

The national comprehensive cancer network distress thermometer as a screening tool for the evaluation of quality of life in uveal melanoma patients

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ABSTRACT.

Purpose: To assess quality of life (QoL) status via the National Comprehensive Cancer Network (NCCN) distress thermometer as a psychooncological screening tool in uveal melanoma patients.

Methods: One hundred and six consecutive patients suffering from uveal melanoma completed the distress thermometer between 04/2018 and 12/2018. Practical, emotional, family concerned, spiritual, physical and overall distress levels, distribution of distress and subgroup analyses defining groups of potential high distress levels in need of intervention were assessed. Descriptive statistics, cross-tabulations, chi-square and Fisher's exact test as well as correlation coefficients (Spearman's rho) and receiver operating characteristic (ROC) were used for analysis.

Results: Patients with higher T-category had significantly more emotional problems and spiritual concerns ($p = 0.046$ and $p = 0.023$, respectively). Female patients accounted for higher rates of physical issues ($p = 0.034$). Lower best corrected visual acuity (BCVA) was correlated with higher distress levels ($p = 0.037$). Patients resulting in loss of BCVA of ≥ 3 lines reported higher distress levels ($p = 0.029$). A distress threshold of 5 on the basis of ROC analysis showed a corresponding sensitivity of 100% and specificity of 76%.

Conclusion: The NCCN distress thermometer could be integrated well into our clinical routine and proved to be a rapid, yet sensible screening tool for emotional and physical distress in patients with uveal melanoma. Special attention should be paid to patients with higher T-category and patients resulting in lower levels of BCVA. As in patients with different tumour entities, the established distress threshold of ≥ 5 proposing intervention proved to be adequate for uveal melanoma patients.

Key words: cancer – NCCN distress thermometer – psychosocial distress – quality of life – uveal melanoma

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Introduction

Uveal melanoma is the most frequent primary intraocular tumour in adults (Singh & Topham 2003) with a reported incidence of 5–7 per million (Hu et al. 2005) and must be considered as a severe ocular and, due to the risk of the development of metastases, possibly life-threatening condition (Lane et al. 2018). To date, good local tumour control can be achieved in the vast majority of cases (Gragoudas et al. 1992) using different techniques from eye-conserving plaque brachytherapy, proton beam therapy, stereotactic radiosurgery to enucleation. As the results of the Collaborative Ocular Melanoma Study (COMS) could prove no survival difference between globe-preserving treatment and enucleation in the long-term follow-up (COMS Group 2001), the effect of the treatment chosen on the quality of life (QoL) of the patients should be considered for treatment planning (Foss et al. 2000). Recent findings within the literature on the development of QoL seem to show no overall treatment-related differences in QoL, (van Beek et al. 2018; Miniati et al. 2018) but enucleated patients have been reported to suffer more from vision related problems (van Beek et al. 2018; Frenkel et al. 2018).

As Ophthalmologists, our focus is, of course, primarily set on the good results of local disease control. Yet, due

to the patients' confrontation with an invasive and potentially metastatic malignancy, their psychological distress during and after local therapy should not be underestimated: the presence of a serious disease by itself can cause depression (Raison & Miller 2003) and high proportions of uveal melanoma patients report reduced QoL and substantial emotional problems compared with other cancer diagnoses and normative data (Brandberg et al. 1995, 2000; Hjermstad et al. 1998). Different physiological and psychological effects on the patients after enucleation and globe-preserving therapy have been reported in the literature reflecting on their QoL (COMS Quality of Life Study Group 1999; Chabert et al. 2004).

In contrast to ongoing systemic treatment regimen of different cancer entities, uveal melanoma is commonly treated in a single-session or hypofractionated procedure and severe ocular adverse effects such as loss of vision, optic neuropathy, secondary glaucoma and cataract develop at a later time throughout follow-up. Consequently, patients stand alone soon after therapy and monitoring of the tumour and all related issues often lie within the responsibility of the treating Ophthalmologist. We would therefore like to implement a simple, quick and effective screening tool regarding patients' QoL into our tumour outpatient clinic.

