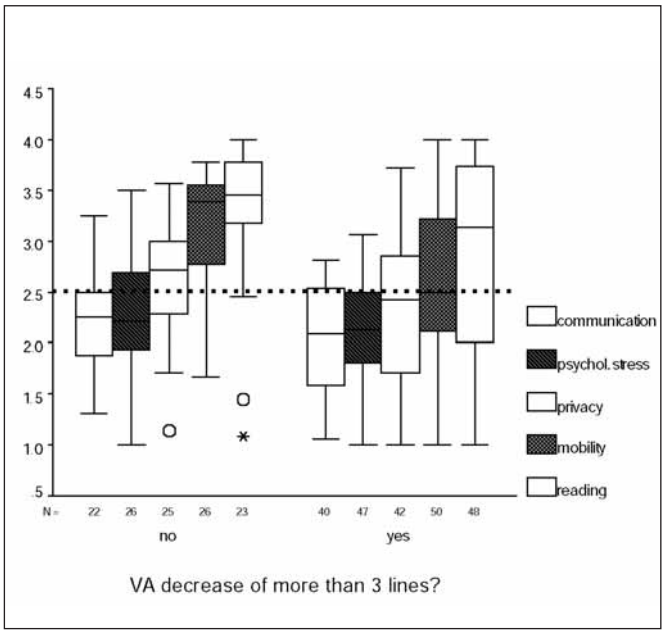

Fig. 4 - *Box plots for the quality of life scores personal communication, psychological stress, flexibility in privacy, mobility, and reading flexibility, stratified for the objective decrease in visual acuity (VA) of more than 3 lines since treatment started (horizontals denote medians and quartiles, verticals minimum and maximum observed values, circles and stars mark statistical outliers and extreme values).*

Interview and clinical investigation

To additionally document the ARMD patients' anamnestic and clinical history, the standardized questionnaire was complemented with an ARMD-specific set of items on surgical history, PDT characteristics (e.g., number of applications), and the patient's visual acuity profile.

All ARMD patients who underwent and finished a one-sided PDT treatment during 2000 and 2001 at the University Eye Hospital of Mainz were asked to take part in this investigation. After written informed consent was obtained from a patient, his or her actual visual acuity and ARMD stage were assessed. Afterwards, a standardized interview based on the extended Mainz questionnaire was performed, where all patients were interviewed by the same person (M.B.). The interviewer did not have any information on the patients' clinical course at the time of the interview to avoid a bias due to unintended variation of his phrasings. With respect to the patients' visual impairment, none of them was asked to fill out the questionnaire; patients were only interviewed, if their final PDT application was more than 3 months previously. The investigation was performed during regular recalls, so that patients did not have to travel for the purpose of this study.

The primary clinical endpoint of this investigation was the patients' change in visual acuity since start of the PDT treatment until the time of the interview; a clinically relevant loss in visual acuity was defined as a decrease of at least 4 lines. Primary subjective endpoints of this study were the patients' ratings, whether they report a subjectively clearer vision since start of the treatment or a subjectively noted stopping of progression since start of the treatment. Secondary clinical endpoints were the patients' ARMD stages before starting the treatment and at the time of the interview, as well as demographic characteristics including age and sex; secondary subjective endpoints were the patients' quality of life scores.

Statistical evaluation

Numerical and graphic statistical evaluation of the clinical and interview data was performed by means of SPSS software (release 10.0 for Windows). The description of the scores and clinical parameters was based on medians and quartiles (graphically on box plots, accordingly); the description of binary and categorical ratings was based on absolute and relative frequencies. Univariate signifi-

cance comparisons along categorical endpoints were based on exact Fisher tests, along continuous endpoints on two sample Wilcoxon tests (2); intraindividual changes in binary quality of life ratings were tested by means of McNemar's test. p Values <0.05 were regarded as indicators of local statistical significance. Correlations between scores and continuous clinical parameters (age, number of lost vision lines) were estimated by means of Spearman's nonparametric correlation coefficient (2).

The primary objective endpoint (change in visual acuity) and the primary subjective endpoints of the interview (vision clearer since start of the treatment and progression stopped since start of the treatment) were linked to the clinical cofactors and the quality of life score by fitting multiple logistic regression models (2). The statistical significance of these factors during exploratory multivariate analyses was assessed using likelihood ratio tests.

RESULTS

A total of 84 of 102 eligible ARMD patients (84%) with a classical CNV could be interviewed and clinically examined (50% female, median age 77 years with interquartile range 73 to 81 years). Their last PDT treatment was reported to be a median of 9 months ago (interquartile range 5 to 11 months); a median of 3 treatments was received (range 1 to 4 treatments).

