Symptom Burden and Palliative Care Needs of Patients with Incurable Cancer at Diagnosis and During the Disease Course

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Palliative care • Symptom burden • Quality of life • Distress • Cancer

ABSTRACT

Background. Although current guidelines advocate early integration of palliative care, symptom burden and palliative care needs of patients at diagnosis of incurable cancer and along the disease trajectory are understudied.

Material and Methods. We assessed distress, symptom burden, quality of life, and supportive care needs in patients with newly diagnosed incurable cancer in a prospective longitudinal observational multicenter study. Patients were evaluated using validated self-report measures (National Comprehensive Cancer Network Distress Thermometer [DT], Functional Assessment of Cancer Therapy [FACT], Schedule for the Evaluation of Individual Quality of Life [SEIQoL-Q], Patients Health Questionnaire-4 [PHQ-4], modified Supportive Care Needs Survey [SCNS-SF-34]) at baseline (T0) and at 3 (T1), 6 (T2), and 12 months (T3) follow-up.

Results. From October 2014 to October 2016, 500 patients (219 women, 281 men; mean age 64.2 years) were recruited at 20 study sites in Germany following diagnosis of incurable metastatic, locally advanced, or recurrent lung (217), gastrointestinal (156), head and neck (55), gynecological (57), and skin (15) cancer. Patients reported significant distress (DT score ≥ 5) after diagnosis, which significantly decreased over time (T0: 67.2%, T1: 51.7%, T2: 47.9%, T3: 48.7%). The spectrum of reported symptoms was broad, with considerable variety between and within the cancer groups. Anxiety and depression were most prevalent early in the disease course (T0: 30.8%, T1: 20.1%, T2: 14.7%, T3: 16.9%). The number of patients reporting unmet supportive care needs decreased over time (T0: 71.8%, T1: 61.6%, T2: 58.1%, T3: 55.3%).

Conclusion. Our study confirms a variable and mostly high symptom burden at the time of diagnosis of incurable cancer, suggesting early screening by using standardized tools and underlining the usefulness of early palliative care. The Oncologist 2021;26:1058–1065.
Implications for Practice: A better understanding of symptom burden and palliative care needs of patients with newly diagnosed incurable cancer may guide clinical practice and help to improve the quality of palliative care services. The results of this study provide important information for establishing palliative care programs and related guidelines. Distress, symptom burden, and the need for support vary and are often high at the time of diagnosis. These findings underscore the need for implementation of symptom screening as well as early palliative care services, starting at the time of diagnosis of incurable cancer and tailored according to patients’ needs.

INTRODUCTION

National and international guidelines recommend early integration of palliative care in the treatment of patients with advanced cancer [1–5]. Numerous studies underscore the positive effects of early integration of palliative care [6–11]. Positive effects include improved symptom control and psychological well-being (less depression and anxiety); better quality of life of patients, relatives, and caregivers; less over-treatment and aggressive care at the end of life [10]; reduced hospital stays; higher treatment satisfaction of patients and their relatives; diminution of the burden on caregiving relatives; and reduction of medical costs [6–8, 12–16].

Even though the efficacy has been proven for patients with cancer, early palliative care is not yet universally available. Information on symptom burden and care needs of patients is incomplete, hampering the implementation of palliative care services.

To develop individual palliative care concepts, similarities and differences between different types of cancers with their disease-specific effects on the well-being of patients must be taken into account. Temel and colleagues [17] reported greater effects of early palliative care interventions in patients with newly diagnosed lung and gastrointestinal cancers if these were specifically adapted to the needs of the respective patient population. Additionally, other studies described that effects depend on the psychosocial, cultural, and ethnic background of patients, their family situation, and place of residence (e.g., urban versus rural areas) [18–20].

Although an increasing number of studies shed light on needs and symptom burden, care needs, and preferences of patients at the end of life [21, 22], surprisingly little is known about the time period immediately after diagnosis of incurable cancer and how these change over the disease trajectory. This knowledge is important to provide adequate, individualized palliative care.

Therefore, the working group on palliative medicine (Arbeitsgemeinschaft Palliativmedizin) of the German Cancer Society initiated a prospective observational multicenter network study to clarify the symptom burden and palliative care needs of patients with newly diagnosed incurable cancer and followed them during the first year after diagnosis. We assessed quality of life, anxiety, depression, and distress to facilitate future implementation of more effective palliative care services.