The NCCN distress thermometer is a screening tool for assessment of psychosocial stress, so-called distress, with high acceptance, concision and good practicability (Mehnert et al. 2006). In brief, it comprises a distress scale from 0 to 10 as well as a problem list including practical, family, emotional, spiritual/religious and physical problems or concerns. Cut-off values ≥ 5 imply that relevant psychological pressure is present and assistance should be offered. A problem list is attached to the distress thermometer designating in which field of life help should be sought (e.g. reference to a social worker, minister, Psychologist or Oncologist) (Mehnert et al. 2006).

In our previous QoL-studies on patients with uveal melanoma, we focused on the devolution of QoL after radiosurgery (Klingenstein et al. 2013) and compared QoL after globe-preserving therapy with that of patients having undergone enucleation

employing the Short-form (SF)-12 Health Survey (Klingenstein et al. 2016). We could not find data about the NCCN distress thermometer as a screening tool for psychological and emotional distress for uveal melanoma patients in common medical databases, so we conducted the present study to evaluate which patients, at what point in time throughout the course of their disease and in which areas of life need our medical and psychological support most. Feasibility and patient acceptance of the distress thermometer in our tumour outpatient department were also recorded.

Material and methods

One hundred and six patients were included consecutively from our tumour consultation outpatient department and gave informed consent to complete the NCCN distress thermometer (https://www.nccn.org/patients/resources/life_with_cancer/pdf/nccn_distress_thermometer.pdf; German version) during their routine follow-up visit. All patients included had sufficient knowledge of the German language in order to complete the questionnaire on their own. At each visit, a complete ophthalmological examination including standardized A- and B-scan echography as well as widefield fundus photography was performed. Relevant patient data that could have an influence on psychooncological distress collected for statistical evaluation included patients' sex, age at primary diagnosis, age at completion of the questionnaire, tumour T-category, tumour anatomic stage, tumour location, local therapy mode, time after therapy, best corrected visual acuity (BCVA) of both eyes and in the tumour eye prior to and after therapy, number of chronic co-morbidities, ocular adverse effects and metastatic status. Patient data were assessed between 04/2018 and 12/2018.

This study has approval of the institutional review board of the Department of Ophthalmology of Ludwig-Maximilians-University Munich/Germany. Tumour staging was performed using the AJCC Cancer Staging Manual (7th ed. New York, NY: Springer; 2009).

Data were collected in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) for Mac 2011. All

statistical analyses were performed using and SPSS 25.0 (IBM Corporation; Armonk, NY, USA) employing descriptive statistics, cross-tabulations including chi-square and Fisher's exact test, calculation of correlation coefficients (Spearman's rho) as well as ROC curve and Youden index. $p < 0.05$ was considered statistically significant. All confidence intervals reported are at 95% level.

Results

Demographic data

For demographic patient data (gender, age, T-category, anatomic stage, tumour location, therapy, BCVA of the tumour eye, number of relevant co-morbidities and metastatic status), see Table 1.

Median time at completion of the survey after primary diagnosis was 2.9 (range 0–29.5; mean 4.4 ± 4.6 SD) years. Median age at primary diagnosis was 58.7 (range 24.1–84.9; mean 57.0 ± 14.0 SD) years, and median age at completion of the distress thermometer was 64.2 (range 26.1–87.9; mean 61.5 ± 13.5 SD) years.

Thirty-five patients had no ocular complications. In 71 of 106 patients (67.0%), one or more ocular complication requiring therapy was noted throughout follow-up (radiation retinopathy $n = 40/106$ (37.7%), persistent subretinal fluid $n = 9$ (8.5%), phthisis $n = 8$ (7.5%), optic neuropathy $n = 6$ (5.7%), secondary glaucoma $n = 5$ (4.7%), vitreous haemorrhage $n = 3$ (2.8%) and epiretinal gliosis $n = 1$ (0.9%); cataract not included). Three patients suffered from local tumour recurrence (two patients after brachytherapy and one patient after CyberKnife® radiosurgery).

