Original Article

Longitudinal Quality of Life in Advanced Cancer Patients: Pilot Study Results from a VA Medical Cancer Center

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Abstract

To document quality-of-life (QOL), symptom distress and Karnofsky Performance Status (KPS) over time, 67 advanced cancer patients completed the Functional Assessment of Cancer Therapy (FACT-G) and Memorial Symptom Assessment Scale - Short Form (MSAS-SF) from the time of determination of no active anti-cancer treatment to death at 3-6 week intervals. The KPS was determined at each time point. Statistical analyses with mixed effects models were performed to examine the association between changes in QOL, symptom distress and KPS at selected time points in the advanced cancer trajectory. Median survival for the population was 115 days, and a median of 5 interviews was completed per patient. Slow steady changes in KPS, MSAS-SF and FACT-G QOL parameters started 6 months prior to death, with accelerated decline in the last 2 to 3 months and dramatic increase in psychological symptoms during the last month. Different domains changed at different rates at different selected time points. The correlation between changes in KPS, FACT-G parameters and MSAS-SF subscales at enrollment and near death suggests that when patients were stable, changes in KPS correlated significantly with changes in sum FACT-G QOL and physical well being, and with changes in the MSAS-SF subscales. However, when patients were near death, changes in KPS did not correlate with any other changes, and only emotional well being reflected changes in physical and psychological symptom distress. The sequence of changes, and how determinants of symptom distress and QOL change over time, may help clinicians assess the prognosis of terminally ill patients and plan appropriate interventions. J Pain Symptom Manage 2003;25:225–235

Key Words

Palliative care, quality of life, symptom distress, KPS, terminal cancer, longitudinal, function

The views expressed herein do not necessarily reflect the views of the Department of Veterans Affairs or of the U.S. Government.

Presented in part at the Annual Scientific Meeting of the American Society of Clinical Oncology in Philadelphia, PA, 1996, and at the Annual Scientific Meeting of the American Pain Society in Fort Lauderdale, Florida, 1999.

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Accepted for publication: April 19, 2002.

0885-3924/03/$–see front matter
PII S0885-3924(02)00641-3

Introduction

Palliative care has been defined by the World Health Organization (WHO) as "the active care of patients whose disease is not responsive to curative treatment," and the goal is to improve the patient's quality-of-life (QOL).[1] However, little is known about the form or interpretation of longitudinal QOL data in patients with advanced cancer, and the application of QOL assessment to palliative care remains a challenge. For advanced cancer patients, it is commonly assumed that an inexorable downhill QOL course will occur when death is approaching.[2] This impression is supported by longitudinal QOL data for advanced cancer patients, most of which derives from hospice settings. Morris and Sherwood analyzed the pattern of change in QOL domains starting up to 13 weeks prior to death and concluded that the decline of QOL is not consistent over time, and occurs most dramatically in the last three weeks of life. In addition, the rate of change was not consistent across physical, social, emotional and pain domains. They also reported that patients experienced significant changes in QOL 12 weeks prior to death, followed by another significant decline in the last few weeks.[3, 4] The dying experience for patients with metastatic colon or lung cancer who participated in the "SUPPORT" study was retrospectively analyzed.[5] Patients experienced worsening QOL as death approached, with a significant decline in their functional status in the last three days.[6] These studies have led to the concept of a rapid decline towards the end of life.

There is a lack of longitudinal QOL data from the medical oncology setting.[7] Ryan analyzed the responses to an expanded version of the Quality of Life Index[8] in sample of veterans with metastatic lung or colon cancer who participated in a VA Cooperative clinical trial from diagnosis to death.[9, 10] Both lung and colon cancer patients experienced a rapid deterioration in QOL during the final six months, as well as increasing psychological distress in the final month. Jordhoy et al.[11] reported a cluster randomized trial to compare the impact of comprehensive palliative care on patients' QOL, with the main end points of physical and emotional functioning, pain, and psychological distress. They concluded that there were no significant differences on any of the QOL scores between comprehensive treatment and control groups during the initial four months of follow-up or during the later assessment (within three months of death). However, this study was not designed to document the changes in QOL over time.

Another concern related to QOL and symptom assessment for advanced cancer patients is the role of Karnofsky Performance Status (KPS).[12] Current clinician assessments of cancer patients are centered on the KPS, a clinician-rated physical and functional status related to the cancer and its' treatment. The KPS is a well-established prognostic factor for survival in advanced cancer patients.[13–18] It has been used widely in clinical settings and in clinical trials to guide patient selection for treatment. Worsening of the KPS usually is considered as a sign of disease progression. However its utility as an outcome measure in palliative care settings is not clear. Schaafsma and Osoba have compared the KPS to the EORTC QLQ-C30 and found that the KPS does not capture multidimensional QOL information.[19]

In order to better define QOL outcomes and to study the role of symptom measures and performance status along the advanced cancer disease trajectory, a longitudinally designed study which can track the changes within KPS, QOL and symptom distress measurements, and assess the association between these different measurements, is needed. In this type of study, missing data points resulting from disease progression are likely and also need to be addressed when analyzing the longitudinal QOL data.[20]

In this paper, we report the results from a longitudinal descriptive QOL study with two main objectives. The first objective was to identify the patterns of changes over time in various QOL, symptom and functional variables. A mixed effect model was used[21] to accommodate the missing data resulting from disease progression. The information obtained from this analysis can lead to the development of an overall longitudinal QOL model for advanced cancer patients. The second objective was to perform an exploratory analysis to examine the association among changes in KPS, changes in symptom distress, and changes in QOL at selected time points. The association among these changes may provide useful clinical informa-

tion in interpreting the KPS, QOL and symptom distress results along the disease trajectory.

