

Received date: 10-Dec-2015

Accepted date: 14-Jan-2016

Article Type: Original Article: Epidemiology and Genetics

Editor: Werner Aberer

**Development and Validation of the Mastocytosis Quality of Life questionnaire:
MC-QoL**

Frank Siebenhaar^{1*}, Elisabeth von Tschirnhaus¹, Karin Hartmann², Anja Rabenhorst³, Petra Staubach⁴, Adriane Peveling-Oberhag⁴, Nicola Wagner⁵, Peter Martus⁶, Melody C. Carter⁷, Dean D. Metcalfe⁷, Martin K. Church¹, Marcus Maurer¹, Karsten Weller¹

¹Interdisciplinary Mastocytosis Center Charité, Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Berlin, Germany

²Department of Dermatology, University of Lübeck, Lübeck, Germany

³Department of Dermatology, University of Cologne, Cologne, Germany

⁴Department of Dermatology, University Medical Center Mainz, Mainz, Germany

⁵Department of Dermatology, Clinical Center Darmstadt, Darmstadt, Germany

⁶Department of Medical Biostatistics, Universitätsklinikum Tübingen, Tübingen, Germany

⁷Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

*Corresponding author:

PD Dr. med. Frank Siebenhaar

Department of Dermatology and Allergy

Allergie-Centrum-Charité

Charité - Universitätsmedizin Berlin

Charitéplatz 1, 10117 Berlin, Germany

Phone: +49 30 450 518419

Fax: +49 30 450 518972

E-mail: frank.siebenhaar@charite.de

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.12842

This article is protected by copyright. All rights reserved.

Abstract

Background: Mastocytosis is a heterogeneous disease characterized by a clonal expansion of mast cells in various organs. The vast majority of patients affected suffer from signs and symptoms caused by mediator release from mast cells. Although the disease burden is high, there is currently no specific instrument to measure health-related quality of life (HRQoL) impairment in patients with mastocytosis.

Objective: To develop and validate a disease-specific tool to assess HRQoL impairment in patients with cutaneous and indolent systemic mastocytosis, the Mastocytosis Quality of Life questionnaire (MC-QoL).

Methods: Sixty-two potential MC-QoL items were developed in a combined approach consisting of semi-structured patient interviews, expert input, and literature research. Item selection was performed by impact analysis with 76 patients and a final review for face validity. The resulting MC-QoL was tested for validity, reliability and influence factors. In parallel, an US American-English version of the MC-QoL was developed.

Results: 158 patients (41 CM, 41 MIS, and 76 ISM) took part in the MC-QoL validation study. The final 27-item questionnaire was found to have a four-domain structure ('symptoms', 'emotions', 'social life/functioning', 'skin'), a valid total score and an excellent test-retest-reliability. Multiple regression analysis revealed disease duration, but not age, gender or skin involvement to be a significant determinant of HRQoL impairment in mastocytosis.

Conclusions: The MC-QoL is the first disease-specific HRQoL questionnaire for adult patients with cutaneous and indolent systemic mastocytosis. This short, validated and reliable instrument will serve as a valuable tool in future clinical studies and in routine patient care.

Introduction

Mastocytosis is characterized by an excessive increase in the number of mast cells in different tissues. Most often, the skin and the bone marrow are involved, but mast cell infiltrates may also be found in other organs, e.g. the spleen, liver, lymph nodes and the gastrointestinal tract (1, 2). Symptoms result either from organ infiltration or, more frequently, from the release of pro-inflammatory mast cell mediators, including

histamine, platelet activating factor (PAF), prostaglandins, leukotrienes and cytokines (3-7). Whereas in cutaneous mastocytosis (CM) the increase in mast cell numbers is limited to the skin, systemic mastocytosis is characterized by the accumulation of neoplastic mast cells in the bone marrow and/or other extracutaneous organs (1, 8, 9). The majority of adult patients presents with indolent systemic mastocytosis (ISM) and commonly show symptoms resulting from mast cell mediator release, including pruritus, flushing, headaches, bone pain, nausea, vomiting, diarrhoea, abdominal pain and anaphylaxis (10-15). Accordingly, many mastocytosis patients experience a major impairment of their HRQoL (16), and require continuous treatment, aimed at the prevention of mast cell mediator-induced signs and symptoms.

H₁-antihistamines are first line therapy and routinely used for the treatment of mastocytosis symptoms (3, 17). Recently, a second-generation H₁-antihistamine and the PAF receptor blocker rupatadine was shown to be effective and safe and to significantly improve quality of life (QoL) in patients with CM and ISM (18). QoL improvement is an important goal in the management of patients with mastocytosis, and patient-reported outcomes (PROs) such as HRQoL are becoming increasingly important in both clinical studies and routine patient care. PRO tools determine the unfiltered patient perspective on diseases and their impact, and prevent a loss of useful information that may occur in the case of isolated clinician evaluations (19). Therefore, it is strongly recommended by leading health authorities to include PROs into the study design of randomized controlled trials (19, 20).

Disease- or symptom-specific HRQoL instruments are more robust and sensitive than generic tools in obtaining meaningful QoL data. As of yet, however, a specific HRQoL tool is not available for mastocytosis. We thus herein report the development and validation of the first disease-specific HRQoL questionnaire for use in adult patients with cutaneous and indolent systemic mastocytosis, the Mastocytosis Quality of Life questionnaire (MC-QoL).

Methods

The development of the MC-QoL consisted of three major phases: 1) item generation, 2) item selection, and 3) MC-QoL validation.

MC-QoL item generation

MC-QoL item generation was performed following current recommendations for PRO development (21, 22). In the first step, an expert working group was convened to specify fields of mastocytosis-related QoL impairment that should be assessed by the MC-QoL, in order to guide the generation of specific MC-QoL items, to define both criterion measures of mastocytosis symptoms and impact (anchors) to be used for the evaluation of the MC-QoL's performance, and to design and conduct the item selection and MC-QoL validation study. To identify and generate potential items for the MC-QoL, a combined approach of three strategies was applied: 1) exploratory semi-structured interviews with 10 patients suffering from CM (n=3) and ISM (n=7), 2) a literature research for published data on HRQoL impairment in mastocytosis patients, and 3) mastocytosis expert opinions on potentially relevant items.

Item responses were designed as 5-point Likert scales with the answer options 'never', 'seldom', 'occasionally', 'often', 'very often'. The recall period for all items was chosen to be the last two weeks.