Statistical evaluation

Median distress levels were 3.4 (range 0–10; mean 3.0 ± 2.5 SD; box-plot see Figure 1). Out of 106 patients, 25 (23.6%) reported practical problems, 11 (10.4%) family problems, 7 (6.6%) religious or spiritual concerns, 64 (60.4%) emotional and 73 (68.9%) physical problems (Figure 2, for list of distress levels and problems reported please see Table 2). Figure 3 shows the distribution of emotional problems in detail. Regarding patients' physical

Table 1. Demographic patient characteristics (*n* = 106)

Sex	Male: Female [47:59]
Median age at primary diagnosis	59 [range 24–85] y
Median age at interview	64 [range 26–88] y
T stage	T1 = 43 T2 = 38 T3 = 21 T4 = 4
Anatomic stage	1 = 41 2A = 36 2B = 19 3A = 7 4 = 3
Tumour location	Peripapillary = 20 Posterior pole = 16 Mid-periphery = 43 Periphery = 25 Ciliary body = 2
Eye	Right = 45 Left = 61
Therapy	CyberKnife® radiosurgery = 82 Brachytherapy = 10 Enucleation = 10 Proton beam therapy = 3 Gammaknife radiosurgery = 1
BCVA [log(MAR)]	Prior to therapy: Median 0.5, mean 0.5, SD ± 0.3 After therapy: Median 1.1, mean 1.4, SD ± 1.1
N° of relevant co-morbidities	None = 46 1 = 37 2 = 17 3 = 6
Development of metastases	5

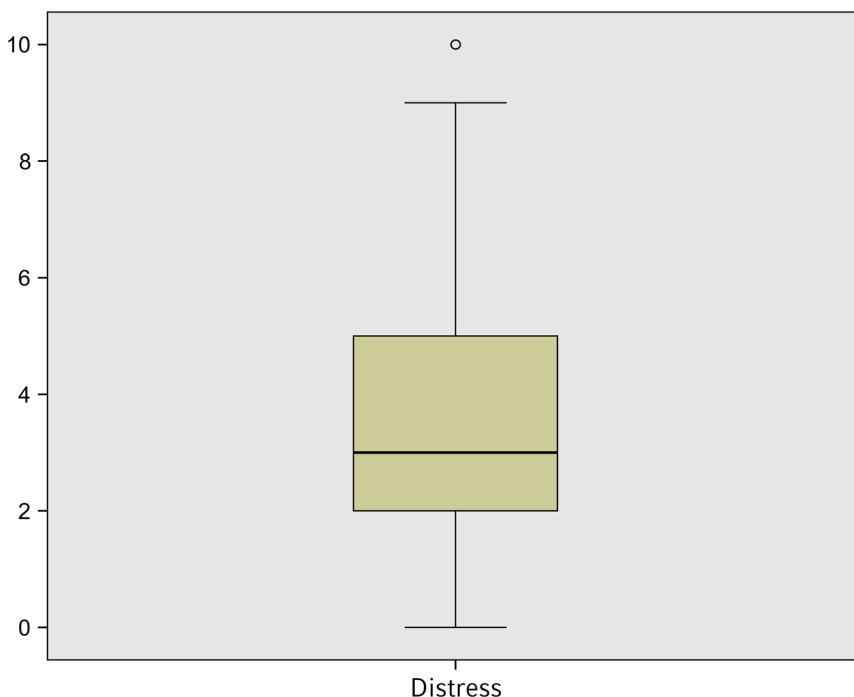


Fig. 1. Box-plot showing the overall distribution of distress on the NCCN distress thermometer (*n* = 106 patients).

problems, we considered the items pain, fatigue, sleep and appearance as most relevant after treatment of uveal

melanoma as patients do not undergo chemotherapy and we think that therefore, further physical items listed are

not influenced directly by the treatment of our patients. For detailed distribution of these physical problems, see Figure 4a (for gender distribution see Figure 4b).