MATERIALS AND METHODS

Study Setting
The study was designed as a multicenter, prospective, longitudinal, observational study, which was activated at 22 sites.

Selected cancer treatment centers reflect the different areas of the medical health care landscape, reaching from the university to the community environment and from outpatient to inpatient care. The study was registered at ClinicalTrials.gov (NCT02751723) and approved by the responsible ethics committees of all participating centers. All patients gave their written informed consent prior to enrollment.

Patient Selection Criteria
Individuals were eligible if they had a confirmed diagnosis of incurable cancer (metastatic, locally advanced, or recurrent). They were 18 years or older, not affected by immediately life threatening complications of cancer, and were able to speak and read German. Exclusion criteria included severe physical, cognitive, and/or verbal impairments that interfered with the ability to give informed consent for research and to comply with study requirements.

Patients were enrolled after diagnosis of incurable cancer and before start of any anticancer therapy.

Data Collection
Data were collected at four time points: T0 at baseline and at three (T1), six (T2), and 12 (T3) months follow-up. Patients were asked to answer questionnaires either Web or paper-and-pencil based. Additionally, medical data including demographics, Eastern Cooperative Oncology Group performance status (ECOG PS), cancer diagnosis, and cancer treatment were provided by the treating physicians and documented in a case report form.

Data were pseudonymously stored in a central study database, audited for accuracy, and analyzed using SPSS v. 24.0 for Windows (SPSS Inc., Chicago, IL) and Microsoft Excel version 2010 (Microsoft, Redmond, WA).

Measures
The global level of patients’ psychological distress during the past week was assessed using the single item visual analog scale of the National Comprehensive Cancer Network Distress Thermometer (DT), ranging from 0 (“no distress”) to 10 (“extreme distress”). A score of ≥5 at the visual analog scale is recommended as a cut off for a clinically significant level of distress [23].

Anxiety and depression were assessed by the ultrashort Patients Health Questionnaire (PHQ-4, [24, 25]). The 4-items measure comprises the 2-item Patient Health Questionnaire (PHQ-2), which contains the diagnostic core criteria for depressive disorder, and the Generalized Anxiety Disorder containing the two core criteria for generalized anxiety disorder. PHQ-4 total score can range from 0 to 12. It categorizes psychological distress as none (0–2), mild (3–5), moderate (6–9), and severe (10–12).

Excel version 2010 (Microsoft, Redmond, WA).
A total score above the cutoff 6 indicates a higher risk for anxiety and depression [25].

The Functional Assessment of Cancer Therapy-General (FACT-G) with organ-specific modules was used to analyze patients’ symptom burden and health-related quality of life (QoL) [26, 27]. The FACT-G questionnaire contains 27 questions grouped in four different quality of life domains: physical well-being, social and family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB). Answers are given according to a five-point rating scale (0: not at all to 4: very much). Domain-specific scores range from 0 to 28 (except EWB: 0–24). The QoL total score, which ranges from 0 to 108, is obtained from the results of the four subdomains and is calculated if at least 80% of the questions were answered. The lower the score value, the worse the patient’s well-being.

The Schedule for the Evaluation of Individual Quality of Life (SEIQoL) assesses the importance and satisfaction of some aspects of daily life. On a 5-point Likert scale, the patients were asked to weigh 12 life domains regarding their importance and how satisfied they were with these domains ranging from 0 (not at all) to 100 (extremely important/satisfied). An individual Life-Quality-Index can be calculated on a range from 0 to 100, with higher scores expressing higher QoL [28, 29].

Sample Size and Statistics
The intended study size was 500 patients. This was a pragmatic approach decided by the study steering board taking into consideration the power of the network to recruit a robust number of patients in a reasonable time frame. Statistical analyses were performed by SPSS Version 24.0. Descriptive statistics were used to interpret baseline data and to estimate frequencies, means, and SDs. One-way analysis of variance was performed to test for differences between clinical outcomes in the course of the study. Homogeneity of variances was determined using Levene’s test. If equal variances could be assumed, a post hoc analysis using Tukey tests to detect significance ($p < .05$) was performed. If there was no homogeneity of variances, $p$ values were calculated using Welch’s tests and Games-Howel post hoc analysis.