During the treatment period the treated eye's visual acuity declined 3 lines in median from 0.125 to 0.063 (interquartile range 1 to 4 lines); 54 patients (64%) showed a visual acuity loss of 4 lines or more. However, a total of 22 patients (26%) reported a persistent subjective increase in vision clarity during the treatment period; 55 patients (66%) furthermore reported a subjective stop of ARMD progression since start of the treatment. Among the 54

TABLE I - DESCRIPTION OF THE FIVE CENTRAL INTERVIEW ASPECTS (PSYCHOMETRIC DIMENSIONS) WITH ONE EXAMPLE ITEM AND THE TOTAL NUMBER OF ITEMS CORRESPONDING TO EACH ASPECT

Dimension	Example item	No. of items
Communication	It is easy for me to follow a friend's invitation	18
Psychological stress	Being alone at home often results in being sad	12
Flexibility in privacy	As soon as I need something I can go shopping	16
Mobility	Taking buses (seeing line numbers, etc.) does not cause problems	18
Reading	I can read the advertised prices when shopping in a supermarket	18

TABLE II - P VALUES OF LIKELIHOOD RATIO TESTS DERIVED BY MULTIPLE LOGISTIC REGRESSION MODELLING OF THE ENDPOINTS VISION BECAME CLEARER SINCE TREATMENT STARTED, PROGRESSION WAS STOPPED SINCE TREATMENT STARTED, AND VISUAL ACUITY (VA) DECREASE OF MORE THAN 3 LINES SINCE TREATMENT STARTED AND THE QUALITY OF LIFE DIMENSIONS PERSONAL COMMUNICATION, PSYCHOLOGICAL STRESS, FLEXIBILITY IN PRIVACY, MOBILITY, AND READING FLEXIBILITY CORRECTED FOR COFACTORS AT THE TIME OF THE INTERVIEW AS EXPLANATORY FACTORS

Dimension	Vision clearer	Progression stopped	VA decrease more than 3 lines
Communication	0.967	0.658	0.324
Psychological stress	0.558	0.026	0.520
Private flexibility	0.670	0.130	0.399
Mobility	0.528	0.708	0.303
Reading	0.001	0.989	0.015
Age	0.411	0.089	0.532
Sex	0.363	0.167	0.130
VA (at interview)	0.219	0.550	—
Duration since last treatment	0.098	0.211	0.440

patients with a visual acuity loss of more than 3 lines, 69% (37 patients) reported a subjective stagnation of the progression (versus 60% of the patients with an objective decline of less than 4 lines). In summary, 60 (75%) of the interviewed patients report a good or very good overall satisfaction with the result of the PDT treatment, and 74 (91%) considered the clinical and postoperative medical and nursery care as good or very good. However, these subjective ratings were not significantly associated with the objective outcome in visual acuity (Fisher p=0.442 and p=0.250, respectively). At the end of the interview the patients were asked to grade their actual quality of life (school marks between A and F): only 12 (15%) patients rated their well-being as A or B; the median grade for overall quality of life assessment was D.

Figure 1 shows the distribution of the scores that rate the 5 quality of life dimensions of the Mainz questionnaire. Mainly the aspects reading and mobility were rated pessimistically and might therefore be regarded as ARMD-specific quality of life determinants.

Among those patients who report clearer vision since start of the treatment, the private and daily life flexibility score shows a median estimate of 1.86 (1.04–2.64) versus 2.71 (2.25–3.04) among those patients who did not report a subjective gain in visual clarity. For the dimension mobility median estimates in these subgroups were 2.00 (1.11–2.78) versus 3.00 (2.44–3.50), reading flexibility was rated 1.91 (1.09–3.14) versus 3.64 (2.95–3.82) in median, psychological stress medians were estimated 1.56 (1.19–2.52) versus 2.25 (1.97–2.69), and the communication flexibility score was 1.72 (1.31–2.31) versus 2.25 (1.88–2.56). Figure 2 shows the scores' distribution where all group differences were statistically significant (Wilcoxon p<0.001 for each score) in a univariate analysis. Table II shows the p values derived from a multivariate logistic regression analysis and demonstrates that only the reading flexibility score is significantly associated with the subjective gain of vision clarity by PDT treatment (likelihood ratio p=0.001) after correction for putative confounders.

If the quality of life scores are related to the subjective impression of progression stopping since start of the treatment, Table II demonstrates the psychological stress score to be the only statistically significant determinant of this outcome (likelihood ratio p=0.026). However, this statistical difference between patients with and without the subjective impression of a progression inhibition only corresponds to a median score difference of 2.00 (1.56–2.50) versus 2.28 (1.88–2.56), which is smaller than the non-significant difference in the reading score displayed in Figure 3. In particular, those patients with the subjective impression of inhibited progression since start of the treatment were observed to rate their reading flexibility slightly less optimistically than did the others.

Similarly, patients with a loss of more than 3 lines in visual acuity since start of the treatment showed a median rating of 3.39 for their mobility score versus 2.50 for the other patients (Wilcoxon p=0.003), whereas none of the remaining 4 quality of life determinants were statistically significant during univariate analysis (Wilcoxon p=0.134, 0.157, 0.261, and 0.361, respectively). After multivariate correction for cofactors, however, again only the reading flexibility score turned out to be significantly associated (likelihood ratio p=0.015) with the objective visual acuity profile during PDT treatment. Patients with a decrease of more than 3 lines showed a median reading flexibility score of 3.45 (3.18–3.82) versus 3.14 (2.00–3.73). It should be mentioned that this median difference is of smaller order than the above difference between patients with a subjectively clearer vision since start of the treatment (Figs. 2 and 4); it could therefore hardly be considered clinically relevant.