MC-QoL item selection

Item selection (reduction) was performed by impact analysis in combination with a review of its results for their face validity. All questions identified in the item generation phase were administered to 76 mastocytosis patients with CM or ISM (55 females; mean age $\pm$ SD: 51.6 $\pm$ 13.5 years, median: 52.5, range: 20-77) recruited from the outpatient clinic at the Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Germany. The patients completed all potential MC-QoL items and subsequently evaluated their relevance and importance (for details see below). In addition, all patients were asked to rate the understandability and comprehensibility of the items.

Impact analysis

An impact analysis was performed to exclude all potential MC-QoL items with a low impact score. To this end, the participating patients evaluated the importance of each potential item (response options: 1 = not important to 5 = extremely important) and specified whether they had experienced the item content during the last year (response options: yes or no). Each item's 'importance' and 'frequency' was

then computed as the mean of all response values and the proportion of patients who experienced the item content, respectively. The 'impact' score of each item was calculated by multiplication of its 'frequency' and 'importance'.

Expert review for face validity and regression analysis

As a final step of item selection, the impact analysis was complemented by a review of the expert working group. The face validity assessment suggested an 'impact' score of 1.7 points as the best suitable cut-off value for item selection. All items that reached this score were included in the final MC-QoL, unless they were redundant to other selected items or the face validity assessment clearly argued against an inclusion.

MC-QoL validation

A total of 158 patients with mastocytosis (CM or ISM) from four mastocytosis specialist centres in Germany (Berlin, Cologne, Mainz and Darmstadt) were included in the MC-QoL validation phase (**Table 1**). Each centre's ethics committee approved the study, and all patients provided written informed consent. All participating patients were asked to complete the validation study survey twice in an interval of 2 weeks. The survey consisted of all final MC-QoL items, a patient global assessment of their disease severity (PGA-disease severity) and of their mastocytosis-related QoL impairment (PGA-QoL) during the previous two weeks (4-point Likert scales), different validated, generic or symptom-specific HRQoL measures (see below) and questions on patient characteristics, i.e. age, gender and disease duration.

Exploratory factor analysis

To determine the domain structure of the MC-QoL, we performed an exploratory factor analysis. The approach chosen was a principal component analysis with Varimax rotation and Kaiser normalization (23-26). The criterion chosen to determine factors (domains) was an eigenvalue ≥ 1 . Items were assigned to the domains for which they showed the highest factor loading. Single exceptions were made for reasons of face validity based on discussions in the expert working group.

Internal consistency reliability

Internal consistency measures the homogeneity of total and domain scores. The internal consistency reliability of the MC-QoL total score and its domain scores were assessed by computing Cronbach's α coefficient. A commonly suggested interpretation of Cronbach's α coefficient values is: <0.60: unacceptable; 0.60 to 0.65: undesirable; 0.65 to 0.70: minimally acceptable; 0.70 to 0.80: respectable; 0.80 to 0.90: excellent; >0.90: excessive consistency (27).

MC-QoL score computation

The five answer options of each MC-QoL item were scored from 0-4 points. The total and domain raw scores were calculated by summing all relevant item scores. Subsequently, all raw scores were linearly transformed to a 0 to 100 scale, with higher scores indicating a higher HRQoL impairment. In the case of missing items, the total of the items in each domain was related to the number of non-missing items. A total score was not computed when >25% of items (>6 items) were missing. A domain score was not computed when >50% of items were missing in that domain.

Convergent validity

To assess the convergent validity of MC-QoL, we correlated its total and domain scores (Pearson correlation) with different anchors for HRQoL, i.e. the Dermatology Life Quality Index (DLQI), the 12-item Short Form Survey (SF-12), the Itchy-QoL, and the EQ-VAS of EuroQoL-5D (EQ-5D). The DLQI is a HRQoL instrument specifically designed for dermatologic disorders (28, 29). It is the most widely used HRQoL tool in the field of dermatology and consists of 10 items. In addition to the computation of a total score, it can be analysed under six headings ('symptoms and feelings', 'daily activities', 'leisure', 'work and school', 'personal relationships', 'treatment'). Higher scores indicate higher impairment. The SF-12 is a generic tool to assess disease burden (30). It is a short form of the 36-item Short Form Survey (SF-36) and its results are expressed as a physical component summary (PCS) and a mental component summary (MCS), each ranging from 0 to 100 points, with higher scores indicating a higher self-reported health. The ItchyQoL is the first symptom-specific HRQoL instrument for patients with chronic pruritus (24). It consists of 22 items and the validated German version applied in this work has a four-domain structure. Higher ItchyQoL scores indicate higher impairment. The EQ-5D is a

generic tool that is used to measure health status (31, 32). The EQ-VAS applied in this work records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'best imaginable health state' and 'worst imaginable health state'.

Known-groups validity

The known-groups validity of the MC-QoL was determined by calculating and comparing its total score in patients with different disease severity (PGA-disease severity) and different levels of QoL impairment (PGA-QoL).

Test-retest reliability

The test-retest reliability of the MC-QoL was examined in a subgroup of patients, who completed all items twice in an interval of two weeks (14 ± 2 days). The mean values of the first and second assessments were compared. In addition, the intraclass correlation coefficient (ICC) was computed. An ICC of 0.5 to 0.7 was considered to indicate moderate-to-good reproducibility, and an ICC of greater than 0.7 was considered to demonstrate excellent reproducibility (25).

Multiple linear regression analysis

Multiple linear regression was used to detect factors that influence MC-QoL scores. Age (in years), gender, duration of disease (in months) and skin involvement were included as independent variables, the MC-QoL total score was set as dependent variable.

Development of an US American English version

Two independent forward translations of the original German MC-QoL version to US American-English (AE) were performed by native AE speakers bilingual in German. The two forward translations were reconciled by two national US American experts (Dean D. Metcalfe and Melody C. Carter) and subsequently back-translated by a German native speaker bilingual in AE. The backward translation was then reviewed against the original German version and the German team and the US American experts agreed on a final US AE consensus version.

Statistical analysis

All statistical analyses were performed using SPSS (IBM SPSS Statistics Version 19, IBM Corporation, Armonk, NY, USA). The statistical methods applied are described in the respective methods and results sections of this article. $P < 0.05$ was considered statistically significant.