Results

Study Conduct
Between October 2014 and October 2016, 20 of the 22 activated centers in Germany recruited 500 eligible patients with incurable cancer.

Out of 1,050 screened patients (retrospectively determined number based on recent comparative data from the participating centers), 505 patients (participation rate of 48%) gave their informed consent to participate. Three patients were subsequently excluded from analysis because the inclusion criteria were not fully met, one participant refused participation after having given consent, and for one participant, no baseline data were transmitted. Finally, data from 500 eligible patients were analyzed. The number of evaluable patient questionnaires was 475 (95.0%) at T0, 327 (65.4%) at T1, 238 (47.4%) at T2, and 161 (32.1%) at T3 (Fig. 1).

Patient Characteristics
Table 1 summarizes the demographic and clinical characteristics of the 500 study participants. Slightly more men (56.2%) than women (43.8%) were enrolled. The mean age was 64.2 years (range, 25–89). The median ECOG PS was 1, with a range from 0 to 4.

Distress Level
At baseline, 67.1% of patients reported significant distress (Table 2). Although the mean distress levels declined slightly over time (T0: 5.49 [SD = 2.64], T1: 4.60 [SD = 2.58], T2: 4.36 [SD = 2.52], and T3: 4.34 [SD = 2.85]), approximately half of the patients remained significantly distressed (T1: 51.7%, T2: 47.9%, and T3: 48.7%). When comparing patients with different tumor entities, patients suffering from stomach, esophageal, hepatobiliary, or head and neck cancer showed the
highest levels of distress over the entire observation period (supplemental online Table 1).

### Anxiety and Depression

The mean score of the PHQ-4 at T0 was 4.62 (SD = 3.18; 95% confidence interval [CI], 4.33–4.91) and therefore significantly higher than at T1 (3.70; SD = 2.81; 95% CI, 3.39–4.01), T2 (3.30; SD = 2.62; 95% CI, 2.96–3.65) and T3 (3.33; SD = 3.02; 95% CI, 2.84–3.82). Nearly one-third of patients (30.8%) reported moderate or severe psychological distress at T0. This number decreased over time (T1: 20.1%, T2: 14.7% and T3: 16.9%; supplemental online Fig. 1). The highest numbers of...
patients with significant anxiety and depression at baseline were found in the head and neck (52.0%), hepatobiliary (37.7%), and esophageal cancer (33.3%) groups (supplemental online Fig. 1). During the observation period, the number of patients with significant anxiety and depression remained higher in patients with head and neck and with esophageal cancer compared with other cancers. Patients with malignant melanoma showed the lowest psychological distress (T0: 7.7%, T1: 11.1%, T2: 0%, and T3: 0%).

A total of 41.4% of patients with moderate or severe psychological distress wished to receive professional support, whereas 55.0% refused it, and 3.6% did not answer this question at T0. However, 16.6% of patients with no or only mild psychological distress also indicated their wish to receive professional psychological support at T0. After 12 months (T3), 48% of patients with high and 8.9% of patients with low psychological distress wanted access to professional palliative and supportive help.

Symptom Burden and Health-Related Quality of Life

The results of the evaluation of the FACT-G questionnaires including subscores of the four different quality of life domains are shown in Table 2. At baseline, the FACT-G total score of the general study population was 67.91 (SD = 17.52; 95% CI, 66.29–69.52) and increased slightly over time (T1: 70.67, SD = 17.32; 95% CI, 68.76–72.59; T2: 73.93, SD = 16.95; 95% CI, 71.73–76.12; T3: 73.75, SD = 18.69; 95% CI, 70.80–76.71). Patients with head and neck cancer and with hepatobiliary cancer had the lowest total score values in comparison with patients with other cancers (supplemental online Table 2). Patients scored lowest for FWB and EWB and highest for SWB during all four visits, independent of the underlying cancer. Figure 2 displays patient statements on specific symptom burden.

