

Effective symptom relief through continuous integration of palliative care in advanced renal cell carcinoma patients: comprehensive measurement using the palliative care base assessment

Anne Dörr , Insa Vogel, Friedrich Wittenbecher, Jörg Westermann, Peter Thuss-Patience, Johann Ahn , Uwe Pelzer, Juliane Hardt, Lars Bullinger and Anne Flörcken 

Abstract

Background: Due to modern therapies, survival in metastatic renal cell carcinoma (mRCC) has been significantly prolonged. Nevertheless, patients suffering from advanced disease often present with severe symptoms. Early integration of palliative care into anti-cancer treatment has been shown to improve quality of life and may even prolong survival. Therefore, it is recommended to offer palliative care to patients with complex symptoms at the beginning of an advanced disease stage. To our knowledge, so far, no study has been conducted to examine the role of palliative care in patients with mRCC.

Objectives: This study aimed to assess the symptom burden and quality of life before and after an inpatient palliative care treatment.

Design: The study design is a retrospective observational study.

Methods: We included patients with mRCC, who were admitted to our palliative care unit between 2011 and 2017 due to severe symptoms. The symptom burden was assessed at admission, throughout treatment, and at discharge. The evaluation consisted of the palliative care base assessment and daily documentation of relevant symptoms.

Results: We evaluated 110 hospitalizations of 58 RCC patients. On average, patients were admitted to the palliative care unit 7 years after initial diagnosis (range 1–305 months). The median age was 70.5 years, 69% of the patients were male, 3% female. The main causes for admission were pain (52%) and dyspnea (26%), and the most frequent patient-reported symptoms were fatigue/exhaustion (87%), weakness (83%), and need for assistance with activities of daily living (83%). Multidisciplinary palliative care treatment led to a significant reduction in the median minimal documentation system (MIDOS) symptom score (15.6–9.9, $p < 0.001$), the median numeric pain rating scale (3–0, $p < 0.001$), and a significant reduction in mean ratings of the distress thermometer (5.5–3.1, $p = 0.016$).

Conclusion: Our analysis shows that the integration of palliative care treatment is effective throughout the disease in mRCC and could measurably reduce the symptom burden in our patient population. Palliative care should not be equated with end-of-life care but should rather be integrated throughout advanced disease, particularly as soon as a cure is impossible.

Keywords: renal cell carcinoma, specialized palliative care, symptom control

Received: 5 December 2023; revised manuscript accepted: 22 May 2024.

Palliative Care & Social Practice

2024, Vol. 18: 1–14

DOI: 10.1177/
26323524241260424

© The Author(s), 2024.
Article reuse guidelines:
sagepub.com/journals-
permissions

Correspondence to:

Anne Dörr
Department of
Hematology, Oncology,
and Tumor Immunology,
Campus Virchow-
Klinikum, Charité
– Universitätsmedizin
Berlin, Augustenburger
Platz 1, Berlin 13353,
Germany
Anne.doerr@charite.de

Insa Vogel
Department of Gynecology,
Immanuel Klinikum
Bernau, Herzzentrum
Brandenburg, Bernau,
Germany

Friedrich Wittenbecher
Jörg Westermann
Peter Thuss-Patience
Johann Ahn
Charité -
Universitätsmedizin
Berlin, corporate member
of Freie Universität Berlin,
Humboldt-Universität zu
Berlin, and Berlin Institute
of Health, Department of
Hematology, Oncology,
and Tumor Immunology,
Campus Virchow-
Klinikum, Berlin, Germany

Uwe Pelzer
Department of
Hematology, Oncology,
and Tumor Immunology,
Campus Virchow-
Klinikum, Charité
– Universitätsmedizin
Berlin, Berlin, Germany

Juliane Hardt
Institute of Biometry
and Clinical
Epidemiology, Charité
– Universitätsmedizin
Berlin, Berlin, Germany
Department for Human
Medicine, Institute for
Integrative Medicine,
Faculty of Health, Witten/
Herdecke University,
Herdecke, Germany

Lars Bullinger
Anne Flörcken
Department of
Hematology, Oncology,
and Tumor Immunology,
Campus Virchow-
Klinikum, Charité
– Universitätsmedizin
Berlin, Berlin, Germany
German Cancer
Consortium (DKTK),
German Cancer Research
Center (DKFZ), Heidelberg,
Germany

Introduction

Renal cell carcinoma (RCC) is one of the more common malignant tumors in adults and accounts for 90% of all kidney cancers.¹ At the time of diagnosis, 30% of patients present with metastatic RCC (mRCC) disease and about 30% develop metastases throughout their disease.²

Partial or radical nephrectomy is the main curative treatment for most RCCs, and some patients may even benefit from surgery if the tumor has spread to other organs for reasons of symptom relief such as pain and bleeding.³ Nevertheless, therapy for mRCC, and therefore for the majority of the patients, is almost always considered palliative. For many years, therapy with tyrosine kinase inhibitors (TKI) such as sunitinib and pazopanib was the standard of care to prolong survival and improve quality of life, but first-line therapy has changed dramatically in the past 2 years.^{4,5} Depending on the International Metastatic RCC Database Consortium (IMDC) risk score, different combinations of TKI and immune checkpoint inhibitors (CI) are now indicated.^{6–11}

Due to these modern therapies, survival in mRCC has been significantly prolonged. In the TKI era, the 5-year overall survival (OS) was ~75% comprising all disease stages. While patients with localized tumors have 5-year OS rates of >90%, distant metastases result in poor outcomes with survival rates of ~15%.^{12,13} The new combination therapies (TKI + CI) significantly prolong progression-free survival (PFS) and even OS, turning RCC for many patients into a chronic condition. However, there is still a high unmet need for adequate palliative care strategies when the disease is advanced.

Patients suffering from advanced RCC often present with severe symptoms such as pain, bilateral lower extremity edema, or paraneoplastic disease, manifested by hypertension, hypercalcemia, and polycythemia. Fever, weight loss, cough, adenopathy, and bone pain may indicate advanced disease.¹⁴ Along with survival, the FDA oncology division considers symptom improvement to be one of the primary measures of clinical benefit.¹⁵ Consistent with other tumors, there is some evidence linking survival and the symptom burden in RCC, suggesting a strong association between these two parameters.