Results

MC-QoL development

The item generation phase resulted in 62 items possibly relevant to patients with CM and ISM, each of which covered a recall period of 2 weeks. Sixty-four of 76 patients (84%) included in the item selection phase evaluated the 62-item set as comprehensive, and 75 patients (99%) had no problems in understanding the items. For item selection, the impact of each item was computed (**Table 1**). Twenty-nine items with an impact score < 1.7 were excluded. An exception was made for the items p3 ('flush episodes'), p4 ('diarrhoea'), and p13 ('headache') that just failed the cut-off but cover relevant symptoms. After discussions in the expert working group, these items were not removed for reasons of face validity. In addition, the expert group recommended to exclude the items p28, p25, p26, p30, p35, and p62 despite an impact score > 1.7 due to redundancy. In addition, item p45 was replaced by a more precise question on the limitation in sexual life in the last two weeks. Eventually, 27 items remained in the final MC-QoL.

MC-QoL validation and first results

Exploratory factor analysis

The final 27-item MC-QoL was used in the validation study that included a total of 158 adult patients with CM and ISM. **Table 2** shows the demographic and clinical data of this population.

Exploratory factor analysis identified a four-domain structure of the questionnaire (**Table 3**) that explained 67.6% of its variance. According to the content of the domains, these received the headings 'symptoms', 'emotions', 'social life/functioning', and 'skin'. While 25 of the 27 items could be clearly assigned to one domain, item 'school/university/work' and item 'eating and drinking' were assigned to the domain 'social life/functioning' despite a minimally higher factor load to the domain 'symptoms' for reasons of face validity.

In a final review of the domain structures, the expert working group regarded no further changes as necessary. The final German version and US American-English version of MC-QoL can be found as supporting information (**supplemental Figures 1 and 2**).

Internal consistency reliability

The internal consistency of each MC-QoL domain was tested by computing Cronbach's α coefficient (**Table 4**). Its value was >0.9 for all domains, indicating excellent internal consistency, except for the domain 'skin' with a value of 0.67, indicating a minimal acceptable internal consistency. The Cronbach's α coefficient for the whole instrument was 0.96, which indicates that it is appropriate to calculate a total score in addition to the domain scores.

MC-QoL results

The distribution of MC-QoL total and domain scores of the mastocytosis population investigated in the validation study are shown in **Figure 1**. The domain 'symptoms' showed the highest mean score, followed by 'skin', 'social life/functioning', and 'emotions'. The exact mean MC-QoL scores $\pm$ SD were 35.7 ± 23.1 (total score), 40.7 ± 25.2 (domain 'symptoms'), 31.8 ± 27.1 (domain 'emotions'), 32.9 ± 27.1 (domain 'social life/functioning'), and 37.4 ± 23.3 (domain 'skin'). The distributions of the total and domain scores were broad.

Convergent validity

To test for the convergent validity of the MC-QoL, we correlated the MC-QoL total and domain scores with the results of the anchor instruments DLQI, SF-12 PCS and MCS, ItchyQoL and the EQ-VAS of the EQ-5D (**Table 5**). All correlations were significant and in the expected direction. The correlations between the MC-QoL total score and the total scores of the applied anchors were all good ($r > 0.6$). The correlation between the MC-QoL total score and the SF12 'PCS' and the EQ-VAS were particularly high ($r > 0.7$).

Known-groups validity

The MC-QoL total score values were found to discriminate between patients with different levels of disease severity and mastocytosis-related QoL impairment (**Table 6**). The MC-QoL total scores increased with increasing disease severity and HRQoL impairment (PGA-disease severity and PGA-QoL). In addition, the MC-QoL total score values of the interquartile range of the different levels of disease severity and HRQoL impairment did not overlap.

Test-retest reliability

Data of 120 patients were available for the computation of the test-retest reliability. The mean MC-QoL scores of the first and second assessment, which showed no major differences, are depicted in **Table 7**. The intraclass correlation coefficient (ICC) was 0.91 for the MC-QoL total score and >0.80 for the MC-QoL domain scores 'symptoms', 'emotions' and 'social life/functioning', indicating excellent reproducibility. Only the ICC of the 'skin' domain was lower (0.55), indicating moderate reproducibility.

Influence factors of the MC-QoL total score

In multiple linear regression analyses, duration of disease, but not age, gender or skin involvement, was found to significantly influence the MC-QoL total score (**Table 8**). Patients with a longer duration of their mastocytosis showed higher MC-QoL total scores ($p < 0.002$).

Discussion

Many patients with mastocytosis have a severely impaired QoL (16) and there is a clear need for more research in this field. However, this is currently hampered by the lack of appropriate and validated outcome instruments (3, 17). Here, we report the development and validation of the first disease-specific instrument to measure HRQoL impairment in patients with CM and ISM, the Mastocytosis Quality of Life questionnaire (MC-QoL). The MC-QoL consists of 27 items that can be summed up to a total score, but also to four domain scores. The validation study demonstrates high validity and reliability of the MC-QoL. In addition, it was found to be easy to administer and fast to complete.

The MC-QoL was found to have a valid total score but also to have 4 domains ('symptoms', 'emotions', 'social life/functioning', 'skin'), all but one characterized by high levels of internal consistency. The only exception is the 'skin' domain, which showed a lower but still acceptable internal consistency. Accordingly, the MC-QoL may be used as an index instrument to measure overall mastocytosis-related QoL impairment by assessing the total score but may also be used to assess the profile of impairment by determining the four domain scores. Notably, the domain structure of the MC-QoL nicely corresponds to the WHO-definition of health as a state of complete physical, mental and social well-being (33).

The MC-QoL results obtained in the validation study suggest that the 'symptoms' domain is most affected in patients with mastocytosis. However, the differences between the mean domain scores were rather small (between 32 and 41 points), indicating an overall even impact of mastocytosis on the different aspects of HRQoL represented by the four domains. The distributions of the MC-QoL total and domain scores were broad, demonstrating that a considerable variation of HRQoL impairment exists in cutaneous and indolent systemic mastocytosis patients. In addition, it shows that the patient population included in the study consisted of patients with different levels of disease severity and QoL impairment, as is the case in real-life daily clinical care.

The convergent validity of the MC-QoL was found to be good. The MC-QoL scores strongly and significantly correlated with all scores of the validated anchor tools DLQI, SF-12, ItchyQoL and EQ-VAS. This indicates that the MC-QoL really measures what it intends to measure. Importantly, the MC-QoL total score, correlated strongly with both, the mental component summary (MCS) and the physical component summary (PCS) of the SF-12. This demonstrates that both dimensions of health determined by the SF-12 seem to be adequately represented in the MC-QoL. In addition, the MC-QoL total score also correlated strongly with the functioning domain of the ItchyQoL and the social life/functioning representing subheadings of the DLQI ('daily activities', 'leisure', 'work and school', 'personal relationships'), indicating that the important area of social life/functioning is also well represented in the MC-QoL.