Higher T-category was correlated with a higher level of emotional problems (*p* = 0.046) and spiritual concerns (*p* = 0.023; Fisher’s exact test, respectively). Emotional problems and spiritual concerns were correlated (*p* = 0.040; Fisher’s exact test and Spearman’s rho). Spiritual concerns were also significantly higher in patients with higher anatomic tumour stage (*p* = 0.001; Fisher’s exact test).

Subgroup analysis showed that female patients reported more physical issues (*p* = 0.034; Fisher’s exact test).

BCVA of the untreated eye did not correlate significantly with distress levels (with BCVA of the non-melanoma eye being median 0.0 (range –0.1 to 1.3, mean 0.07, ±SD 0.2) log (MAR)). Yet, correlation coefficients proved a significant correlation between BCVA of the tumour eye after therapy and patients’ distress levels (*p* = 0.037; Spearman’s rho). We hypothesized that at a BCVA < 0.5 log(MAR) of the tumour eye, stereopsis and binocularity can be maintained and near-distance vision is above reading ability which is important for patients’ independence in everyday life. We therefore performed a more detailed subgroup analysis and could find no statistical difference of distress levels in patients with BCVA of < 0.5 log(MAR) and ≥ 0.5 log(MAR) in the tumour eye, but patients that suffered a loss of BCVA ≥ 3 lines in the tumour eye after therapy reported significantly higher distress levels (*p* = 0.029; Fisher’s exact test).

All other items tested did not result in statistically significant correlations to the distress levels. Particularly subgroup analysis of the time of completion of questionnaire after primary diagnosis (0 to ≤ 6 months, *n* = 11/106 (10.4%); 6 to ≤ 36 months, *n* = 40/106 (37.7%) and > 36 months, *n* = 55/106 (51.9%)) could prove no significant differences of distress levels. This subdivision was performed in order to assess possible differences around primary diagnosis as well as regarding short-term and long-term complications.

We calculated the area under the curve (AUC) via receiver operating

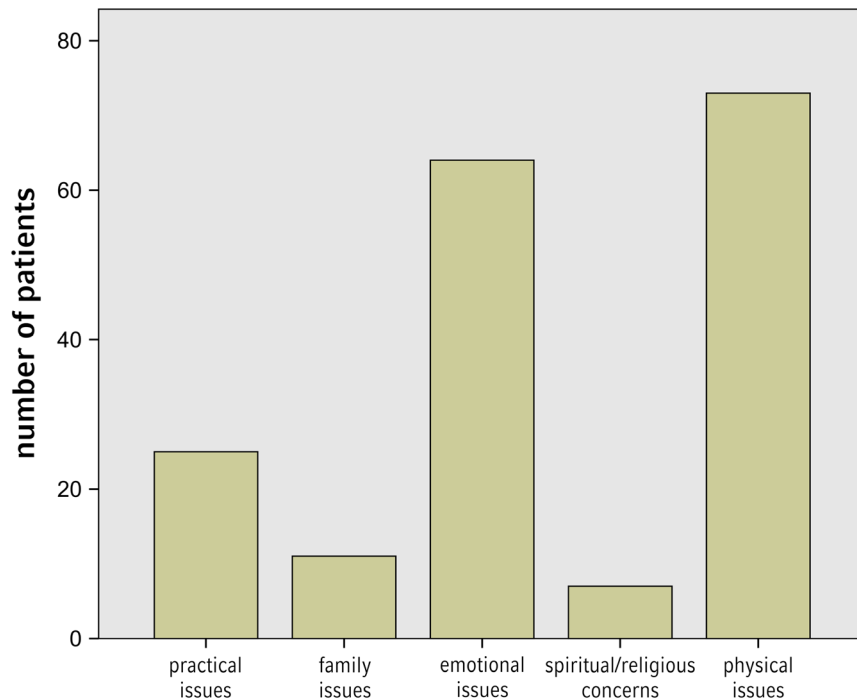


Fig. 2. Overall frequency distribution of practical and family problems, religious or spiritual concerns, emotional and physical problems via vertical bar graph (*n* = 106 patients).

characteristic (ROC) analysis and came to the conclusion, that the best combination of sensitivity (100%) and specificity (76%) regarding psychooncological distress was at a cut-off of a level of ≥ 5 on the distress thermometer (highest Youden index 0.76).