Methods

Conceptual Approach

We adapted the QOL definition proposed by Cella and colleagues,[22] and modified it based on the conceptual model proposed by Gill and Feinstein[23] and by Wilson and Cleary[24] to study the broader QOL construct longitudinally at a VA Medical Center. "QOL refers to patients' appraisal of, and satisfaction with, their current level of functions as compared to what they perceive to be possible of ideal."[22] Furthermore, the QOL is a reflection of the way that patients perceive and react to their health status,[23] which may be affected by clinical factors such as disease status, biological factors, physical and psychological symptom status, and functional level.[24] This approach has been used by other investigators.[25]

Patient Selection and Instruments

In this prospective, longitudinal study, patient recruitment took place between May, 1994 and December, 1995 at the VA New Jersey Health Care System at East Orange (VANJHCS). The VANJHCS is the sole tertiary care teaching hospital, which provides Hematology/Oncology services for veterans residing in the State of New Jersey. Most cancer patients treated by the Hematology/Oncology section are followed from referral to death.

The Institutional Review Board approved the study and all patients signed informed consent before participating. Patients with incurable disease after failure of standard and/or experimental systemic therapy were eligible for this study. All the patients were followed by the same oncology palliative care team at VA New Jersey Health Care System and received intensive pain and symptom management and palliative radiation therapy when indicated. Pain management information has been reported elsewhere.[26] Moribund or delirious patients who were not able to fill out the questionnaires were excluded. Initial assessment included age, sex, marital status, primary site, KPS, FACT-G and MSAS-SF. Patients were then reassessed every 3–6 weeks with the KPS, FACT-G and MSAS-SF until death; patients could refuse an interview if they felt too ill to answer questions.

The KPS is an 11-point rating scale ranging from 0–100 (0 = dead, 100 = normal function) that assesses patients' physical functional level related to cancer and its treatment. The principal investigator (SSH) and Co-PI (VTC) assessed the patient's KPS at each time point. A separate person (CC) administered the symptom and QOL instruments, and the health caregivers did not know these results.

The Functional Assessment of Cancer Therapy (FACT-G)[27] (Version 3) is a validated 28-item general patient-rated measure of quality of life for cancer patients with any tumor type. Each item is scored from 0 to 4, anchored from "not at all" to "very much." There are 5 subscales: Functional Well-Being (FWB) (7 items), Physical Well-Being (PWB) (7 items), Social/Family Well-Being (SFWB) (7 items), Relationship with MD (RMD) (2 items), and Emotional Well-Being (EWB) (5 items). The sum of FACT-G subscales (SUMQOL) score ranges from 0 to 112. The FACT-G has been used widely in clinical trials, is easy to complete, and has demonstrated sensitivity according to performance status and extent of disease.

The Memorial Symptom Assessment Scale - Short Form (MSAS-SF)[28] is a validated patient-rated instrument in which patients rate symptom frequency or distress for 32 highly prevalent physical and psychological symptoms. Each symptom is scored from 0 to 4 ranging from "no symptom" to "very much." MSAS-SF subscales include: the Global Distress Index (GDI) measuring 4 psychological symptoms (feeling sad, worrying, feeling irritable, and feeling nervous) and 6 physical symptoms (lack of energy, pain, lack of appetite, feeling drowsy, constipation, dry mouth). The Physical Symptom distress score (PHYS) comprises 12 prevalent physical symptoms: lack of energy, pain, lack of appetite, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated, and dizziness. The Psychological Symptom distress score (PSYCH) includes 6 prevalent psychological symptoms: worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable, and difficulty concentrating. The number of symptoms (NS) is derived from screening for the presence of 32 symptoms at each interview. The validity of

Table 1
Demographic and Clinical Characteristics

Characteristic	*n*	%
Gender		
Male	65	97
Female	2	3
Race		
White	35	52
Black	31	46
Hispanic	1	2
Cancer Diagnosis		
Lung	24	36
Prostate	16	24
Colorectal	11	17
Bladder	3	4
Esophagus	3	4
Sarcoma	2	3
Gastric	2	3
Pancreatic	2	3
Other	4	6
Previous Cancer Treatment Received Prior to Study Participation		
Chemotherapy and Radiation	24	36
Chemotherapy only	21	31
Hormonal Therapy + Chemotherapy + Radiation	9	13
Hormonal Treatment and radiation	7	10
Radiation only	5	7
Chemotherapy + Radiation + Bone Marrow Transplantation	1	2
Used Analgesics at Day 1		
Number of patients	38	57
MEDD (median, range)	60 mg	10 mg–16,000 mg