Accepted Article

Important criteria for the validity and reliability of a HRQoL tool are its ability to distinguish different patient groups (known-groups validity) as well as to yield stable results when applied twice in short intervals (test-retest reliability). Notably, the mean MC-QoL total score values were found to be clearly different in patients with mastocytosis exhibiting different levels of disease severity and mastocytosis-related QoL impairment. Mean MC-QoL total scores of 29, 50, and 71 points (around one quarter, half, and three quarters of the maximum possible score) are found in patients who self-rated their overall mastocytosis-related QoL impairment as 'mild', 'moderate' and 'severe', respectively. This may help to interpret the MC-QoL results in individual patients, keeping in mind that the interquartile ranges are up to 20 points. The fact that the MC-QoL total score values of the interquartile range of the different levels of disease severity and HRQoL impairment did not overlap further stresses the good discriminative ability of the MC-QoL. The test-retest reliability of the MC-QoL was generally excellent. Only the 'skin' domain showed a moderate level of reproducibility. This may be due to the fact that the items in this domain primarily assess symptoms ('itching', 'skin redness', 'flush episodes') that may vary considerably, even in short intervals of 2 weeks, as was the case between the first and second assessment during the validation study.

Multiple linear regression analysis identified disease duration as an important influence factor of MC-QoL total scores. A more detailed analysis of the distribution of scores over the MC-QoL domains in groups of different disease durations revealed that in all groups the scores of the domains "emotions" and "functioning" rise with increasing disease duration. This indicates that the functional and particularly the emotional burden of the disease increases with disease duration. The mean scores in the domains "symptoms" and "skin" show quite homogeneous levels in patients suffering from mastocytosis less than 20 years. Interestingly, these domains exhibit higher scores in patients with disease duration of more than 20 years as compared to patients with shorter disease duration (data not shown).

Limitations of this work include that our study was performed in four specialized centres in Germany but not in populations of other cultural and ethnic backgrounds and different levels of medical care, which may have led to a selection bias. However, this may affect the absolute values of the MC-QoL scores, but should be of

minor impact on the results on the validity and reliability of the instrument. The MC-QoL in this study was validated only in patients with CM and ISM, but not in patients with advanced categories of mastocytosis such as ASM, SM-AHNMD and MCL. Therefore, MC-QoL is not validated to be used in these categories of the disease and will not work as well in advanced patients, since they have less mediator related symptoms, but more symptoms such as fatigue and depression. In future, we would also need specific questionnaires for advanced categories of mastocytosis. It should also be noted that the selected study population did not include children and adolescents. Therefore, it is currently unclear if the results of this work may be transferred to minors. Finally, the MC-QoL's responsiveness and minimal clinically important difference have not been assessed. Projects to assess these properties of the MC-QoL are underway.

In conclusion, the MC-QoL is the first valid and reliable instrument to assess disease-specific HRQoL impairment in patients with CM and ISM. It may help to improve the quality and performance of future clinical studies, but may also help to determine and monitor the extent and profile of HRQoL impairment in individual patients. As of yet, only German and US American-English versions of the MC-QoL are available. A linguistic validation and cross-cultural adaptation for other countries and languages is encouraged in order to make it a multi-linguistic tool, which is needed for conducting international, multicentre clinical trials for a better management of this rare and often burdensome disease.

Acknowledgement

We wish to thank the European Centre for Allergy Research Foundation (www.ecarf.org), the urticaria network e. V. (www.urticaria.net), the COST Action BM1007 "Mast cells and basophils", and the European Mast Cell and Basophil Research Network (www.embrn.org) for their support. Participation of DDM and MC in this work was supported by the Division of Intramural Research/NIAID/NIH. In addition, we thank all patients who took part in the item generation, item selection and in the MC-QoL validation study.

Author contributions

All authors provided significant contribution to the manuscript by collecting data and providing scientific input. Specifically, F.S., E.T., K.W., M.K.C, and M.M. wrote the manuscript. K.H., A.R., P.S., A.P., N.W. gave significant expert input and provided scientific advice. D.M. and M.C. performed the cross validation of the AE version of MC-QoL, P.M. performed statistical analyses.

Conflict of interest

The authors declare no conflict of interest in association with this manuscript.

References

1. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol* 2012;**157**(3):215-225.
2. Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001;**25**(7):603-625.
3. Siebenhaar F, Akin C, Bindslev-Jensen C, Maurer M, Broesby-Olsen S. Treatment strategies in mastocytosis. *Immunol Allergy Clin North Am* 2014;**34**(2):433-447.
4. Brockow K. Epidemiology, prognosis, and risk factors in mastocytosis. *Immunol Allergy Clin North Am* 2014;**34**(2):283-295.
5. Krause K, Gimenez-Arnau A, Martinez-Escala E, Farre-Albadalejo M, Abajian M, Church MK, et al. Platelet-activating factor (PAF) induces wheal and flare skin reactions independent of mast cell degranulation. *Allergy* 2013;**68**(2):256-258.
6. Hawro T, Saluja R, Weller K, Altrichter S, Metz M, Maurer M. Interleukin-31 does not induce immediate itch in atopic dermatitis patients and healthy controls after skin challenge. *Allergy* 2014;**69**(1):113-117.
7. Serra-Pages M, Torres R, Plaza J, Herrerias A, Costa-Farre C, Marco A, et al. Activation of the Prostaglandin E2 receptor EP2 prevents house dust mite-induced airway hyperresponsiveness and inflammation by restraining mast cells' activity. *Clin Exp Allergy* 2015;**45**(10):1590-1600.