The World Health Organization (WHO) recommends to offer palliative care not only to those patients who are suffering from end-stage disease

but also to patients with complex symptoms.¹⁶ The well-discussed prospectively randomized trial by Temel *et al.*¹⁷ showed that lung cancer patients receiving early palliative care not only had a better quality of life but also a significantly longer survival than the patients in the control group (11.6 months *versus* 8.9 months, $p=0.002$). Based on these study results and additional data,¹⁸ the American Society of Clinical Oncology, the WHO, and the National Comprehensive Cancer Network (NCCN) now independently emphasize that patients should receive dedicated palliative care services, early in the disease course, concurrent with active treatment independent of the entity.^{16,19} The NCCN guidelines suggest the integration of early palliative care within 8 weeks of diagnosis for newly diagnosed patients with advanced cancer.¹⁹ Importantly, palliative care should not be equated with end-of-life care, but should rather be integrated throughout illness, even when cure is impossible, as in many patients with advanced RCC. Several studies indicate that even in terminally ill patients, palliative care consultation is underutilized.^{20,21} According to Lec *et al.*, only in ~20% of patients with RCC palliative treatments were utilized (national cancer data base, 2004–2013). It was concluded that palliative treatments were rather seldomly used among patients with advanced urological malignancies.²² To meet the need for measures of symptom control at the interface between urologic, oncologic, and palliative care, it is necessary for the partners from special outpatient palliative care (German term: ‘spezialisierte ambulante Palliativversorgung’, SAPV), medical centers, and other service units to cooperate.²³

To our knowledge, no study has been conducted yet to examine the role of inpatient palliative care in mRCC patients. We therefore performed a retrospective analysis of patients with mRCC who were admitted to the palliative care unit at the Charité – Universitätsmedizin Berlin. Quality of life and symptom burden were assessed with the help of the palliative care base assessment (PBA) consisting of different assessment dimensions (physical and psychological symptom burden as well as evaluation of the individual need for assistance).

Methods

Patients

We performed a retrospective analysis of patients with symptomatic advanced RCC who were

admitted to the palliative care unit at our institution between 2011 and 2017. The analysis was conducted with patients' consent and according to the local ethical guidelines. Patient consent was given as part of the standardized consent form on admission. The study was approved by the local ethics committee. The prerequisite for inclusion in the analysis was the availability of data from the PBA at admission. The analysis included $n_p = 58$ patients with mRCC. Please see Table 1 for detailed patients' characteristics, n = number of patients. The Memorial Sloan Kettering Cancer Center (MSKCC) score, which predicts survival based on clinical and laboratory data in metastatic RCC patients, was used for the risk assessment of the patient cohort.²⁴

Data acquisition

The palliative care unit at the Campus Virchow-Klinikum of the Charité – Universitätsmedizin Berlin belongs to the oncology department and consists of an inpatient ward with 10 single bedrooms as well as a consultancy team of palliative care. The treatment is conducted by a multi-professional team, including specialized palliative care physicians, nurses, social workers, physiotherapists, psychologists, as well as dieticians, enabling a multi-professional team approach with daily team meetings to evaluate the needs of the patients and to tailor the treatment. The palliative care unit is also equipped with specific spatial conditions, for example, a single bedroom, shared kitchen, and terrace. Patients were offered supportive programs, including psycho-oncological counseling (for the whole family) and physiotherapy in addition to the general medical care.

The patient-oriented services are coordinated in daily interprofessional team meetings. In addition to medical treatment, the focus lies on physiotherapy services, psycho-oncological sessions, and the evaluation of further care modes. Relatives of the patients are included in the treatments and therapy planning and may spend the night on the ward if requested by a patient.

In our cohort, an individualized therapeutic plan was generated after the primary assessment of patients' symptom burden. Thorough documentation and symptom-oriented adjustments were performed according to the standards of specialized inpatient palliative care treatment defined by the German Association for Palliative Medicine.²⁵

Table 1. Patient characteristics.

<i>n</i>	Characteristics	Total	
58	Median age in years, (range)	70.5 (33–85)	
58	Gender – <i>N</i> (%)		
	Male	40 (69)	
	Female	18 (31)	
55	Histologic subtype – <i>N</i> (%)	♂- 39	♀- 16
	Clear cell	28 (72)	14 (88)
	Papillary	10 (26)	1 (6)
	Collecting ducts	1 (3)	0
	Chromophobe	0	1 (6)
58	Disease duration until admission – months		
	Average	83	
	Median (range)	66 (1–305)	
42	ECOG at admission – <i>N</i> (%)		
	0	0 (0)	
	1	5 (9)	
	2	8 (14)	
	3	24 (41)	
	4	5 (9)	
51	MSKCC score ² – <i>N</i> (%)		
	Favorable	0 (0)	
	Intermediate	33 (57)	
	Poor	18 (31)	
50	BMI ³ – kg/m ²		
	Average	25	
	Median	24	
	Range	17–37	

BMI, body mass index; MSKCC, Memorial Sloan Kettering Cancer Center.

The symptom burden was assessed at admission and discharge. The assessment consisted of the PBA, including the minimal documentation system (MIDOS) symptom score (MIDOS for patients in palliative care),²⁶ the Eastern Cooperative Oncology Group (ECOG) performance status, pain (numeric rating scale, NRS),

the type of pain (somatic, visceral, neuropathic), the social history, the distress thermometer (psychosocial screening tool), and personal situational challenges (Supplemental Appendix 1).²⁷ To adapt MIDOS as a German version of the Edmonton Symptom Assessment Scale, a revised version of MIDOS(2) has been validated. MIDOS is a validated instrument for self-assessment of the patient's symptoms indicating the intensity of vomitus, nausea, constipation, weakness, lack of appetite, sleeping disorders, dyspnea, drowsiness, depressive mood, anxiety, and well-being on verbal categorical scales.²⁸ The scale ranges from 0 (no symptoms) to 3 (severe symptoms); thus, a high MIDOS score is a surrogate for a high symptom burden. The PBA needs to be completed partly by the patients and partly by a healthcare professional, for example, nurses or doctors. The distress thermometer is a screening tool that was developed by the NCCN in the United States. With this short and practicable distress thermometer, the stress of the last few weeks can be assessed on a numerical 11-point ranking scale – 0 stands for 'not at all stressed' and 10 for 'extremely stressed'. A score ≥ 5 is considered internationally established and clinically significant. This indicates significant psychological stress in cancer patients and suggests that the patient needs support. To substantiate the distress, closed questions are asked, which are answered with yes or no. The problems are divided into practical, family, emotional, and physical problems, as well as spiritual and religious issues.²⁹ Furthermore, we gathered information on pain medication and discharge location from the patient's records. The use of different standardized measurement methods in combination ensures the standardized recording of symptoms in our patient cohort.

For the analyses, only the cases with a complete questionnaire were included, unless otherwise specified.