MEDD: Morphine equivalent daily dose orally

the MSAS-SF and FACT-G instruments in our patients has been demonstrated.[29]

Statistical Analyses

Demographic data, instrument completion rates and missing data points are summarized and tabulated in Tables 1 and 2. Four intervals were defined relative to the time of death: 1 month (20–40 days), 2 months (50–70 days), 3 months (75–100 days) and 6 months (165–191 days). The median scores for MSAS-SF, and FACT-G subscale were calculated for the groups at the four selected time points (Table 3). Rates and patterns of change over time in symptom distress, KPS, and QOL dimensions were estimated with a mixed effects model. The mixed effects model was chosen because it allows the timing and number of assessments to differ across patients, as well as the inclusion of time-varying covariates, and appropriately adjusts variance estimates for the correlation of repeated observations from the same patient. The rate of change in QOL, KPS and symptom distress was estimated by fitting piecewise linear mixed effects models that were allowed to vary at 6, 3, 2 and 1 months prior to death, with days prior to death as the explanatory variable. While the terminal phase of a patient's life is probably more complex, the assumptions of linear changes over short periods of time provides us with a useful approach for examining the patterns of change. A backward elimination procedure was used to select a more parsi-

Table 2
Instrument Completion and Missing Data Points

Number of Missing Data Points	Number of Patients	%
Patients who expired at time of analysis	54	80
No missing data point	40	60
1 missing data point prior to death	5[a]	7
2 missing data points prior to death	6[b]	9
Lost to follow-up	3[c]	4
Patients still alive at time of analysis	13	20
No missing data points	11	17
Lost to follow-up	2[d]	3

Reason for missing data points prior to death:
[a]Physical deterioration (2 patients), mental confusion (2 patients) and relocation (1 patient).
[b]Poor physical condition (3 patients), mental confusion (2 patients) and refusal (1 patient).
[c]One patient lost to follow-up for up to 480 days and two patients were lost to follow-up during the study participation, but then came back again for the last two interviews.
[d]Refused further interviews after 6 months of study participation.

Table 3
QOL, Symptom Distress, and KPS at 6 Months, 3 Months, 2 Months and 1 Month Prior to Death

	6 Months		3 Months		2 Months		1 Month	
FACT-G QOL[a]	$n = 16$ Median	Range (25%–75%)	$n = 32$ Median	Range (25%–75%)	$n = 39$ Median	Range (25%–75%)	$n = 41$ Median	Range (25%–75%)
PWB	25	22–28	21	18–26	20	16–25	19	12–22
EWB	20	16–20	18	16–20	19	16–20	18	15–19
SFWB	25	21–28	25	20–28	25	21–28	23	17–28
FWB	18	14–22	16	11–21	14	11–20	11	8–15
SUMQOL	94	86–99	83	74–98	83	73–94	75	61–87
MSAS-SF[b]								
PHYS	0.33	0.20–0.83	0.9	0.60–1.26	1.13	0.80–1.60	1.53	1.00–1.93
PSYCH	0.30	0.00–0.58	0.33	0.00–0.97	0.67	0.27–1.33	0.67	0.00–1.38
GDI	0.38	0.26–0.97	1.00	0.60–1.39	1.20	0.68–1.80	1.36	1.06–2.08
NS	7	6–12	10	5–13	11	8–14	12	12–14
KPS	80	70–80	60	50–70	60	40–60	40	30–50

Median duration from interview to death: 1 month—median 28 days (range 20–40 days), 2 months—median 58 days (range 50–70 days), 3 months—median 88 days (range 75–110 days), 6 months—median 178 days (range 165–191 days).
The interquartile range is reported, where the lower value is the 25th percentile and the upper value is the 75th percentile of the total range.
[a]Functional Assessment of Cancer Therapy (FACT-G) parameters: PWB—physical wellbeing, EWB—emotional wellbeing, SFWB—social/family wellbeing, FWB—functional wellbeing, SUMQOL—total sum of FACT-G QOL subscales.
[b]Memorial Symptom Assessment Scale—Short Form (MSAS-SF) subscales: PHYS—physical symptom distress, PSYCH—psychological symptom distress, GDI—global distress index, NS—number of symptoms.

monious model for the data. Results of these analyses are illustrated in Table 4 and Fig. 1.