8. Valent P, Escribano L, Broesby-Olsen S, Hartmann K, Grattan C, Brockow K, et al. Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis. *Allergy* 2014;**69**(10):1267-1274.
9. Hartmann K, Escribano L, Grattan C, Brockow K, Carter MC, Alvarez-Twose I, et al. Cutaneous manifestations in patients with mastocytosis: Consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. *J Allergy Clin Immunol* 2015.
10. Broesby-Olsen S, Oropeza AR, Bindslev-Jensen C, Vestergaard H, Moller MB, Siebenhaar F, et al. Recognizing mastocytosis in patients with anaphylaxis: value of KIT D816V mutation analysis of peripheral blood. *J Allergy Clin Immunol* 2015;**135**(1):262-264.
11. Gulen T, Hagglund H, Dahlen B, Nilsson G. High prevalence of anaphylaxis in patients with systemic mastocytosis - a single-centre experience. *Clin Exp Allergy* 2014;**44**(1):121-129.
12. Gulen T, Hagglund H, Sander B, Dahlen B, Nilsson G. The presence of mast cell clonality in patients with unexplained anaphylaxis. *Clin Exp Allergy* 2014;**44**(9):1179-1187.
13. Matito A, Alvarez-Twose I, Morgado JM, Sanchez-Munoz L, Orfao A, Escribano L. Anaphylaxis as a clinical manifestation of clonal mast cell disorders. *Curr Allergy Asthma Rep* 2014;**14**(8):450.
14. Reiter N, Reiter M, Altrichter S, Becker S, Kristensen T, Broesby-Olsen S, et al. Anaphylaxis caused by mosquito allergy in systemic mastocytosis. *Lancet* 2013;**382**(9901):1380.
15. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 2008;**63**(2):226-232.
16. Jennings S, Russell N, Jennings B, Slee V, Sterling L, Castells M, et al. The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions. *J Allergy Clin Immunol Pract* 2014;**2**(1):70-76.
17. Cardet JC, Akin C, Lee MJ. Mastocytosis: update on pharmacotherapy and

future directions. *Expert Opin Pharmacother* 2013;**14**(15):2033-2045.

18. Siebenhaar F, Fortsch A, Krause K, Weller K, Metz M, Magerl M, et al. Rupatadine improves quality of life in mastocytosis: a randomized, double-blind, placebo-controlled trial. *Allergy* 2013;**68**(7):949-952.

19. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research; U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research; U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes* 2006;**4**:79.

20. European Medicines Agency (EMA), COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP). Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003637.pdf. Last accessed June 2012.

21. Baiardini I, Bousquet PJ, Brzoza Z, Canonica GW, Compalati E, Fiocchi A, et al. Recommendations for assessing patient-reported outcomes and health-related quality of life in clinical trials on allergy: a GA(2)LEN taskforce position paper. *Allergy* 2010;**65**(3):290-295.

22. Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E, et al. Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force report: part 2--assessing respondent understanding. *Value Health* 2011;**14**(8):978-988.

23. Kocaturk E, Weller K, Martus P, Aktas S, Kavala M, Sarigul S, et al. Turkish version of the chronic urticaria quality of life questionnaire: cultural adaptation, assessment of reliability and validity. *Acta Derm Venereol* 2012;**92**(4):419-425.

24. Krause K, Kessler B, Weller K, Veidt J, Chen SC, Martus P, et al. German version of ItchyQoL: validation and initial clinical findings. *Acta Derm Venereol* 2013;**93**(5):562-568.

25. Weller K, Groffik A, Church MK, Hawro T, Krause K, Metz M, et al.

Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol* 2014;**133**(5):1365-1372, 1372 e1361-1366.

26. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development and construct validation of the angioedema quality of life questionnaire. *Allergy* 2012;**67**(10):1289-1298.

27. Streiner DN, G. Health Measurement Scales: A Practical Guide to Their Development and Use. *Oxford University Press* 1995;**2nd edition**.

28. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994;**19**(3):210-216.

29. Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008;**159**(5):997-1035.

30. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol* 1998;**51**(11):1171-1178.

31. Group E. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**(3):199-208.

32. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;**37**(1):53-72.

33. Callahan D. The WHO definition of 'health'. *Stud Hastings Cent* 1973;**1**(3):77-88.

Table 1. Impact analysis. High impact scores (>1.7) are printed in bold

Item no.*	Item	Frequency	Importance (mean)	Impact
p1	Itching	0.778	3.33	2.59
p2	Skin redness	0.883	3.51	3.10
p3	Flush episodes	0.559	3.02	1.69
p4	Diarrhoea	0.583	2.76	1.61
p5	Nausea	0.458	2.50	1.15

p6	Flatulence	0.525	2.62	1.38
p7	Abdominal pain/cramps	0.517	2.48	1.28
p8	Fatigue	0.770	3.05	2.35
p9	Palpitation	0.559	2.82	1.58
p10	Sweating attacks	0.614	2.64	1.62
p11	Dyspnoea	0.475	2.58	1.23
p12	Dizziness	0.508	2.73	1.39
p13	Headache	0.600	2.74	1.64
p14	Muscle or joint pain	0.705	2.97	2.09
p15	Difficulty in concentrating	0.593	2.88	1.71
p16	Hot flushes	0.576	2.54	1.46
p17	Forgetfulness	0.550	2.52	1.39
p18	Mood swings	0.607	2.47	1.50
p19	Hypertension	0.534	2.61	1.39
p20	School/University/Work	0.621	2.88	1.79
p21	Sport/Physical activities	0.800	2.97	2.38
p22	Sleep	0.721	3.08	2.22
p23	Leisure time	0.684	2.86	1.96
p24	Social relationships	0.721	2.81	2.03
p25	Activities with other people	0.629	2.72	1.71
p26	Nutrition	0.774	3.30	2.55
p27	Daily activities	0.600	2.73	1.64
p28	Difficulties falling asleep	0.689	3.01	2.07
p29	Tired during the day	0.726	3.12	2.27
p30	Feeling of being watched in public	0.688	2.96	2.04
p31	Fear of being a burden for others	0.623	2.68	1.67
p32	Eating and drinking	0.726	3.14	2.28
p33	Less capable	0.700	3.00	2.10
p34	Burdened by symptoms	0.787	3.30	2.60
p35	Ashamed to visit public places	0.721	2.85	2.05
p36	Mobility	0.581	2.75	1.60
p37	Choice of cosmetics/body care	0.581	2.60	1.51
p38	Choice of clothes	0.726	2.85	2.07
p39	Drug side effects	0.576	2.85	1.64
p40	Fear of anaphylaxis	0.740	3.39	2.51

p41	Fear of wrong treatment	0.700	3.27	2.29
p42	Fear of further course of disease	0.839	3.37	2.83
p43	Uncomfortable in public	0.726	2.87	2.08
p44	Partnership	0.639	2.57	1.64
p45	Love life	0.557	2.48	1.38
p46	Treatment associated with problems	0.467	2.48	1.16
p47	Helpless	0.587	2.53	1.49
p48	Aggressive	0.540	2.39	1.29
p49	Moody	0.619	2.46	1.52
p50	Unfair towards others	0.492	2.30	1.13
p51	Lacking in motivation	0.698	2.92	2.04
p52	Uncertain	0.587	2.57	1.51
p53	Embarrassed	0.556	2.26	1.26
p54	Frustrated	0.645	2.50	1.61
p55	Being mad at oneself	0.556	2.20	1.22
p56	Alone with the disease	0.758	3.06	2.32
p57	Nervous	0.548	2.56	1.40
p58	Concerned	0.651	2.64	1.72
p59	Discouraged	0.651	2.56	1.67
p60	Sad	0.651	2.63	1.71
p61	Not knowing what to do next	0.587	2.61	1.53
p62	Fear of future	0.778	3.07	2.39

*The p in the item number indicates that these items are potential MC-QoL items

Table 2. Patient sample characteristics of MC-QoL validation study.