Thirty three patients (31.1%) reported a distress level of ≥ 5 and thus were offered specific support in relation to their problems by employing this cut-off level. Upon direct approach, 11 of these patients (10.4%) had already been provided with psychooncological support. Acute intervention to lessen emotional or practical problems was initiated in 10 patients by the treating physicians of the study team (9.4%). These patients were advised psychooncological help; additionally, rehabilitation was planned for 2 (1.9%) patients in order to improve practical issues.

Acute ophthalmological intervention was performed as follows to relieve physical problems resulting in high distress levels: Enucleation due to secondary glaucoma and associated pain in 2 (1.9%), intravitreal therapy due to radiation neuropathy and consequent macular oedema in 2 (1.9%) as well as exoresection and pars-plana-vitrectomy in one patient due to vitreous haemorrhage in order to improve BCVA in the tumour eye, respectively.

The remaining seven patients either declined active support and/or stated that their distress level did not result from their uveal melanoma (e.g. recent death of a close family member).

Overall, the distress thermometer proved rapid and feasible during routine examination of the tumour patients in our outpatient department and was well tolerated and accepted by our patients.

Discussion

Health-related QoL research is indispensable as it provides insights into domains that are not directly observable (Desouky et al. 2012) for the treating clinician.

In this patient collective, over 60% of patients reported emotional problems with higher T-category leading to significantly more emotional problems and spiritual concerns. Screening of these patients and early intervention is crucial as different meta-analyses have shown that QoL can be improved through psychosocial interventions and relaxation trainings (Meyer & Mark 1995; Lübbert et al. 2001).

Over 68% of patients reported physical issues upon request with female patients accounting for significantly higher rates of physical issues

Table 2. Patients' answers on the NCCN Distress Thermometer and complete problem list (*n* = 106)

Distress levels	0 = 11 (10.4%)
	1 = 15 (14.2%)
	2 = 21 (19.8%)
	3 = 12 (11.3%)
	4 = 14 (13.2%)
	5 = 14 (13.2%)
	6 = 3 (2.8%)
	7 = 8 (7.5%)
	8 = 4 (3.8%)
	9 = 1 (0.9%)
	10 = 3 (2.8%)
Practical problems overall	25 (23.6%)
Child care	1 (0.9%)
Housing	4 (3.8%)
Insurance/financial	8 (7.5%)
Transportation	12 (11.3%)
Work/school	15 (14.2%)
Family problems overall	11 (10.4%)
Dealing with children	8 (7.5%)
Dealing with partner	6 (5.7%)
Emotional problems overall	64 (60.4%)
Depression	11 (10.4%)
Fears	41 (38.7%)
Nervousness	31 (29.2%)
Sadness	21 (19.8%)
Worry	36 (34.0%)
Loss of interest in usual activities	14 (13.2%)
Spiritual/religious concerns overall	7 (6.0%)
Loss of faith	4 (3.8%)
Relating to God	3 (2.8%)
Physical problems overall	73 (68.9%)
Appearance	4 (3.8%)
Bathing/dressing	1 (0.9%)
Breathing	7 (6.0%)
Changes in urination	6 (5.7%)
Constipation	3 (2.8%)
Diarrhea	4 (3.8%)
Eating	3 (2.8%)
Fatigue	31 (29.2%)
Feeling swollen	3 (2.8%)
Fevers	0 (0.0%)
Getting around	24 (22.6%)
Indigestion	8 (7.5%)
Memory/concentration	21 (19.8%)
Mouth sores	10 (9.4%)
Nausea	4 (3.8%)
Nose dry/congested	14 (13.2%)
Pain	25 (23.6%)
Sexual	7 (6.0%)
Skin dry/itchy	19 (18.0%)
Sleep	33 (31.1%)
Tingling in hands/feet	13 (12.3%)

(*p* = 0.034). This is in accordance with a recent cross-sectional study that reported women tending to express more dissatisfaction with care (Afshar et al. 2018).