In any longitudinal QOL study with extensive morbidity and/or mortality, there is concern about missing data. In this mixed effects model, we have assumed that the data are missing at random conditional on the observed data and the days prior to death. For example, we are assuming that if there were two patients who were 3 weeks from death and had reported the same scores previously, the one with the poorer QOL at 3 weeks would not be more likely to have a missing assessment. If that assumption is untrue, the rates of change over time are likely to be underestimated.[30, 31]

To compare changes between the initial period and the last period, we defined the initial period as the first two initial assessments upon

Table 4
Estimated Rate of Change Per Month During the Last Six Months of Life

	Months Prior to Death			
	3–6 months Est (s.e.)	2–3 months Est (s.e.)	1–2 months Est (s.e.)	0–1 months Est (s.e.)
Continuous Change				
FACT-G EWB	−0.42 (0.07)	−0.42 (0.07)	−0.42 (0.07)	−0.42 (0.07)
MSAS-SF Number of symptoms	1.00 (0.12)	1.00 (0.12)	1.00 (0.12)	1.00 (0.12)
Changes at 2 months				
FACT-G SUMQOL	−1.68 (0.46)	−1.68 (0.46)	−6.37 (1.31)	−6.37 (1.31)
FACT-G FWB	−0.83 (0.21)	−0.83 (0.21)	−4.52 (1.09)	N.S.S.
FACT-G PWB	−0.82 (0.55)	−0.82 (0.55)	−2.14 (0.57)	−2.14 (0.57)
KPS	−5.48 (0.55)	−5.48 (0.55)	−14.95 (1.69)	−14.95 (1.69)
MSAS-SF PHYS	0.12 (0.02)	0.12 (0.02)	0.33 (0.06)	0.33 (0.06)
Changes at 3 months				
MSAS-SF GDI	0.12 (0.03)	0.26 (0.04)	0.26 (0.04)	0.26 (0.04)
Changes at 1 and 3 months				
MSAS-SF PSYCH	N.S.S.	0.12 (0.05)	0.12 (0.05)	0.60 (0.19)
No change				
FACT-G SFWB	N.S.S.	N.S.S.	N.S.S.	N.S.S.

N.S.S.—not statistically significant, Est.—estimate, s.e.—standard error.
Functional Assessment of Cancer Therapy (FACT-G) parameters: PWB—physical wellbeing, EWB—emotional wellbeing, SFWB—social/family wellbeing, FWB—functional wellbeing, SUMQOL—total sum of FACT-G QOL subscales.
Memorial Symptom Assessment Scale—Short Form (MSAS-SF) subscales: PHYS—physical symptom distress, PSYCH—psychological symptom distress, and GDI—global distress index.

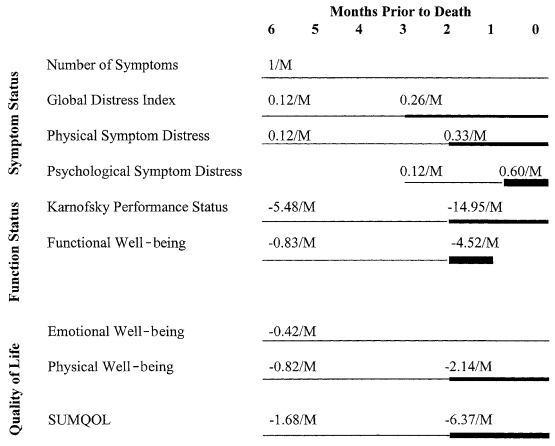

Fig. 1. Longitudinal terminal decline QOL model: Summary of rates and patterns of change in QOL and symptom distress in the last six months of life.

study enrollment, with the second assessment performed at least more than 30 days prior to death. The last period consisted of the last two assessments for patients who had completed at least three assessments, with the last assessment performed within 30 days of death. Changes within individuals in MSAS-SF parameters, KPS and total FACT-G scores were calculated in both the initial period and last period. The Pearson univariate correlation was used to examine the relationship between the changes in QOL, changes in KPS and changes in MSAS-SF subscales for both periods. Results are summarized in Tables 5 and 6.

To examine the association between symptom distress and QOL, changes in SUMQOL at 6, 3, 2, and 1 months prior to death were examined by using a mixed effect model. Symptom distress and worst pain were included as time-varying covariates.

Results

Patient Characteristics and Instrument Completion

Sixty-seven consecutive eligible patients participated and were followed at 3–6 week intervals until the time of their death. Demographic data and previous anti-cancer treatment information are summarized in Table 1. At time of analysis, 54 patients had expired. The median number of interviews was 5 (range 1–22) and the median length of survival was 115 days (range 2–583 days). Thirteen patients were still alive, with a median number of interviews of 21 (10–28). The joint mixed effect model included all 67 patients. The median age of the patients was 65 years (range 28–89), and the median education level was 12th grade (range 2–18). The instrument completion and missing data points are summarized in Table 2.

At the initial interview, 38 patients (57%) received analgesics for pain control, with median morphine equivalent daily dose (MEDD) of 60 mg (range 10–16,000 mg orally). During the study participation period, 61 patients (91%) received analgesics, with a median total number of pain medication used for each patient of 2 (range 0–4) and a medium maximum MEDD for each patients of 180 mg (range 0–16,000 mg) orally. Forty-four (66%) patients received adjuvant analgesics and 25 patients (37%) received radiation for pain palliation. Hormonal treatment was continued for prostate cancer patients as standard practice; no other patients received any chemotherapy after study participation.