	<i>n</i>	%
Gender		
Female	111	70.3
Male	47	29.7
Age		
18-30 years	15	9.1
31-50 years	71	44.9
51-70 years	58	36.7
>70 years	14	8.9
Diagnosis		
Cutaneous mastocytosis (CM)	41	25.9

Pre-diagnosis mastocytosis in the skin (MIS)	41	25.9
Indolent systemic mastocytosis + cutaneous manifestation (ISMs ⁺)	58	36.7
Indolent systemic mastocytosis without cutaneous manifestation (ISMs ⁻)	18	11.4
Duration of mastocytosis		
≤5 years	45	28.5
6 - 15 years	66	41.8
16 - 25 years	25	15.8
26 - 35 years	17	10.8
>35 years	4	2.5
missing information	1	0.6

Table 3. Factor analysis. Items with a factor loading >0.5 are printed in bold.

Item	Factor 1 (Symptoms)	Factor 2 (Social life/ Functioning)	Factor 3 (Emotions)	Factor 4 (Skin)
Diarrhoea	0.587	0.098	0.025	0.095
Fatigue	0.742	0.169	0.343	0.134
Headache	0.665	0.077	0.242	0.059
Muscle or joint pain	0.701	0.205	0.245	0.131
Difficulty in concentrating	0.772	0.141	0.281	0.129
Sleep	0.516	0.377	0.288	0.404
Tired during the day	0.619	0.260	0.278	0.309
Less capable	0.669	0.434	0.296	0.335
Lacking in motivation	0.657	0.243	0.385	0.161
Eating and drinking	0.473	0.272	0.190	0.368
School/University/Work	0.606	0.515	0.097	0.347
Sport/Physical activities	0.486	0.678	0.229	0.229
Sexual activity	0.510	0.591	0.174	0.121
Leisure time	0.522	0.710	0.250	0.135
Social relationships	0.503	0.698	0.194	0.068
Burdened by symptoms	0.483	0.518	0.261	0.451
Choice of clothes	-0.111	0.669	0.359	0.228
Uncomfortable in public	0.040	0.649	0.521	0.262
Fear of anaphylaxis	0.164	0.116	0.786	0.107
Fear of wrong treatment	0.274	0.068	0.699	0.223
Fear of further course of	0.341	0.351	0.707	0.117
Feel alone with the	0.311	0.431	0.613	0.021

Feel concerned	0.330	0.349	0.712	0.119
Feel sad	0.381	0.418	0.639	0.100
Itching	0.225	0.124	0.063	0.778
Skin redness	0.077	0.166	0.131	0.840
Flush episodes	0.384	0.130	0.276	0.435

Table 4. Domain structure and internal consistency of the MC-QoL.

Domain	Item	Cronbach's α
Symptoms	Diarrhoea	0.918
	Fatigue	
	Headache	
	Muscle or joint pain	
	Difficulty concentrating	
	Sleep	
	Tired during the day	
	Less capable	
	Lacking in motivation	
Social life/ Functioning	School/University/Work	0.924
	Sport/Physical activities	
	Sexual activity	
	Leisure time	
	Social relationships	
	Eating and drinking	
	Burdened by symptoms	
	Choice of clothes	
	Uncomfortable in public	
Emotions	Fear of anaphylaxis	0.911
	Fear of wrong treatment	
	Fear of further course of disease	
	Feel alone with the disease	
	Feel concerned	
	Feel sad	
Skin	Itching	0.667
	Skin redness	
	Flush episodes	
Total Instrument		0.961

Table 5. Convergent validity of the MC-QoL. Correlations were computed between the MC-QoL scores and the DLQI scores, ItchyQoL scores, SF12 component scores and the EQ-VAS of the EQ-5D. The results are expressed as Pearson correlation coefficients.

	MC-QoL scores				
	Total score	Symptoms	Emotions	Social Life/ Functioning	Skin
DLQI					
Total score	0.603***	0.477***	0.523***	0.631***	0.447***
Symptoms and feelings	0.360***	0.260**	0.362***	0.352***	0.318***
Daily activities	0.508***	0.375***	0.443***	0.544***	0.409***
Leisure	0.479***	0.397***	0.397***	0.511***	0.296***
Work and school	0.210**	0.159*	0.176*	0.244**	0.174*
Personal relationships	0.465***	0.400***	0.396***	0.480***	0.282***
Treatment	0.396***	0.339***	0.329***	0.391***	0.294***
ItchyQoL					
Total score	0.689***	0.550***	0.586***	0.675***	0.676***
Symptoms	0.652***	0.579***	0.517***	0.586***	0.680***
Functioning	0.686***	0.549***	0.590***	0.678***	0.636***
Feelings	0.584***	0.440***	0.510***	0.588***	0.579***
Self-perception	0.577***	0.423***	0.528***	0.592***	0.496***
SF12**					
MCS	-0.637***	-0.610***	-0.621***	-0.558***	-0.315***
PCS	-0.719***	-0.711***	-0.553***	-0.699***	-0.402***
EQ-VAS	0.756***	0.716***	0.643***	0.720***	0.485***

*p < 0.05; **p < 0.01; ***p < 0.001; MCS (mental component summary), PCS (physical component summary)

**Correlations with the SF-12 are negative, because, in contrast to MC-QoL, lower scores in this instrument represent a stronger QoL impairment.