Statistical analyses

Data analysis was performed using IBM SPSS Statistics 27 and Microsoft Excel 2016. Data with normal distribution are reported with mean and standard deviation, else with medians and ranges (and quartiles/interquartile ranges). For the statistical analysis, we used the following tests: the Wilcoxon test (independent samples),

Mann–Whitney *U*-test (paired samples), paired two-sample *t*-test (paired samples), and the Spearman rank correlation. When processing missing values, these were excluded from the respective analyses (pairwise deletion of missing data).

All *p* values were two-sided and $p < 0.05$ was considered statistically significant. However, as this is an explorative, retrospective study, *p* values are only given as an orientation and not to be interpreted as confirmative.

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Supplemental Appendix 2).³⁰

Results

Patient cohort and admissions

We retrospectively analyzed the palliative care treatment of 58 mRCC patients who were admitted for 110 hospitalizations (14 of which with 2, and 9 with 3 or more hospitalizations). Median age was 70.5 years (range 33–85 years) and notably more male than female patients were admitted to the palliative care unit, corresponding to the known incidence of RCC (Table 1). Clear cell RCC (76%) and papillary RCC (20%) were the predominant subtypes. On average, it took 83 months (1–305 m) from the first diagnosis before treatment in the palliative care unit was initiated, with no notable difference among the subtypes. A proportion of 66% of patients in this cohort were considered 'early palliative' treatment. They were discharged home or transferred to another ward after the palliative care treatment. By contrast, 25% of the patients received 'end-of-life care' with 22% of the patients dying in our palliative care unit and 3% being referred to a hospice (Figure 1).

None of the patients presented with a normal performance status (ECOG 0). The majority (41%) were capable of only limited self-care and thus confined to a bed or a chair for more than 50% of their waking hours (ECOG 3). The MSKCC score indicated exclusively intermediate (57%) or high risk (31%) in our patient cohort. Cachexia, often intertwined with anorexia and lethargy in what some clinicians call

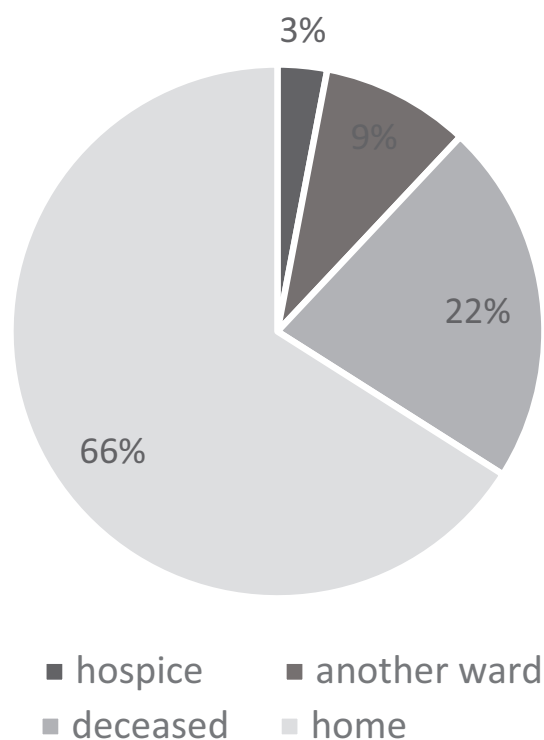


Figure 1. Mode of further care, $n = 58$.

‘anorexia–cachexia syndrome’, is a common problem for patients with RCC.³¹ Nevertheless, in our patient cohort, the body mass index (BMI) of 25 on average (17–37) was higher than normal, despite the advanced disease at the time of clinical presentation. For detailed patient characteristics, please refer to Table 1.

In 40% of the patients ($n_p = 23$), more than one palliative care treatment was performed, ranging from two to nine hospitalizations over several years. The mean duration of hospitalization was 12 days (range 2–31 days). The duration of hospitalization was 12 days on average.

Parts of the PBA questionnaires were filled out by the patients themselves. With regard to these parts on admission, only 62% were filled out completely, 26% were incomplete, and 11% were not filled out by the patients at all. At discharge, only 31% of the questionnaires were filled out completely, which is also in part explained by the number of patients who died on our ward. The most frequently filled-out feature was the MIDOS symptom score, maybe due to its position on the first page (primacy effect). It was complete in almost 90% at admission and 40% at discharge (Table 2). For the

Table 2. Completeness of the questionnaires.

Completeness	N (%)
PBA at admission	
Yes	36 (62)
No	6 (10)
Partially	16 (28)
PBA at discharge	
Yes	18 (31)
No	35 (60)
Partially	5 (9)
MIDOS at admission	
Yes	52 (90)
No	6 (10)
MIDOS at discharge	
Yes	23 (40)
No	35 (60)