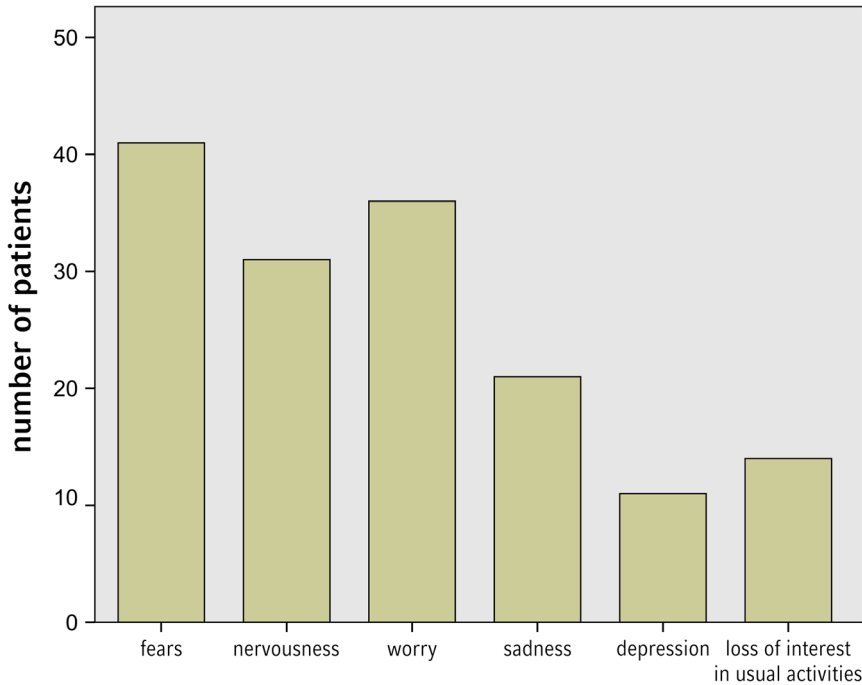


Fig. 3. Detailed distribution of emotional problems via vertical bar graph ($n = 106$ patients).

Moschos et al. (2018) recently proved that level of depression is correlated with decrease in BCVA in uveal melanoma patients. In our previous QoL-study employing the SF-12 health survey on uveal melanoma patients after CyberKnife[®] radiosurgery, patients with better BCVA reported higher QoL at 2 years of follow-up (Klingenstein et al. 2013). This finding could now be confirmed by the NCCN distress thermometer: Lower BCVA in the tumour eye was correlated with higher distress levels ($p = 0.037$). When looking more into detail, patients suffering from loss of BCVA of ≥ 3 lines of the treated eye had significantly higher distress levels ($p = 0.029$). Thus, preservation of BCVA should be a key point of local tumour therapy. Continuous long-term psychosocial treatment is needed from the time of diagnosis in a subgroup of patients suffering from eye-related disabilities (Frenkel et al. 2018).

We found that the distress thermometer form can be included easily into daily practice. As department of Ophthalmology, we received positive feedback from the patients in distributing the form, saying that they often felt left alone with emotional and physical problems. Patients reported that as non-metastatic uveal melanoma does not require chemotherapy, therapy is often single-session or hypofractionated and visual impairment following

therapy is often not directly visible and delayed, acceptance within society as a highly malignant disease is poor. Other than in oncological patients who have to undergo months of difficult treatment cycles, offering psychological assistance to uveal melanoma patients may not be a top priority for the treating doctors. According to the literature, only few uveal melanoma patients (13.3%) reported an offer of psychological support and most dissatisfaction in this US American patient collective was with lack of advice on financial aspects of care and lack of psychological counselling (Afshar et al. 2018).