QOL, Symptom Distress, and KPS

The MSAS-SF, KPS and FACT-G measures at 6, 3, 2 and 1 months prior to death are summarized in Table 3. We used the mixed effect model to estimate the rate of change per month in each parameter and to identify the patterns of change during the last 6 months of life in QOL, symptom distress and functional domain (Table 4). The longitudinal terminal decline QOL model was generated from these results and is illustrated in Fig. 1. The thickness of the line represents the changes of the estimated rate of change for each measure at certain time point.

Symptom Dimension. The MSAS-SF symptom distress started to change at 6 months prior to death. The number of symptoms continuously changed at a steady rate over 6 months. There was a significant acceleration in the deterioration of each symptom distress score 2 to 3 months prior to death. The rate of increase of the GDI doubled from 0.12/month to 0.26/month 3 months prior to death. The PSYCH started to increase by 0.12/month steadily from 3 months, with a significant increment by 5

Table 5
Correlation Among Changes in QOL, KPS and Changes in Symptom Distress Scores in Initial Period (n = 45)

	Changes in SUMQOL	Changes in PWB	Changes in EWB	Changes in FWB	Changes in PHYS	Changes in PSYCH	Changes in GDI	Changes in KPS
Changes in SUMQOL	1.00							
Changes in PWB	0.68[a]	1.00						
Changes in EWB	0.43[b]	0.17	1.00					
Changes in FWB	0.83[a]	0.50[a]	0.14	1.00				
Changes in PHYS	−0.11	−0.35[c]	0.07	−0.10	1.00			
Changes in PSYCH	−0.10	−0.16	−0.17	0.03	0.53[a]	1.00		
Changes in GDI	−0.25	−0.43[b]	−0.15	−0.11	0.84[a]	0.74[a]	1.00	
Changes in KPS	0.36[c]	0.43[b]	0.13	0.31	−0.46[b]	−0.40[b]	−0.55[a]	1.00

Pearson correlation coefficients, [a]$p < 0.001$, [b]$p < 0.01$, [c]$p < 0.05$
Initial Period: First two initial assessments upon study enrollment and the second assessment was performed at least more than 30 days prior to death. Duration from 2nd interview to death: median 113 days, (range 30–400 days).
Memorial Symptom Assessment Scale—Short Form (MSAS-SF) subscales: PHYS—physical symptom distress, PSYCH—psychological symptom distress, and GDI—global distress index.
Functional Assessment of Cancer Therapy (FACT-G) parameters: PWB—physical wellbeing, EWB—emotional wellbeing, FWB—functional wellbeing, SUMQOL—total sum of FACT-G QOL subscales.

times in the final month to 0.60/month. The rate of increase in PHYS nearly tripled in the last 2 months from 0.12/month to 0.33/month.

Functional Status. Two measures provided a functional status assessment: KPS, and FACT-G FWB. The KPS and FWB started to change 6 months prior to death, with an accelerated decline in the last two months (KPS from −5.48/month to −14.95/month, FWB from −0.83/month to −4.52/month). There is a floor effect for FWB at 1 month prior to death.

Overall QOL. In the domains of QOL as measured by FACT-G, SFWB remained unchanged over time; the EWB, PWB, and SUMQOL began to change 6 months prior to death. Changes in PWB and SUMQOL scores at 2 months prior to death were 3 to 5 times faster than in the first 4 months (SUMQOL from −1.68/month to −6.37/month, PWB from −0.82/month to −2.14/month,). The EWB demonstrated steady change each month over time at −0.42/month.

In summary, symptom distress, functional status and QOL all demonstrated steady deterioration from 6 months prior to death, with significant acceleration in the last 2–3 months prior to death. Each measurement demonstrated its own pattern of acceleration.

Relationships Between Changes in QOL and Changes in Symptom Distress

For the 54 patients who expired, there were 45 patients with two assessments in the initial period and 31 patients with two assessments in

Table 6
Correlation Among Changes in QOL, KPS and Changes in Symptom Distress Scores in Last Period (n = 31)

	Changes in SUMQOL	Changes in PWB	Changes in EWB	Changes in FWB	Changes in PHYS	Changes in PSYCH	Changes in GDI	Changes in KPS
Changes in SUMQOL	1.00							
Changes in PWB	0.74[a]	1.00						
Changes in EWB	0.50[b]	0.20	1.00					
Changes in FWB	0.68[a]	0.30	0.08	1.00				
Changes in PHYS	−0.41[c]	−0.50[b]	−0.43[c]	0.02	1.00			
Changes in PSYCH	−0.22	−0.14	−0.41[c]	−0.20	0.33	1.00		
Changes in GDI	−0.21	−0.26	−0.45[c]	0.06	0.85[a]	0.60[a]	1.00	
Changes in KPS	0.16	0.02	−0.06	0.28	−0.24	−0.02	−0.99	1.00