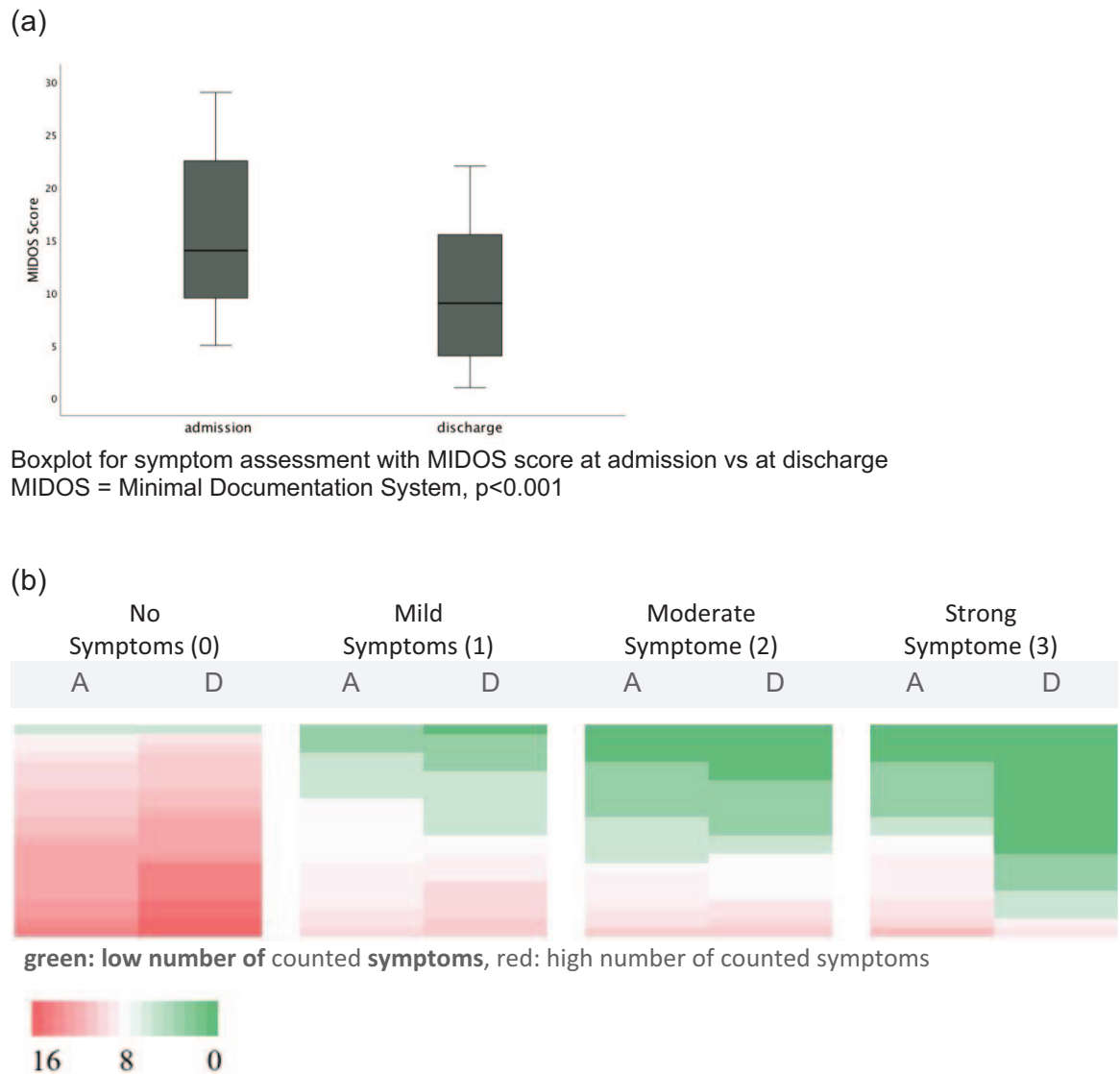
MIDOS, minimal documentation system; N, number of patients; PBA, palliative care base assessment.

subsequent analyses, only cases with a complete questionnaire were included, unless otherwise specified.

Symptom burden

The symptom burden in our patient cohort was assessed using the MIDOS score. Of the overall 58 patients, we could include 23 in the analysis. After the specialized palliative care treatment, we documented a significant reduction in the score from a median of 15.6 points at admission to 9.9 points at discharge [$p < 0.001$, Figure 2(a)]. Ninety-six percent of the cases (22 out of 23 patients) had a higher score at admission than at discharge.

As shown in Figure 2(b), especially patients suffering from severe symptoms at admission benefited from a significant relief of those symptoms during the treatment. We found a decrease in the number of symptoms ($p = 0.001$, $r_s = 0.63$; 22 percentage points). Concomitantly, the decrease in severe symptoms at discharge was statistically significant as well ($p < 0.001$).



Heat map: number of symptoms mentioned per patient; Comparison of (A) admission and (D) discharge by category (none, mild, moderate and severe symptoms according to MIDOS score) ($n = 23$, patients - 1st hospitalization) (sorted in ascending order)

Figure 2. MIDOS symptom burden. (a) Boxplot for symptom assessment with MIDOS score at admission versus at discharge. MIDOS, minimal documentation system, $p < 0.001$. (b) Heat map: number of symptoms mentioned per patient; Comparison of (A) admission and (D) discharge by category (none, mild, moderate, and severe symptoms according to MIDOS score) ($n = 23$, patients - first hospitalization) (sorted in ascending order).

The most frequently reported symptoms upon admission were fatigue/exhaustion (86%), weakness (82%), and the need for assistance in activities of daily living (ADL) (82%). After the inpatient palliative care treatment, a reduction of 28% was achieved concerning difficulties with ADL and even a 71% reduction concerning difficulties with caretaking (Table 3).

In the category of severe symptoms (MIDOS 3), the lack of appetite was the dominant symptom (admission: 32%, discharge: 23%). Severe fatigue/exhaustion (admission: 27%, discharge: 18%) also played a significant role in the symptom burden upon admission. The intensity of severe sleep disorders (23% at admission) could be completely reduced so that no participant

Table 3. MIDOS symptom burden, $n=23$.

Symptom*	Admission (%)	Discharge (%)
Fatigue	19 (86)	15 (68) ↓
Weakness	18 (82)	15 (68) ↓
Need for assistance in ADL	18 (82)	13 (59) ↓
Insomnia	15 (68)	8 (36) ↓
Loss of appetite	14 (64)	13 (59) ↓
Caretaking problems	14 (64)	4 (18) ↓
Family distress	12 (55)	6 (27) ↓
Dyspnea	11 (50)	9 (41) ↓
Fear	10 (46)	9 (41) ↓
Constipation	10 (46)	8 (36) ↓
Depression	9 (41)	12 (54) ↑
Nausea	7 (32)	4 (18) ↓
Lymphedema	6 (27)	7 (32) ↑
Vomiting	5 (23)	4 (18) ↓
Wound lesions	5 (23)	7 (32) ↑
Confusion/disorientation	4 (18,0)	1 ↓

*Including all symptoms, independent of the grade. ADL, activities of daily living; MIDOS, minimal documentation system; n, number of patients.

reported insomnia at the time of discharge. The reduction in pronounced weakness from 23% to 14% was notable but not significant.

Despite the small cohort size of our study, statistical significance could be demonstrated for the improvement of six symptoms of the MIDOS score across all categories: fatigue/exhaustion ($p=0.029$), need for assistance with ADL ($p=0.042$), dyspnea ($p=0.048$), insomnia ($p=0.001$), caretaking problems ($p=0.006$), and nausea ($p=0.026$). Altogether, patients benefited significantly from the specialized palliative care treatment.

Patients who died during the palliative care treatment presented with a significantly higher MIDOS score on admission (median 21, $n_p=11$) than the patients who could be discharged (median 16, $n_p=41$, $p=0.034$, Table 4). The main reasons for admission among the patients who died were pain, weakness, and dyspnea. The highest MIDOS scores were counted for weakness (54%), fatigue/exhaustion (38%), need for assistance with ADL (31%), and caretaking problems (31%). Especially pain and dyspnea were successfully reduced by the specialized palliative care treatment.

Performance status

The median ECOG did not change during the inpatient palliative care treatment ($n_p=18$, median = 2). Among all patients, seven presented

Table 4. Symptom burden at admission of patients alive in comparison to deceased patients.