Our patients tended to report their fears (e.g. of blindness) or feelings that the disease was not taken seriously solely upon means of targeted questioning. The NCCN distress thermometer functioned as an ice-breaker in these cases and uncovered the need of assistance not only for new patients, but also for patients whom we have been accompanying for long-term follow-up. Critical points in time throughout the course of cancer are reportedly the primary diagnosis, treatment endpoint, recurrence or disease progression as well as the palliative stage (McCormick & Conley 1995). A survey polling uveal melanoma patients one and 3 months after diagnosis cited most importantly the need of health

information and psychological needs (Williamson et al. 2018). This suggests that early on, the severity of such needs and psychosocial factors that may be associated can be identified for proactive supportive intervention (Williamson et al. 2018). In our study, we found no statistical impact of time after diagnosis on distress levels using the NCCN distress thermometer. Neither freshly diagnosed patients nor patients after more than 3 years of follow-up, after which time all treatment-related adverse effects would be expected. In consequence, continuous long-term psychosocial screening is needed, but with the NCCN distress thermometer, this can be integrated into clinical practice easily.

Apart from the NCCN distress thermometer, there are a multitude of valuable questionnaires for assessment of patients' QoL (e.g. the SF-36 or -12 Health Survey or the European Organisation into Research and Treatment of Cancer (EORTC) QLQ-C30). The authors have reported their study experience with the SF-12 Health Survey previously (Klingenstein et al. 2013, 2016). For the EORTC, there is an additional EORTC QLQ-OPT30 module consisting of 30 items for uveal melanoma patients (Brandberg et al. 2004). Yet, a combination of questionnaires and modules may exceed the recommended maximum of 30 items (Sprangers et al. 1998), needing more time and concentration for fulfilment, possibly influencing the patients' compliance.

The NCCN distress thermometer that we employed now is an ultra-short screening tool on just one single page including the distress thermometer as a visual analog scale, thus allowing very rapid completion. No complex additional scoring software is needed for interpretation, which in our experience with the SF-12 Health Survey might result in a delay of therapy initiation. Another advantage of the NCCN distress thermometer is very clear interpretation of the data acquired with a distress level of 5 or above resulting in proposition and initiation of proactive support by the caregivers. The area of life that needs active intervention can also be distinguished at a glance (e.g. practical problems are presented to a social worker or the patients' health insurance, emotional and family problems require psychooncological