Pearson correlation coefficients, [a]$p < 0.001$, [b]$p < 0.01$, [c]$p < 0.05$
Last Period: The last period includes the last two assessments for patients who had completed at least three assessments with the last assessment performed within 30 days of death. Duration from last interview to death: median 15 days (range 2–29 days).
Memorial Symptom Assessment Scale—Short Form (MSAS-SF) subscales: PHYS—physical symptom distress, PSYCH—psychological symptom distress, and GDI—global distress index.
Functional Assessment of Cancer Therapy (FACT-G) parameters: PWB—physical wellbeing, EWB—emotional wellbeing, FWB—functional wellbeing, SUMQOL—total sum of FACT-G QOL subscales.

the last period, as defined previously. The changes in MSAS-SF parameters, KPS and FACT-G scores between two consecutive interviews were calculated in both groups.

In the initial period, changes in KPS were significantly correlated with changes in SUMQOL ($r = 0.36$, $p < 0.05$), changes in PWB ($r = 0.43$, $p < 0.005$), and changes in the MSAS-SF subscales: PHYS, PSYCH and GDI ($r = -0.46$, -0.40, and -0.55, $p = 0.003$, < 0.01 and < 0.0005 respectively). Second, the changes in PHYS were significantly associated with changes in PSYCH ($r = 0.53$, $p < 0.0005$). Third, there was no correlation between changes in EWB or changes in FWB with changes in KPS or symptom distress. (See Table 5).

A different pattern was observed in the last period. First, there was no correlation between changes in KPS and changes in any FACT-G or MSAS-SF parameters. Second, the changes in PHYS were no longer correlated with changes in PSYCH. Third; the changes in EWB were significantly correlated with changes in PHYS ($r = -0.43$, $p < 0.05$) and changes in PSYCH ($r = -0.41$, $p < 0.05$) (See Table 6), but not with the KPS.

The changes in SFWB were not correlated with any other changes in both periods.

Finally, changes in SUMQOL scores at 6, 3, 2, and 1 months prior to death were examined by using a mixed effect model, with the symptom distress included as a time-varying covariate. The estimated SUMQOL for patients more than 2 months prior to death without any symptom distress was 96.9 (standard error 1.71). The changes in the SUMQOL score can be summarized as follows: (1) decrease by 5.7 (standard error 0.95) for each point increase in PSYCH and (2) decrease by 6.52 (standard error 1.10) for each point increase in PHYS. After adjusting for changes associated with these measures, there was a residual decline in SUMQOL scores starting two months prior to death of 4.12 (standard error 1.08) points/month. This is in contrast to the estimated rate of change of SUMQOL of 6.37/month in the absence of these explanatory measures.

Discussion

Terminal illness represents a profound transition. This study used patient's self-report with validated symptom and QOL scales, and observer rated KPS, to prospectively examine the longitudinal course of patients with advanced cancer in a medical oncology setting. We were able to summarize the group values for different measures at selected time points. In this way, we have started to address the challenge of how to interpret longitudinal symptom and QOL data by estimating rates of change at points along the advanced cancer disease trajectory. We have been able to make a number of observations.

First, patterns of change up to 6 months before death in different domains were detected and the results suggest that different domains of symptom distress, functioning status and QOL change at different rates at different selected time points. The results also confirm that there was a marked decline in QOL, symptom distress and functioning starting 2–3 months prior to death.[3, 4, 9] The changes over time are often associated with clinical changes and hospitalizations.[32, 33] Recognizing such changes may provide a way of understanding how life changes for patients from their perception of QOL and symptom distress, and may provide clinicians a way to follow, elicit, and interpret symptom and QOL assessment data on their patients.[34]

These findings have led us to propose the "longitudinal terminal decline QOL model" illustrated in Fig. 1. It suggests that the preterminal phase is characterized by multiple parameters of decline. First, there are slow steady changes in symptom distress, functional status and QOL dimensions starting at 6 months prior to death. Second, worsening in symptom distress with initiation of change in PSYCH starts at 3 months before death. Third, following the increase in symptom distress, accelerated worsening is seen in KPS and QOL parameters at two months prior to death. Finally, one month before death, changes in FWB showed a floor effect while there was a dramatic increase in PSYCH. Interestingly, the SFWB remains steady over time for our patients. Perhaps the items in the SFWB subscale are not sensitive to the changes that occur in the terminal phase.

Further exploration with the mixed effect model quantified a relationship between the changes in symptom distress scores and changes in QOL scores. These kinds of estimates may be helpful for interpreting changes between different instruments, and in further

understanding the meaning of symptom and QOL scores. Further studies with larger sample sizes are needed to confirm these results.