Importance and Satisfaction with Life Domains

The average individual QoL Index determined by SEIQoL-D was 58.9 at baseline (SD = 17.14; 95% CI, 57.4–60.5) for the general study population and did not change significantly in the further course (T1: 60.4 (SD = 17.44; 95% CI, 58.4–62.3), T2: 64.1 (SD = 17.44; 95% CI, 61.8–66.3), and T3: 62.3 (SD = 16.1; 95% CI, 59.8–64.8; Table 2). The lowest QoL-indices were found in patients with head and neck cancer. Patients reported “family” (86.4, SD = 22.0) and “physical health” (85.7, SD = 18.2) as the most important life domains, followed by “emotional well-being” (85.0, SD = 17.9), and “home/housing” (83.1, SD = 19.3). The importance of “religion/spirituality” (30.6, SD = 30.4) and “work/occupation” (34.6, SD = 32.3) was lowest. Highest satisfaction scores were found for “family” (78.3, SD = 24.6), “partnership” (75.2, SD = 33.4), and “home/housing” (73.4, SD = 23.1), whereas patients were not at all satisfied with their “physical health” and “emotional well-being.” These findings remained unchanged at all points of measurement and were not different among the cancer groups. Only “partnership” increased in importance and satisfaction (T3: 85.0, SD = 25.4; 81.4, SD = 23.0; supplemental online Table 3).

Supportive Care Needs

A total of 71.8% of patients reported at least one unmet supportive care need. This number of patients decreased over time (T1: 61.6%, T2: 58.1%, and T3: 55.3%) (Table 2). A
The main finding of our study is that two-thirds of patients who are newly diagnosed with incurable cancer reported significant distress. Therefore, according needs for supportive and palliative care can be postulated for the majority of patients early in the course of the disease. The study realized by de Boer et al. [31] showed a high prevalence of distress (64%), apathy (53%), depressive symptoms (46%), and loneliness (36%) among older patients with metastatic breast cancer and concluded that timely detection by a geriatric assessment or specific screening and interventions for psychosocial problems could potentially increase quality of life for these patients. Also, Carduff et al. [32], who elicited the longitudinal experiences of living and dying with incurable metastatic colorectal cancer by conducting serial interviews with patients for 12 months or until they died, concluded that a palliative care approach should be integrated into oncological and primary care from diagnosis of advanced disease.

The number of patients showing distress declined significantly over the disease trajectory. In a recent study, Cutillo et al. [33] also showed that patients endorsed more distress 1–4 weeks after receiving the diagnosis than at any other time of the disease trajectory. Fang et al. [34] found the relative risk of suicide among patients receiving a cancer diagnosis was 12.6 during the first week and decreased rapidly during the first year after diagnosis. We confirm an urgent need for early access to supportive and palliative care including psychological interventions for patients who are diagnosed with incurable cancer, as stated in various national and international guidelines [1–5].

Additionally, we found that measures of anxiety and depressive symptomatology also showed the highest value at the time of diagnosis, with decrease during the disease trajectory. Obviously, the patients need professional help especially at the time of diagnosis. The problem is that more than half of the patients showing moderate or severe psychological distress do not wish to get professional support. Whether because of a lack of education about the usefulness of psychosocial support or a stigma associated with mental health care, highly affected patients may not even show interest in or use mental health services [35]. This known discrepancy between a high degree of suffering and low commitment to therapeutic intervention is problematic and should be addressed by low threshold access to professional care.

At the time of diagnosis of incurable cancer, we found a general health-related quality of life measured by the FACT-G total score comparable with other studies performed in France and the U.S. [36]. Interestingly, patients with breast cancer, melanoma, and ovarian cancer reported the highest scores, whereas patients with head and neck and hepatobiliary cancers reported the lowest health-related QoL. This probably underlines the particularly strong physical and psychosocial burden of these cancer patient populations. In contrast, even patients with breast cancer, melanoma, and ovarian cancer show a significant burden compared with the healthy population [37]. Overall, the lowest values were found for the quality of life domains FWB and EWB, thus confirming data from other studies [37, 38]. The data are presented in terms of relationship to the time point of diagnosis of incurable cancer but could also be examined in relationship to proximity to death, because 382 patients died during 1 year and before study completion. Previous research has shown growth in burden of disease with greater proximity to death. Lo et al. [39] found that moderate to severe depressive symptoms were almost three times more common in the final 3 months of life than 1 year or more before death. The levels of burden and distress may be bimodal, peaking early and then rising later with disease progression. This may be obscured because our study sample included those with more and less progressive disease.