Table 6. Known-groups validity of the MC-QoL. The results are expressed as MC-QoL total score in relation to the patients self-rated disease severity and QoL impairment

Patients global assessment^a	<i>n</i>	MC-QoL total score mean $\pm$ SD (median)	1st quartile	3rd quartile
Disease severity				
None	28	10.9 $\pm$ 9.5 (9.3)	3.2	16.0
Mild	68	26.6 $\pm$ 15.0 (23.1)	14.1	37.0
Moderate	47	52.0 $\pm$ 13.3 (51.9)	42.6	61.5
Severe	15	72.6 $\pm$ 12.9 (76.9)	65.7	80.6
QoL impairment				
None	37	13.7 $\pm$ 12.9 (12.9)	5.6	17.6
Mild	56	28.5 $\pm$ 14.7 (27.8)	16.7	38.0
Moderate	45	49.5 $\pm$ 14.9 (50.9)	39.8	61.1
Severe	18	71.1 $\pm$ 14.3 (76.4)	63.9	80.8

^awith regard to the previous two weeks

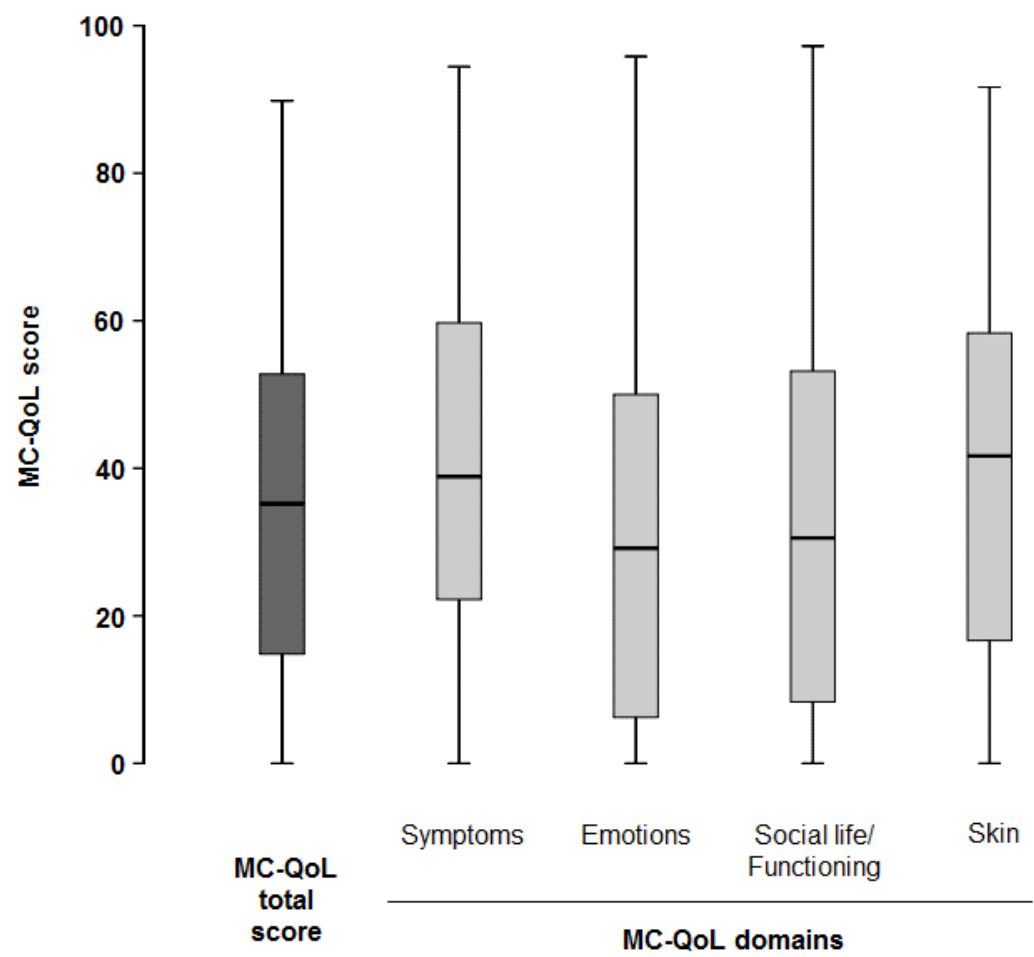
Table 7. Test-retest reliability of the MC-QoL. A subsample of 120 mastocytosis patients completed the MC-QoL twice in an interval of 2 weeks. The results are expressed as mean MC-QoL scores as well as intraclass correlation coefficient (ICC).

MC-QoL	Mean score $\pm$ SD (1 st assessment)	Mean score $\pm$ SD (2 nd assessment)	ICC
Total score	35.7 $\pm$ 21.2	33.7 $\pm$ 23.3	0.905
Symptoms	40.7 $\pm$ 25.2	38.5 $\pm$ 25.1	0.898
Emotions	31.8 $\pm$ 27.1	29.2 $\pm$ 26.7	0.878
Social life/ Functioning	32.9 $\pm$ 27.1	32.0 $\pm$ 26.4	0.852
Skin	37.4 $\pm$ 23.3	25.9 $\pm$ 25.3	0.549

Table 8. Influence factors of the MC-QoL. Multiple linear regression analysis identified duration of disease, but not age, gender and skin involvement as significant influence factors of the MC-QoL total score.

	Unstandardized Coefficient B	Standard Error	<i>p</i> -value
Age (in years)	-0.013	0.140	0.926
Gender	-3.874	3.964	0.330
Disease duration (in months)	0.045	0.015	0.004
Skin involvement (yes or no)	1.735	0.024	0.762

Figure 1. MC-QoL results.



Supplemental figure 1. German version of MC-QoL**MC-QoL**

(Deutsche Version)

Fragebogen zur Lebensqualität von Patienten mit Mastozytose

Anleitung: Liebe Patientinnen und Patienten, im folgenden Fragebogen finden Sie eine Reihe von Fragen zu Ihrer Lebensqualität. Bitte lesen Sie sich jede Frage durch und wählen Sie aus den fünf Antworten diejenige aus, die für Sie am besten zutrifft. Überlegen Sie bitte nicht lange und denken Sie daran, alle Fragen zu beantworten. Bitte geben Sie für jede Frage nur eine Antwort, d.h. kreuzen Sie bitte nur ein Kästchen pro Frage an.