A second interesting set of findings concerns the relationship between changes in QOL, KPS, and symptom distress. In our study, the changes in the initial period can be considered as changes that occur when the patient may be stable clinically and is not thought to be at risk for immediate death. In this period, changes in the MSAS-SF symptom distress subscale scores correlated with changes in the KPS, and changes in the PHYS correlated with changes in PSYCH ($r = 0.53$, $p<0.0005$). The SUM-QOL was also significantly but modestly associated with changes in KPS ($r = 0.36$, $p < 0.05$). These findings suggest that the changes in KPS may reflect the global QOL and symptom distress outcomes, and that changes in physical symptoms are important for understanding changes in KPS. These results also suggest that treatment of multiple physical symptoms may also improve PSYCH in the initial period. This conclusion is supported by reports that unrelieved severe pain may increase anxiety and fear about the future[35] and the adequate treatment of pain can improve psychological symptom distress significantly.[36, 37]

Interestingly, during the last period, when patients are facing impending death, the dramatic declines in the KPS are no longer significantly associated with changes in QOL dimensions or MSAS-SF symptom distress. Rather, changes in PHYS and PSYCH are correlated with changes in EWB. The role of EWB has been conventionally recognized as "suffering", which can be defined as "an aversive emotional experience characterized by perception of personal distress that is generated by adverse factors that undermine quality of life."[38] Even though aggressive symptom management may alleviate physical symptoms in this period, a feeling of suffering may persist. Psychological assessment and interventions may be more important at this point. This observation is supported by reports that the KPS does not capture multidimensional QOL information in this phase.[19] The data in this study illustrate how symptom and QOL measurements can enrich the understanding of changes in KPS. The association between changes in KPS, QOL scores, symptom distress, need to be further studied in larger samples of patients.

Our results highlight the importance of psychological symptom distress in terminal cancer patients. Routine psychological distress screening, early recognition of psychological symptoms and psychosocial interventions may add substantial benefits to the care of advanced cancer patients in this phase. In addition, our results also suggest that in VA patients with poor performance status and advanced disease, the presence of psychological distress and the rate of increase of psychological distress may be an important prognostic factor for survival. Further studies are needed to explore these possibilities.

There are many limitations in our study, which limit our conclusions to hypothesis -generating findings. First, the mixed effect model used in the study has the potential for bias if data are not missing at random. This is always a risk in observational studies of this type, and larger studies will be needed to confirm these conclusions. Second, as the study was conducted at a VA Medical Center, the results may not be generalized to all advanced cancer patients. Further studies to include both genders in the community settings are needed. Third, there are overlapping items between FACT-G and MSAS-SF instruments used in the study, such as pain and lack of energy. It will always be a concern when we study symptoms and QOL together. Nevertheless, QOL and symptoms are different constructs, and this is supported by the modest correlation coefficients between these scales, approximately 0.5–0.7 in our population.[29] Finally, a significant confounding variable also was introduced into our study since patients received pain and symptom management as well as palliative radiation when indicated. It is likely that such treatment would change the trajectory in this palliative care setting. However it would be clinically impossible to perform a pure natural history study in this population. Further work to characterize the impact of standardized intensive symptom management protocols on the longitudinal QOL trajectory of a larger sample of patients is currently underway.

In summary, the results suggest that more attention to palliative care concerns in advanced cancer patients should be given when the patient starts to experience a slow decline in various domains. Serial measurements over one month may help identify where patients are in

their course of disease, and enhance the prognostic information from the KPS. In situations where the change in KPS may be subtle, the findings of changes in symptom distress or QOL may be more informative and can be used to guide clinical assessment. Routine careful symptom and QOL assessment, along with the recognition of multiple trends of decline, may eventually help to define a clinical threshold or transition point whereby patients are entering a clinically unstable state and are at risk for imminent death. Identification of such a phase may be clinically useful in framing the clinical context for therapeutic interventions and hospice referral.

Acknowledgments

The source of financial support for this study was the New Jersey Commission on Cancer Research, Grant Award No. 19-CCR-00. The authors also would like to thank Ms. Chris Corpion, who assisted with patient interviews.

References

1. WHO Expert Committee Report. Cancer pain relief and palliative care. Technical Report Series No. 804. Geneva. WHO,1990.

2. Lynn J. An 88-year-old woman facing the end of life. JAMA 1997;277:1633–1640.

3. Morris JN, Sherwood S. Quality-of-life of cancer patients at different stages in the disease trajectory. J Chron Dis 1987;40:545–553.

4. Morris JN, Suissa S, Sherwood S, et al. Last days: a study of the quality of life of terminal ill cancer patient. J Chron Dis 1986;39:47–62.

5. The SUPPORT Principal Investigators. A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). JAMA.1995;274:1591–1598.

6. McCarthy EP, Phillips RS, Zhong Z, et al. Dying with cancer: patients' function, symptoms, and care preferences as death approaches. J Am Geriat Soc 2000;48:S110–S121.

7. Council on Scientific Affairs. Council Report. Good care of the dying patient. JAMA 1996;275:474–478.

8. Padilla GV, Presant C, Grant MM, et al. Quality of life index for patients with cancer. Res Nurs Health 1983;6:117–126.