By using the SEIQoL-D, we found that the life domains “family,” “physical health,” “emotional well-being,” and “home/housing” were most important for patients with incurable cancer. This is in line with observations from other investigators [28, 40, 41]. In contrast, the life domain “work/occupation” was less important for our patients. This might reflect the fact that the average age of our study population was 64.2 years, and the majority of study participants might have already retired or at the end of their professional life, as the normal retirement age in Germany is 65 years. We observed the largest discrepancy between the score for importance and the score for satisfaction for the domains “physical health” and “emotional well-being.” The patients declared these items as very important, but they were not satisfied with them. This confirms previous study results of Becker et al. [28].

Especially at the time of diagnosis, more patients declared unmet needs than in the further course. Puts et al. [42] described a similar phenomenon in older patients newly diagnosed with cancer. Otherwise, criteria that correlated with unmet needs were younger age, female gender, depression, physical symptoms, marital status, type of treatment, income, and education [42]. Wang et al. [43] showed in their review of 50 studies that patients with advanced cancer reported a broad spectrum of context-bound unmet needs.

Study Strengths and Limitations
Our study provides prospectively sampled data on symptom burden and palliative care needs of patients with cancer treated in different sectors of the German health care system from the diagnosis of incurability and before any anticancer treatment with palliative intention, followed by 1 year.
longitudinal follow-up of palliative cancer care. It comprises a large variety of solid cancer diagnoses among which we collected data from the most common malignant disease groups. We used validated measuring instruments in a homogenous way and at predefined time. The involvement of one of the biggest National Cancer Societies worldwide representing almost 8,000 individual members enables a realistic picture of the oncological care landscape in the country where the study was performed (Germany). Also worth mentioning is the high response rate from enrolled patients. This underlines high investigators’ and patients’ commitment to the study aims and a professional study management.

However, this study has a number of limitations. First, not all tumor entities were recorded. The decision for the selected solid tumors was based on the interests of the different working groups of the German Cancer Society. Because the uro-oncology and the neuro-oncology working groups were involved in other competing studies at the time when our study was initiated, these diagnoses are not represented in our study. Second, the case number of 500 patients is not based on a biometrically supported hypothesis but on empirical values regarding feasibility in a 2-year recruitment phase, to obtain robust descriptive results. Additionally, all eligible patients were recruited consecutively, regardless of the number of patients who had already been enrolled previously. As a consequence, the different tumor entities are not evenly distributed and some groups are too small to allow for robust subgroup analyses with a sufficient statistical power. Third, patients who were critically ill were not recruited for the study. By specifying the inclusion criterion “patient is not in a critical health condition and is not directly threatened by the cancer or complications resulting from it,” a conscious decision was made to exclude them. We still believe that “end-of-life care” is a different scope, and care needs must be addressed in a different way compared with our target cohort. Fourth, it was not systematically recorded which patients did not participate in the study and for which reasons they declined or were not asked by the investigators. For example, not all patients were suitable for such complex self-report measures. Patients who were not suitable for this type of questionnaires could not participate in the study or needed the support of the study staff. Therefore, we cannot exclude a systematic selection bias. In general, the feasibility of complex questionnaire concepts without personal support for patients with communication and understanding limitations because of their critical disease status should be critically questioned.

Fifth, because of the advanced cancer disease, many study participants with particularly poor prognosis died before the fourth study visit. Therefore, we cannot exclude the possibility that the remaining study population was selected for better quality of life and less need for support.

Sixth, because of patients’ death before the fourth study visit, the number of evaluable data for individual tumor entities reached a critical level [44]. Thus, the feasibility of a longitudinal study in the palliative situation has reached the limit of feasibility for some tumor entities.

**Conclusion**

Patients reported high levels of distress and psychological symptoms such as anxiety and depression already at time of diagnosis of incurable cancer disease. We observed a broad spectrum of symptoms and disease burden even at the very beginning of a palliative disease trajectory, with strong variation in intensity both between and within the different tumor entities. At time of diagnosis, more patients have unmet needs than at a later stage. However, patients showed a great variance of supportive care needs over the disease trajectory. In summary, our results confirm that patients need an early individualized offer of multifaceted support, including palliative care services, starting already at the time of diagnosis of incurable cancer. To provide patients with individualized support, structured assessment or regular screening tools to evaluate patient’s burden and care needs should be used.

**Acknowledgments**

The study was funded by the German Cancer Society (DKG). Open Access funding enabled and organized by Projekt DEAL.

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**Disclosures**

The authors indicated no financial relationships.

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