Symptoms	Alive ($n=45$)			Deceased ($n=13$)			p
	n	$M \pm SD$	MD	n	$M \pm SD$	MD	
MIDOS score	41	15.6 ± 6.6	16	11	20.6 ± 6.6	21	0.034
Range 0–48							
ECOG	32	2.5 ± 0.9	3	10	3.2 ± 0.4	3	0.023
Range 0–4							
Distress	32	6.5 ± 2.4	7	6	6.8 ± 3.7	8	0.453
Range 0–10							
Pain at rest	44	3.2 ± 2.7	3	12	2.2 ± 3.0	0.5	0.17
Range 0–10							

M, mean; MD, median; MIDOS, minimal documentation system; n , number of patients; SD, standard deviation.

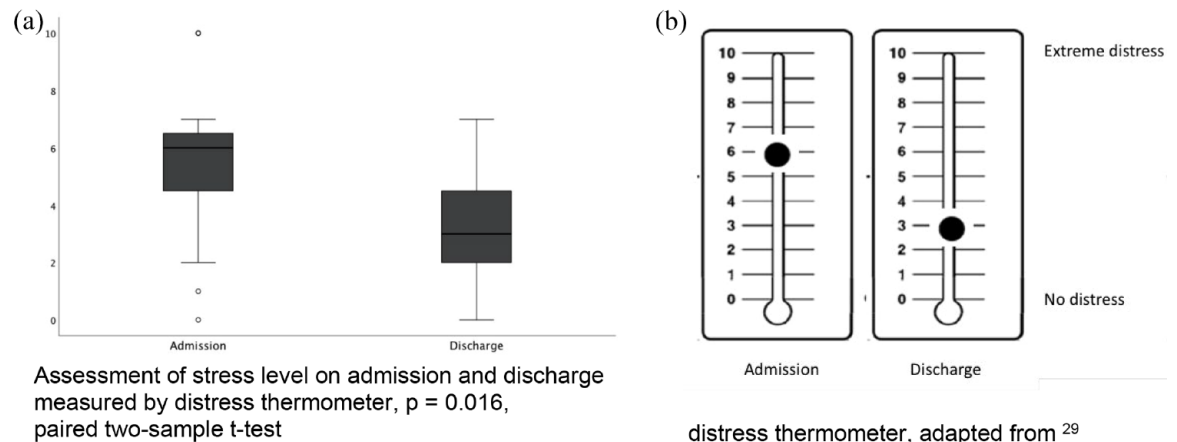


Figure 3. Distress level. (a) Assessment of stress level on admission and discharge measured by distress thermometer, $p=0.016$. (b) distress thermometer. Source: Adapted from Mehnert *et al.*²⁹

with a stable ECOG on admission and at discharge, five with a decrease, and six with an increase. Interestingly, the MIDOS score on admission and at discharge positively correlates with the ECOG score ($r_s=0.558$, $p<0.001$ and $r_s=0.474$, $p=0.35$, respectively). Patients who died during the palliative care treatment presented with a significantly higher ECOG score on admission than the patients who could be discharged (median 3.2 in $n_p=10$ versus 2.5 in $n_p=21$, $p=0.023$).

Distress level

To assess the quality of life and the psychosocial stress level, a visual measurement tool, the distress thermometer was used. After the palliative care treatment, distress levels were significantly reduced from 5.5 to 3.1 [$p=0.016$, $n_p=15$, Figure 3(a) and (b)]. Additional questions revealed an increasing, yet not significant, emotional distress. A high MIDOS score on admission also correlated with a high psychosocial stress level ($r_s=0.356$, $p=0.028$; $n=38$), whereas this correlation was not significant at discharge ($r_s=0.286$, $p=0.250$; $n=18$).

Pain management

Individual pain levels were measured using an 11-point scale (from 0 to 10, where 0 is no pain and 10 is severe pain).³² The median pain level was significantly reduced from median NRS 3 to 0 ($p<0.001$) during the palliative care treatment. Nineteen percent of the patients received no pain

medication at all. Regarding the pain medication during the hospitalization, 75% of the patients received WHO level III medication, morphine and hydromorphone being the most commonly used opioids. Fifty-eight percent of the patients additionally received on-demand opioids for breakthrough pain episodes. Patients who died throughout the hospitalization had lower pain levels on admission, most likely due to already-established pain medication according to WHO level III (Table 4).

Patients' discharge management

Figure 1 gives an overview of the patient's discharge destination. After completing the specialized palliative care treatment, the majority of the patients were discharged home (66%, $n_p=38$), while 9% ($n_p=5$) of patients were transferred to another unit at the Charité – Universitätsmedizin Berlin or to other institutions. In total, 23 out of 43 patients were readmitted after discharge.

Of the 'end-of-life care' patients, 3% ($n_p=2$) were transferred to hospices, and 22% ($n_p=13$) of our mRCC patients died in the palliative care unit due to their advanced disease.

There is a potentially strong bias in our analysis due to the incomplete data acquisition of patients who died during their treatment in the palliative care unit. To address this issue, we compared the symptom burden, performance status, distress, and pain at rest for patients who were discharged again and patients who died in our palliative care unit.

The symptom burden and ECOG score in patients who died were significantly higher than in patients who did not die, whereas no significant difference was observed for distress and pain at rest (Table 4).

Discussion

Main results of the study

This retrospective analysis examines the symptom burden and the course of symptoms in 58 patients with mRCC who received an inpatient, specialized palliative care treatment at the Charité – Universitätsmedizin Berlin between 2011 and 2017. The available data demonstrate that a specialized inpatient palliative medical treatment can significantly reduce the burden of symptoms (measured by the MIDOS) and distress (measured by the distress thermometer), especially with regard to pain levels.

As modern therapies, including TKI and immune CI, have significantly extended the survival of mRCC patients in the past decade, long-term care to treat the considerable symptoms has become increasingly important, especially with chronic disease courses. Accordingly, it is of high relevance to provide these patients with appropriate, specialized palliative care. So far, only limited data are available on this specific group of patients suffering from mRCC. Moreover, there is a lack of integration of palliative care in the treatment of individuals with genitourinary cancers.³³ To our knowledge, no prospective studies, especially no randomized controlled trials have been conducted. Since the importance of palliative care for other advanced oncological diseases has been well documented, this analysis focused on understanding the symptom burden and the quality of life in mRCC, as well as examining the influence of a specialized inpatient palliative care treatment in this particular context.