9. Ryan LS. An exploratory study to describe the quality of life of veterans with lung and disseminated colon cancers from diagnosis to death. Ph.D. Dissertation thesis. UMI, 1987

10. Zacharski LR, Moritz TE, Baczek LA, et al. Effect of mopidamol on survival in carcinoma of the lung and colon: final report of Veterans Administration Cooperative Study No. 188. J Natl Cancer Inst 1988; 80:90–97.

11. Jordhoy MS, Fayers P, Loge JH, et al. Quality of life in palliative cancer care: results from a cluster randomized trial. J Clin Oncol 2001; 19:3884–3394.

12. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: Macleod CM, ed. Evaluation of Chemotherapeutic Agents. New York: Columbia University Press, 1949: 191–205.

13. Stanley K. Prognostic factors for survival in patients with inoperable lung cancers. J Natl Cancer Institute 1980;65:25–32.

14. Yates JW, Chalmer B, Mckegney P. Evaluation of patients with advanced cancer using the Karnofsky Performance Status. Cancer 1980;45:2220–2224.

15. Mor V, Laliberte L, Morris JN, et al. The Karnofsky performance status scale: an examination of its reliability and validity in a research study. Cancer 1984;53:2002–2007.

16. Allard P, Dionne A, Potvin D. Factors associated with length of survival in 1081 terminally ill cancer patients. J Palliative Care 1995;11:20–24.

17. Reuben DB, Vor V, Hiris J. Clinical symptoms and length of survival in patients with terminal cancer. Arch Intern Med 1988;148:1586–1591.

18. Maltoni M, Pirovano M, Scarpi E, et al. Prediction of survival of patients terminally ill with cancer. Cancer 1995;75:2613–2622.

19. Schaafsma J, Osoba D. The Karnofsky Performance Status Scale re-examined: a cross-validation with the EORTC-C30. Qual Life Res 1994;3:413–424.

20. Kaasa S, Loge JH. Quality-of-life assessment in palliative care. Lancet Oncol 2002;3:175–182.

21. Fairclough DL, Peterson H, Chang V. Why are missing quality of life data a problem in clinical trials of cancer therapy? Statist Med 1998;17:667–677.

22. Cella DF, Cherin EA. Quality of life during and after cancer treatment. Comprehensive Therapy 1988;14:69–75.

23. Gill TM, Feinstein AR. A critical appraisal of the quality of life measurements. JAMA 1994;272:619–626.

24. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes. JAMA 1995;273:59–65.

25. Hollen PJ, Gralla RJ, Kris MG, et al. Quality of life during clinical trials: conceptual model for the Lung Cancer Symptom Scale (LCSS). Support Care Cancer 1994;2(4):213–222.

26. Hwang SS, Chang VT, Fairclough DL, et al. Longitudinal documentation of pain characteristics in terminal cancer patients and its impact on quality of life. Proc APS 1999;84, Abstract 629.

27. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy Scale: Development and validation of the general measure. J Clin Oncol 1993;11:570–579.

28. Chang VT, Hwang SS, Feurman M, et al. The Memorial Symptom Assessment Scale Short Form (MSAS-SF): Validity and reliability. Cancer 2000;89: 1162–1171.

29. Chang VT, Hwang SS, Feuerman M, et al. Symptom and quality of life survey of medical oncology patients at a Veterans Affairs Medical Center. Cancer 2000;88:1175–1183.

30. Fairclough DL. Methods of analysis for longitudinal studies of health-related quality of life. In: Staquet MJ, Hayes RD, Fayers PM, eds. Quality of Life Assessment in Clinical Trials. New York: Oxford University Press,1998:227–248.

31. Curran D, Fayers PM, Molenberghs G, et al. Analysis of incomplete quality of life data in clinical trials. In: Staquet MJ, Hayes RD, Fayers PM, eds. Quality of Life Assessment in Clinical Trials. New York: Oxford University Press, 1998: 249–280.

32. Hwang SS, Chang VT. The use of QOL and symptom assessment instruments to chart the course of terminal cancer patients over time. Oncol Nurs Forum 1996;23:352. (Abstract 173).

33. Chang VT, Hwang SS, Latorre M,. Palliative hospital admission and quality of life. Proc Am Soc Clin Oncol 1996;15:535a. (Abstract 1733).

34. Newell S, Sanson-Fisher RW, Girgis A et al: How well do medical oncologists' perceptions reflect their patients' reported physical and psychosocial problems? Data from a survey of five oncologists. Cancer 1998;83:1640–1651.

35. Strang P. Existential consequences of unrelieved cancer pain. Palliat Med 1997;11:299–305.

36. Chang VT, Hwang SS, Kasimis, BS. Longitudinal documentation of cancer pain management outcomes: a pilot study at a VA Medical Center. J Pain and Symptom Manage (in press).

37. Hwang SS, Chang VT, Alejandro Y, et al. Cancer pain management and its impact on fatigue, psychological distress and depression in male cancer patients at a VA medical center. J Pain 2002;3(2 Suppl 1):44, Abstract 774.

38. Cherny NI, Coyle N, Foley K. Suffering in the advanced cancer patient: a definition and taxonomy. J Palliat Care 1994;10:57–70.