None of the 5 scores showed a clinically relevant correlation with the change in visual acuity (Spearman correlation 0.28 for the mobility score, remaining absolute correlations < 0.20).

DISCUSSION

The potential of a therapeutic concept to inhibit a disease's progression is associated with the patient's quality of life, since the fear of progression itself is a psychological quality of life determinant. This fact is of increasing relevance regarding the health economics dimension of progressive disorders such as ARMD. Whereas the clinical efficacy of PDT for this indication is established by several independent controlled trials (3, 4), its impact on the patients' quality of life is under investigation (3, 5-8) and earns increasing attention. Therefore, we implemented a cross-sectional study to assess the post treatment quality of life in patients after PDT therapy.

As expected (9), ARMD patients report a poor quality of life concerning their reading flexibility. This dimension furthermore turned out to be the dominant quality of life surrogate, when subjective benefit is considered: for both the

subjective impression of a clearer vision since start of the treatment and the objective decrease in visual acuity this dimension was found as the multivariate determinant of statistical significance. On the other hand, 69% of those patients who reported a subjective gain in progression inhibition showed a loss of at least 4 visual acuity lines during the treatment period. Whether this observation is an indication of a subjective placebo effect of PDT treatment or mirrors an independent subjective benefit of PDT (which cannot be objectively measured in terms of visual acuity profiles) cannot be decided based on the study design at hand.

Efficacy considerations

A small fraction (15%) of patients reported their overall quality of life as good or very good—similar investigations in cataract patients of comparable age show fractions of more than 60% before and 90% after treatment (1). The same trend can be observed by comparing the quality of life scores of cataract patients before and after treatment with those of the recent ARMD sample: whereas the ARMD patients report a median reading flexibility score of 3.42 and a median psychological stress score of 2.38, a sample of 152 cataract patients reported median scores of 2.44 and 1.85 before, even 1.35 and 1.65 after treatment (1). It is well known that cataract surgery makes its patients happier, since the symptoms of the underlying disease can be notably removed. The symptoms of ARMD patients cannot be weakened, but only kept at status quo. This can further be illustrated by the computation of vision quality adjusted life years (6). Brown et al have demonstrated that patients with a visual acuity of finger counting would sell up to 6 of 10 years of their expected life time with their recent visual function if the remaining 4 years could be spent without visual impairment. This astonishing valuation of a better visual function was not expected by the patients' ophthalmologic consultants, who expected a maximum value equivalence of about 3 years (6). This is an independent indication for a non-measurable difference between clinical and subjective outcome, which validates the patients' overall satisfaction with PDT treatment as reported above.

Both clinical (3, 4) efficacy and economical (4, 10) effectiveness of PDT are accepted. Its efficacy can be slightly increased by combination with patient training programs (5, 11) and regional-wide information schedules on early symptom detection (11), but the above quality of life findings encourage the discussion about a subjective benefit dimension of PDT. This benefit complements the recent positive decision of German national health insurance on the reimbursement of PDT therapy, since a better quality of life (even if possibly caused by placebo effects) is known to significantly reduce indirect costs such as caused by psychological treatment (5) and frequent unnecessary parallel medical consultation.

Study design and sources of bias

The lack of a control population in the current study imposes limitations on the study's conclusions: an untreated ARMD control cohort would have allowed us to decide whether some of the positive subjective findings mentioned above are subject to a PDT placebo effect. A further design modification could consist of repeated interviews before starting and shortly after finishing the PDT therapy as well as somewhat later to deconfound short time and long time benefit. This repeated measurement design would enable estimation of the intraindividual PDT-associated gain in quality of life and correlation of the latter with the corresponding change in clinical outcome parameters; note that the cross-sectional study design at hand only provides post treatment information.

Further limitations arise from the retrospective nature of the trial. Patients from 2000 and 2001 were included, which might imply a certain heterogeneity concerning familiarity with the performance of PDT. A sensitivity analysis was performed, which involved each patient's visual acuity assessment at a regular recall visit 3 months after having received the last treatment. The above multivariate findings could be strictly reproduced. Surprisingly (10), neither multivariate correction for the initial visual function of the treated eye nor for that of the fellow eye (before start of the treatment and at the time of the interview) showed a notable impact on the quality of life estimates and p values in Table II and Figures 1-4.

CONCLUSIONS

Despite these limitations, the above results suggest that the assessment of quality of life information in the patient with ARMD can provide new and independent information on the efficacy of PDT; subsequent controlled trials on PDT and its combinations with additional approaches (5, 11) should therefore incorporate this subjec-

tive information and adjust clinical efficacy measures. A subjective benefit of PDT must be validated further in subsequent research.

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Reprint requests to:
Prof. Frank Krummenauer
Clinical Epidemiology and Health Economy Unit
Technical University of Dresden
Fetscherstr 74, Haus 29
D-01307 Dresden, Germany
Frank.Krummenauer@uniklinikum-dresden.de

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