In general, early palliative care treatment in the course of disease is preferable. In our cohort, it took an average of 83 months after the initial RCC diagnosis, that is, almost 7 years, until the implementation of an inpatient specialized palliative care treatment. This is mainly due to the significantly extended PFS and OS in the context of the constantly newly developed therapies and targeted individual treatment options for patients with mRCC. Repetitive treatments on our inpatient palliative care unit (two on average) suggest

that the first inpatient stay had a positive effect on the symptom burden and that the patients accordingly also consented to further specialized palliative treatment.

An interdisciplinary and multi-professional treatment approach for rapid symptom relief is one of the main challenges in palliative care. This is aimed to possibly discharge the patients back into their home environment. In our analysis, this succeeded in 66% of the patients. In a small proportion of the patients, however, the disease and its symptoms progressed rapidly despite the highly specialized measures so that discharge home was not possible. These patients were deceased in the palliative care unit (22%) or were transferred to a hospice (3%). Possible reasons could be the higher symptom burden already at admission, an especially aggressive or advanced disease, or a delayed palliative medical care treatment. The average length of the hospitalization of around 12 days corresponds to the desired, rather short length of stay in a palliative care unit.

To describe the multidimensional needs of the patients, there are a number of suitable methods to choose from. The use of different standardized measurement methods in combination, as it is done in our setting with the PBA, ensures the standardized recording of the situation at the beginning of a palliative treatment. The MIDOS can be recommended for palliative care patients due to its low workload, low time expenditure, and high participation rates for repeated self-assessment of problems and symptoms.²⁶ Moreover, the MIDOS single item on well-being correlated significantly with the quality of life indexes of the EORTC.³⁴ As expected, there was an improvement in the symptom burden, measured by the decrease in the MIDOS score, as a result of the specialized inpatient palliative medical treatment. A similar effect was shown for a cohort of sarcoma patients receiving inpatient palliative treatment.³⁵

In our patient cohort, the most frequently reported symptoms were fatigue and exhaustion, followed by weakness and the need for help with ADL, similar to the results by Bergerot *et al.*³⁶ and Harding *et al.*,³⁷ reflecting that mRCC is a disease that is often associated with a pronounced feeling of illness and systemic symptoms. Harding *et al.*³⁷ found that among patients with advanced disease, the five most frequently reported symptoms came from items reporting fatigue (82%),

weakness (65%), worry (65%), shortness of breath (53%), and irritability (53%).

Considering the intensity of the complaints, we were able to demonstrate the desired therapeutic effect in a statistically significant manner. In the present patient population, depression was the only complaint of the MIDOS questionnaire that increased over time, probably due to the more focused confrontation with the disease. A previous meta-analysis by Fulton *et al.*³⁸ has shown that psychotherapy in palliative care units may reduce the symptoms of depression, encouraging even more frequent psycho-oncological counseling.³⁸

The distress thermometer is another tool used in our work to assess the quality of life. Several studies demonstrated a positive correlation between moderate and severe stress on the distress scale with a lower quality of life for patients with different cancer entities.^{39,40} In the present cohort of patients with mRCC, a clear improvement in quality of life during palliative medical treatment could be observed with the improvement of the MIDOS score and the distress thermometer scale. Other studies with different cancer entities have also shown a higher quality of life through appropriate palliative medical treatments compared to standard care. It was noteworthy that this was shown without improvements in symptom intensity scores.⁴¹⁻⁴³ In contrast to our setting, these data also included randomized trials.

It is well documented that cancer-related pain is relevant in ~70% of all patients. Therefore, adequate pain therapy during the disease is also of great importance for patients with mRCC.⁴⁴ Fortunately, pain was significantly alleviated during the specialized palliative medical treatment in our patient group. A special feature of our cohort was the relatively low pain intensity at the time of admission (median 3, NRS) with an even further significant reduction in pain intensity (0/10 NRS, median) at discharge. The initially low-level pain intensity suggests that many patients had already taken analgesia according to WHO level III at admission, with even further optimization throughout the inpatient stay. One can also assume that patients with chronic pain often underestimate their actual pain level and that this contributes to the relatively low reported pain intensity at admission. In addition to adequate pain medication, other factors implemented by the specialized palliative care treatment such as

intensified individual support including psycho-oncological counseling or specialized care treatments soft tissue manipulation, heat, and massages help to reduce the pain level. A reduction in the psychosocial stress level also influences the perception of pain. As reviewed by Liu *et al.*,⁴⁵ a holistic treatment plan is most beneficial for an optimal and multidimensional treatment of cancer pain. One should also keep in mind that the assessment of the pain intensity is a subjective parameter that should be continuously assessed throughout the disease.

Furthermore, this work shows a statistically significant correlation between the MIDOS score, the ECOG, and the intensity of distress. Patients with a high symptom burden show the highest mean values in the ECOG, or distress thermometer. Differences in the MIDOS score, the ECOG, and the distress become apparent when comparing patients who were discharged and patients who were deceased on the palliative care ward. As expected, the deceased patients reported a higher symptom burden on admission, were more limited in their everyday skills, and had a lower quality of life than the group of patients who were later discharged from the palliative care unit.

With regard to the limitations of the study, our retrospective analysis is a monocentric analysis over only a limited period of time and with only a limited number of patients observed. Furthermore, some limitations are due to incomplete data collection, as unfortunately not all patients had filled out the PBA completely. Missing data at least partially arose from the often times restricted ability of self-assessment, due to the high physical and psychological symptom burden, but also due to the death of some patients. Accordingly, there is a loss of their data, especially with regard to the questionnaire upon discharge. There is a strong bias in the analysis due to the missing data of the deceased patients, as previously described by Diehr and Johnson,⁴⁶ Hussain *et al.*⁴⁷ To counteract any distortion of the evaluation, the cases with missing data were excluded from the analysis, as described in the method section.

El-Jawahri *et al.*¹⁸ have also described these challenges in palliative care research, which is hampered by methodological challenges related to attrition and missing data due to progressive illness and death. The described data gap does not allow any evaluation of the data from the deceased. A survival bias thus limits the informative value of

this analysis. To be able to evaluate the benefits of the specialized palliative medical treatments even better, data collection throughout the inpatient treatment could be performed regularly to minimize this bias.