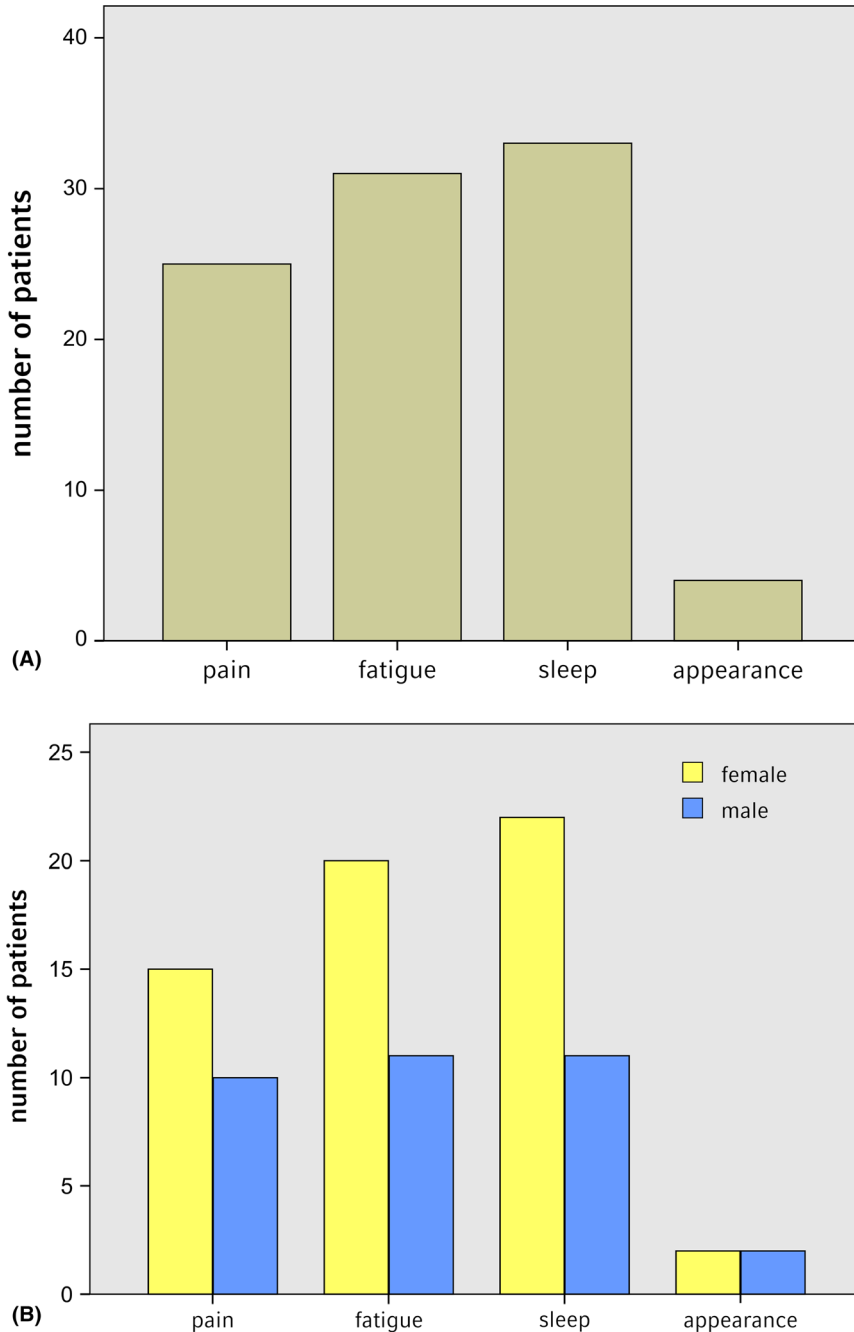


Fig. 4. (a) Detailed distribution of physical problems (pain, fatigue, sleep and appearance) via vertical bar graph ($n = 106$ patients). (b) Subdivision of physical problems by gender via vertical bar graph (47 male and 59 female patients).

counselling, religious or spiritual concerns are taken to the minister and physical impairment should be improved by us as the patients' treating physicians). For the most part, for example when employing the SF-12 Health Survey, after complex evaluation of the different items, only a differentiation between physical and emotional health problems can be performed leaving the initiation of help much less specific for the treating physician.

A sensitivity of 97% and specificity of 41% were reported for the German version of the distress thermometer (Mehnert et al. 2006). We found for our patient collective, that as advised in the guidelines of the distress thermometer (Mehnert et al. 2006), and derived from our ROC analysis, active intervention was sensible and needed in distress values ≥ 5 (100% sensitivity and 76% specificity). This proves that our uveal melanoma patient collective can

be considered comparable to other oncological patient groups within the literature. A brief and direct screening approach of uveal melanoma patients employing the NCCN questionnaire is helpful. It showed well, in which area of life the patients required assistance.

In a recent large multicenter evaluation of an initially cancer-free patient collective diagnosed with cancer later during the study period, death rates in the most distressed group were consistently raised for cancer of all sites in comparison with the least distressed group (Batty et al. 2017). Conversely, detection and early treatment of distress could also be secondarily preventive for further psychiatric as well as somatic diseases (Batty et al. 2017).

This pilot study for the employment of the NCCN distress thermometer in uveal melanoma patients has proven promising results and warrants its advantages as a screening tool. Further studies should be initiated to validate and support these findings.

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