	Gar nicht	Wenig	Mittel-mäßig	Viel	Sehr viel
Wie sehr wurden Sie in den vergangenen 2 Wochen von folgenden Symptomen geplagt?					
1. Juckreiz	☐	☐	☐	☐	☐
2. Hautrötungen/-schwellungen	☐	☐	☐	☐	☐
3. Plötzliche, aufsteigende Hitze und Rötung des Gesichtes (sog. Flushepisoden)	☐	☐	☐	☐	☐
4. Durchfälle	☐	☐	☐	☐	☐
5. Müdigkeit/Abgeschlagenheit	☐	☐	☐	☐	☐
6. Kopfschmerzen	☐	☐	☐	☐	☐
7. Muskel- oder Gelenkschmerzen	☐	☐	☐	☐	☐
8. Konzentrationsschwierigkeiten	☐	☐	☐	☐	☐
	Nie	Selten	Gelegentlich	Oft	Sehr oft
Bitte geben Sie an, wie oft Sie während der vergangenen 2 Wochen , in den nachfolgend aufgeführten Bereichen des täglichen Lebens, durch Ihre Mastozytose eingeschränkt waren.					
9. Schule/Studium/Beruf	☐	☐	☐	☐	☐

10. Sport/Körperliche Betätigung	☐	☐	☐	☐	☐
11. Schlaf	☐	☐	☐	☐	☐
12. Sexualität	☐	☐	☐	☐	☐
13. Freizeitgestaltung	☐	☐	☐	☐	☐
14. Soziale Beziehungen (Freunde, Familie, Partnerschaft)	☐	☐	☐	☐	☐
	Nie	Selten	Gelegentlich	Oft	Sehr oft
Mit den nachfolgenden Fragen möchten wir näher auf Schwierigkeiten und Probleme eingehen, die mit Ihrer Mastozytose verbunden sein können. Bitte beziehen Sie Ihre Antworten auf die vergangenen 2 Wochen .					
15. Waren Sie in den vergangenen 2 Wochen tagsüber müde, weil Sie nachts nicht richtig schlafen konnten?	☐	☐	☐	☐	☐
16. Mussten Sie sich in den vergangenen 2 Wochen aufgrund Ihrer Mastozytose bei der Auswahl an Speisen und Getränken einschränken?	☐	☐	☐	☐	☐
17. Haben Sie sich in den vergangenen 2 Wochen aufgrund Ihrer Mastozytose weniger leistungsfähig gefühlt?	☐	☐	☐	☐	☐
18. Haben Sie die Symptome Ihrer Mastozytose in den letzten 2 Wochen belastet?	☐	☐	☐	☐	☐
19. Waren Sie in den vergangenen 2 Wochen aufgrund der Mastozytose bei der Wahl Ihrer Kleidung eingeschränkt?	☐	☐	☐	☐	☐
20. Hatten Sie in den vergangenen 2 Wochen aufgrund Ihrer Mastozytose Angst einen allergischen Schock zu erleiden?	☐	☐	☐	☐	☐
21. Hatten Sie in den vergangenen 2 Wochen aufgrund Ihrer Mastozytose Angst es könnte im Fall einer Bewusstlosigkeit oder eines Unfalls eine falsche Therapie erfolgen?	☐	☐	☐	☐	☐
22. Fühlten Sie sich in den vergangenen 2 Wochen aufgrund Ihrer Mastozytose in der Öffentlichkeit unwohl?	☐	☐	☐	☐	☐
23. Hatten Sie in den vergangenen 2 Wochen Angst vor dem weiteren Verlauf Ihrer Mastozytose?	☐	☐	☐	☐	☐

	Nie	Selten	Gelegentlich	Oft	Sehr oft
Fühlten Sie sich in den vergangenen 2 Wochen					
24. ...antriebslos	☐	☐	☐	☐	☐
25. ...allein mit Ihrer Erkrankung	☐	☐	☐	☐	☐
26. ...beunruhigt?	☐	☐	☐	☐	☐
27. ...traurig?	☐	☐	☐	☐	☐

Supplementary figure 2. American-English version of MC-QoL.**MC-QoL**

(American-English Version)

Questionnaire Regarding Patient's Quality of Life with Mastocytosis

Instructions: Dear patients, in the following questionnaire you will find a variety of questions regarding your quality of life. Please read through each question carefully and select one of the following five answers that best describes your symptoms. Please do not think too much about your answers, but be careful to answer all the questions. Please provide one answer per question, i.e. please mark only one box per question.

	None	Some- what	Moderately	Very	Very Much
How severely were you affected by the following symptoms in the last 2 weeks ?					
1. Itching	☐	☐	☐	☐	☐
2. Skin Redness/Swelling	☐	☐	☐	☐	☐
3. Sudden feeling of warmth and reddening of the face (Flush episodes)	☐	☐	☐	☐	☐
4. Diarrhea/loose stools	☐	☐	☐	☐	☐
5. Fatigue/Exhaustion	☐	☐	☐	☐	☐
6. Headache	☐	☐	☐	☐	☐
7. Muscle or joint pain	☐	☐	☐	☐	☐
8. Difficulty concentrating	☐	☐	☐	☐	☐
	None	Some- what	Moderately	Very	Very Much
Please indicate how often you have been limited in your daily life in the areas listed below during the past 2 weeks because of your mastocytosis.					
9. School/University/Work	☐	☐	☐	☐	☐
10. Sport/Physical Activity	☐	☐	☐	☐	☐

11. Sleep	☐	☐	☐	☐	☐
12. Sexual activity	☐	☐	☐	☐	☐
13. Leisure time	☐	☐	☐	☐	☐
14. Relationships (Friends, Family, Partner, coworkers)	☐	☐	☐	☐	☐
	Never	Seldom	Occasionally	Often	Very often
We would like to further study difficulties and problems that may be associated with your mastocytosis using the following questions. Please answer according to your experiences from the past 2 weeks .					
15. In the past 2 weeks, were you tired during the day because you did not sleep well at night?	☐	☐	☐	☐	☐
16. In the past 2 weeks, did you have to change your choices of foods and drinks due to your mastocytosis?	☐	☐	☐	☐	☐
17. Have you felt less capable in the past 2 weeks due to your mastocytosis?	☐	☐	☐	☐	☐
18. Have you been burdened by the symptoms of your mastocytosis in the past 2 weeks?	☐	☐	☐	☐	☐
19. Has your choice of what to wear been restricted in the past 2 weeks due to mastocytosis?	☐	☐	☐	☐	☐
20. In the past 2 weeks, were you ever afraid you might suffer an allergic reaction due to mastocytosis?	☐	☐	☐	☐	☐
21. In the past 2 weeks, were you ever afraid that you might receive the wrong treatment if you became or unconscious or suffered an accident due to your mastocytosis?	☐	☐	☐	☐	☐
22. Have you felt uncomfortable in public during the past 2 weeks due to mastocytosis?	☐	☐	☐	☐	☐
23. In the past 2 weeks, have you ever been afraid of the further worsening of your mastocytosis?	☐	☐	☐	☐	☐
	Never	Seldom	Occasionally	Often	Very often
In the past 2 weeks did you feel					

24. ...a lack of motivation?	☐	☐	☐	☐	☐
25. ...alone with your illness?	☐	☐	☐	☐	☐
26. ...concerned?	☐	☐	☐	☐	☐
27. ...sad?	☐	☐	☐	☐	☐