Previous studies on palliative medical treatments are difficult to evaluate due to the different study designs. Most studies are not focusing on specialized inpatient palliative care, but rather on certain criteria, such as psychosocial and spiritual advice, home care, care coordination as well as advice and training for caring relatives.^{18,43,48,49}

Despite these limitations, our results do strongly support the accumulating evidence that palliative care treatments do improve patients' quality of life, satisfaction with care, and end-of-life outcomes, thereby further contradicting studies that show little evidence for the effectiveness of palliative care treatment.¹⁸ While several studies, which have examined the quality of life as a primary outcome, have reported a statistically significant difference favoring the palliative care treatments, data so far were lacking to support the benefit of palliative treatments for reducing physical and psychological symptoms of mRCC patients and can now be provided by us for the first time.^{41,42}

It is well established that an early integration of palliative care leads to more effective use of hospice and palliative structures as the disease progresses and may, among other things, contribute to avoiding unnecessary inpatient admissions, intensive care measures, and invasive tumor therapies at the end of life.⁵⁰ In our patient cohort, the first palliative care contact was established on average after 83 months, which is most likely due to the slow dynamics of mRCC and the effective therapeutic options. Nevertheless, the combination of standard oncological therapy and palliative care could have been offered earlier to all patients and might have even further improved the symptoms resulting from advanced tumor disease.

Conclusion

Overall, the care of patients with advanced cancer requires special resources, such as time and expertise, which are often limited in the standardized peripheral care setting. This emphasizes the need for a highly qualified, multi-professional palliative medical care team to address effective

symptom control. Specialized palliative care teams carry out systematic symptom assessments with standard tools such as the MIDOS, distress thermometer, and NRS and document them regularly. The patients have access to a multi-professional team that is able to act interprofessional not only with physical but also with emotional, functional, social, and spiritual problems. Palliative care can also help prepare patients and their families for post-discharge challenges. Palliative medicine not only treats but also evaluates symptoms and offers psychosocial support for patients and their families. The patient's personal goals for further treatment are identified and integrated into the therapy concepts.

Our data show the positive impact of a specialized palliative care treatment with a multi-professional approach in patients with mRCC. Further analyses are necessary to answer questions concerning possible improvement of symptom relief, quality of life, and even OS through consistent early integration of palliative care in mRCC patients. A standardized and early screening for physical and psychological symptoms should therefore be integrated into medical care throughout the disease to identify patients with special need for intensified support.

Declarations

Author's note

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Patients were included with institutional review board approval and written patient informed consent in accordance with the local ethical guidelines. The Charité Ethics Committee approved the study, operation number: EA2/157/15, Geschäftsstelle Ethikkommission, Charitéplatz 1, 10117 Berlin, Germany.

Consent for publication

Not applicable.

Author contributions

Anne Dörr: Conceptualization; Data curation; Visualization; Writing – original draft.

Insa Vogel: Data curation; Formal analysis; Methodology; Visualization; Writing – review & editing.

Friedrich Wittenbecher: Writing – review & editing.

Jörg Westermann: Writing – review & editing.

Peter Thuss-Patience: Methodology; Supervision; Writing – review & editing.

Johann Ahn: Writing – review & editing.

Uwe Pelzer: Writing – review & editing.

Juliane Hardt: Data curation; Methodology; Supervision; Validation; Writing – review & editing.

Lars Bullinger: Supervision; Writing – original draft.

Anne Flörcken: Conceptualization; Funding acquisition; Supervision; Writing – review & editing.

Acknowledgements

Many thanks to all participating patients and their families, as well as to the treating nurses and doctors.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.


Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data supporting the results reported in the article are available from the authors upon reasonable request and with permission of Charité – Universitätsmedizin Berlin, a corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and the Berlin Institute of Health, Department of Hematology, Oncology, and Tumor Immunology, Campus Virchow-Klinikum, Berlin, Germany.

ORCID iDs

Anne Dörr  <https://orcid.org/0009-0005-4464-307X>

Johann Ahn  <https://orcid.org/0000-0002-5631-4143>

Anne Flörcken  <https://orcid.org/0000-0001-6462-7214>

Supplemental material

Supplemental material for this article is available online.

References

1. Leitlinienprogramm Onkologie. (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms, Langversion 4.0, 2023, AWMF-Registernummer: 043-017OL, <https://www.leitlinienprogramm-onkologie.de/leitlinien/nierenzellkarzinom/>.
2. Abara E, Chivulescu I, Clerk N, *et al.* Recurrent renal cell cancer: 10 years or more after nephrectomy. *Can Urol Assoc J* 2010; 4: E45.
3. Motzer RJ, Jonasch E, Agarwal N, *et al.* Kidney Cancer, Version 3.2022. *J Natl Compr Canc Netw* 2022; 20: 71–90.
4. Schmid TA and Gore ME. Sunitinib in the treatment of metastatic renal cell carcinoma. *Ther Adv Urol* 2016; 8: 348–371.
5. Motzer RJ, Hutson TE, Cella D, *et al.* Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med* 2013; 369: 722–731.
6. Heng DY, Xie W, Regan MM, *et al.* External validation and comparison with other models of the international metastatic renal-cell carcinoma database consortium prognostic model: a population-based study. *Lancet Oncol* 2013; 14: 141–148.
7. Choueiri TK, Powles T, Burotto M, *et al.* Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2021; 384: 829–841.
8. Rini BI, Plimack ER, Stus V, *et al.* Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019; 380: 1116–1127.
9. Motzer R, Alekseev B, Rha S-Y, *et al.* Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med* 2021; 384: 1289–1300.
10. Motzer RJ, Penkov K, Haanen J, *et al.* Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019; 380: 1103–1115.

11. Motzer RJ, Tannir NM, McDermott DF, *et al.* Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018; 378: 1277–1290.
12. American Cancer Society. Survival rates for kidney cancer, <https://www.cancer.org/cancer/kidney-cancer/detection-diagnosis-staging/survival-rates.html> (2024, accessed 26 May 2020).
13. Escudier B, Porta C, Schmidinger M, *et al.* Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019; 30: 706–720.
14. Gray RE and Harris GT. Renal cell carcinoma: diagnosis and management. *Am Fam Physician* 2019; 99: 179–184.
15. Williams G, Pazdur R and Temple R. Assessing tumor-related signs and symptoms to support cancer drug approval. *J Biopharm Stat* 2004; 14: 5–21.
16. WHO. Palliative care, <https://www.who.int/news-room/fact-sheets/detail/palliative-care> (2020, accessed 6 March 2024).
17. Temel JS, Greer JA, Muzikansky A, *et al.* Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; 363: 733–742.
18. El-Jawahri A, Greer JA and Temel JS. Does palliative care improve outcomes for patients with incurable illness? A review of the evidence. *J Support Oncol* 2011; 9: 87–94.
19. Ferrell BR, Temel JS, Temin S, *et al.* Integration of palliative care into standard oncology care: American Society of Clinical Oncology Clinical Practice Guideline update. *J Clin Oncol* 2017; 35: 96–112.
20. Mulvey CL, Smith TJ and Gourin CG. Use of inpatient palliative care services in patients with metastatic incurable head and neck cancer. *Head Neck* 2016; 38: 355–363.
21. Napolskikh J, Selby D, Bennett M, *et al.* Demographic profile and utilization statistics of a Canadian inpatient palliative care unit within a tertiary care setting. *Curr Oncol* 2009; 16: 49–54.
22. Lec PM, Lenis AT, Brisbane W, *et al.* Trends in palliative care interventions among patients with advanced bladder, prostate, or kidney cancer: a retrospective cohort study. *Urol Oncol* 2020; 38: 854.e1–854.e9.
23. Gleißner J. Palliativmedizin im ambulanten urologischen Arbeitsalltag. *Aktuel Urol* 2019; 50: 179–183.
24. MDCalc. Memorial Sloan-Kettering Cancer Center (MSKCC/Motzer) score for metastatic renal cell carcinoma (RCC), <https://www.mdcalc.com/calc/2153/memorial-sloan-kettering-cancer-center-mskcc-motzer-score-metastatic-renal-cell-carcinoma-rcc> (2005–2024, accessed 8 March 2024).
25. German Guideline Programme in Oncology (German Cancer Society, German Cancer Aid, AWMF): Palliative care for patients with incurable cancer, short version 1.1, 2015 AWMF-registration number 128/001OL, <http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html>.
26. Stiel S, Matthes ME, Bertram L, *et al.* Validierung der neuen Fassung des Minimalen Dokumentationssystems (MIDOS2) für Patienten in der Palliativmedizin. *Schmerz* 2010; 24: 596–604.
27. Storek B, Behzadi A, Gockel M, *et al.* Entwicklung eines klinikübergreifenden standardisierten palliativmedizinischen Basisassessment (PBA)-Bogens des Arbeitskreises der Berliner und Potsdamer Palliativstationen zur Qualitätsverbesserung und Identifikation neuer Ansätze von Komplexbehandlungen. *Zeitschrift für Palliativmedizin* 2012; 13: KT_46.
28. Radbruch L, Sabatowski R, Loick G, *et al.* [MIDOS – validation of a minimal documentation system for palliative medicine]. *Schmerz* 2000; 14: 231–239.
29. Mehnert A, Müller D, Lehmann C *et al.* Die deutsche Version des NCCN Distress-Thermometers. *Zeitschrift für Psychiatrie, Psychologie und Psychotherapie* 2006; 54: 213–223.
30. von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61: 344–349.
31. Turner JS, Cheung EM, George J, *et al.* Pain management, supportive and palliative care in patients with renal cell carcinoma. *BJU Int* 2007; 99: 1305–1312.
32. Farrar JT, Young JPJ, LaMoreaux L, *et al.* Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; 94: 149–158.
33. Saraiya B, Dale W, Singer EA, *et al.* Integration of palliative and supportive care into the management of genitourinary malignancies. *Am Soc Clin Oncol Educ Book* 2022; 42: 1–10.

34. Stiel S, Psych D, Kues K, *et al.* Assessment of quality of life in patients receiving palliative care: comparison of measurement tools and single item on subjective well-being. *J Palliat Med* 2011; 14: 599–606.
35. Brandes F, Striefler JK, Dörr A, *et al.* Impact of a specialised palliative care intervention in patients with advanced soft tissue sarcoma – a single-centre retrospective analysis. *BMC Palliat Care* 2021; 20: 16.
36. Bergerot CD, Clark KL, Ashing KT, *et al.* Biopsychosocial distress and clinical outcome in metastatic renal cell carcinoma. *Palliat Support Care* 2019; 17: 353–355.
37. Harding G, Cella D, Robinson D, *et al.* Symptom burden among patients with Renal Cell Carcinoma (RCC): content for a symptom index. *Health Qual Life Outcomes* 2007; 5: 34.
38. Fulton JJ, Newins AR, Porter LS, *et al.* Psychotherapy targeting depression and anxiety for use in palliative care: a meta-analysis. *J Palliat Med* 2018; 21: 1024–1037.
39. Head BA, Schapmire TJ, Keeney CE, *et al.* Use of the Distress Thermometer to discern clinically relevant quality of life differences in women with breast cancer. *Qual Life Res* 2012; 21: 215–223.
40. Ghazali N, Roe B, Lowe D, *et al.* Screening for distress using the distress thermometer and the University of Washington Quality of Life in post-treatment head and neck cancer survivors. *Eur Arch Otorhinolaryngol* 2017; 274: 2253–2260.
41. Rummans TA, Clark MM, Sloan JA, *et al.* Impacting quality of life for patients with advanced cancer with a structured multidisciplinary intervention: a randomized controlled trial. *J Clin Oncol* 2006; 24: 635–642.
42. Bakitas M, Lyons KD, Hegel MT, *et al.* Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. *JAMA* 2009; 302: 741–749.
43. Linn MW, Linn BS and Harris R. Effects of counseling for late stage cancer patients. *Cancer* 1982; 49: 1048–1055.
44. Neufeld NJ, Elnahal SM and Alvarez RH. Cancer pain: a review of epidemiology, clinical quality and value impact. *Future Oncol* 2017; 13: 833–841.
45. Liu WC, Zheng ZX, Tan KH, *et al.* Multidimensional treatment of cancer pain. *Curr Oncol Rep* 2017; 19: 10.
46. Diehr P and Johnson LL. Accounting for missing data in end-of-life research. *J Palliat Med* 2005; 8(Suppl. 1): S50–S57.
47. Hussain JA, White IR, Langan D, *et al.* Missing data in randomized controlled trials testing palliative interventions pose a significant risk of bias and loss of power: a systematic review and meta-analyses. *J Clin Epidemiol* 2016; 74: 57–65.
48. Rabow MW, Dibble SL, Pantilat SZ, *et al.* The comprehensive care team: a controlled trial of outpatient palliative medicine consultation. *Arch Intern Med* 2004; 164: 83–91.
49. Addington-Hall JM, MacDonald LD, Anderson HR, *et al.* Randomised controlled trial of effects of coordinating care for terminally ill cancer patients. *BMJ* 1992; 305: 1317–1322.
50. Qureshi D, Tanuseputro P, Perez R, *et al.* Early initiation of palliative care is associated with reduced late-life acute-hospital use: a population-based retrospective cohort study. *Palliat Med* 2019; 33: 150–159.