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ORIGINAL REPORT

Symptoms and Distress in Children With Advanced Cancer: Prospective Patient-Reported Outcomes From the PediQUEST Study

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
Thousands of children are living with advanced cancer; yet patient-reported outcomes (PROs) have rarely been used to describe their experiences. We aimed to describe symptom distress in 104 children age 2 years or older with advanced cancer enrolled onto the Pediatric Quality of Life and Evaluation of Symptoms Technology (PediQUEST) Study (multisite clinical trial evaluating an electronic PRO system).

Methods
Symptom data were collected using age- and respondent-adapted versions of the PediQUEST Memorial Symptom Assessment Scale (PQ-MSAS) at most once per week. Clinical and treatment data were obtained from medical records. Individual symptom scores were dichotomized into high/low distress. Determinants of PQ-MSAS scores were explored using linear mixed-effects models.

Results
During 9 months of follow-up, PQ-MSAS was administered 920 times: 459 times in teens (99% self-report), 249 times in children ages 7 to 12 years (96% child/parent report), and 212 times in those ages 2 to 6 years (parent reports). Common symptoms included pain (48%), fatigue (46%), drowsiness (39%), and irritability (37%); most scores indicated high distress. Among the 73 PQ-MSAS surveys administered in the last 12 weeks of life, pain was highly prevalent (62%; 58% with high distress). Being female, having a brain tumor, experiencing recent disease progression, and receiving moderate- or high-intensity cancer-directed therapy in the prior 10 days were associated with worse PQ-MSAS scores. In the final 12 weeks of life, receiving mild cancer-directed therapy was associated with improved psychological PQ-MSAS scores.

Conclusion
Children with advanced cancer experience high symptom distress. Strategies to promote intensive symptom management are indicated, especially with disease progression or administration of intensive treatments.

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INTRODUCTION

Cancer remains the leading cause of nonaccidental death in childhood,[1] and thousands of children are living with advanced stages of the disease. Ensuring the best possible quality of life for children with cancer is a high national priority.[2] Yet, findings from retrospective studies of bereaved parents[3-6] and proxy nursing reports[7,8] suggest that children with cancer experience high levels of suffering and poor health-related quality of life (HRQoL) at the end of life, and this has been associated with long-term effects on surviving parents.[9]

Few studies have ascertained patient-reported outcomes (PROs) in children with advanced cancer. A recent systematic review identified 14 studies that used a symptom assessment scale in pediatric oncology.[10] However, none used child self-reports to describe the experiences of children with advanced cancer. To update the review, we used similar strategies to search for studies published between January 2012 and July 2014 in MEDLINE. We also reviewed reference lists of identified articles, including three systematic reviews.[11-13] The search yielded 554 articles, of which only three reported PROs in the context of advanced pediatric cancer.[14-16] Two studies focused on describing the child's experience, one restricted analyses to psychological outcomes, and the other included a relatively small cohort of children. No PRO studies assessed determinants of

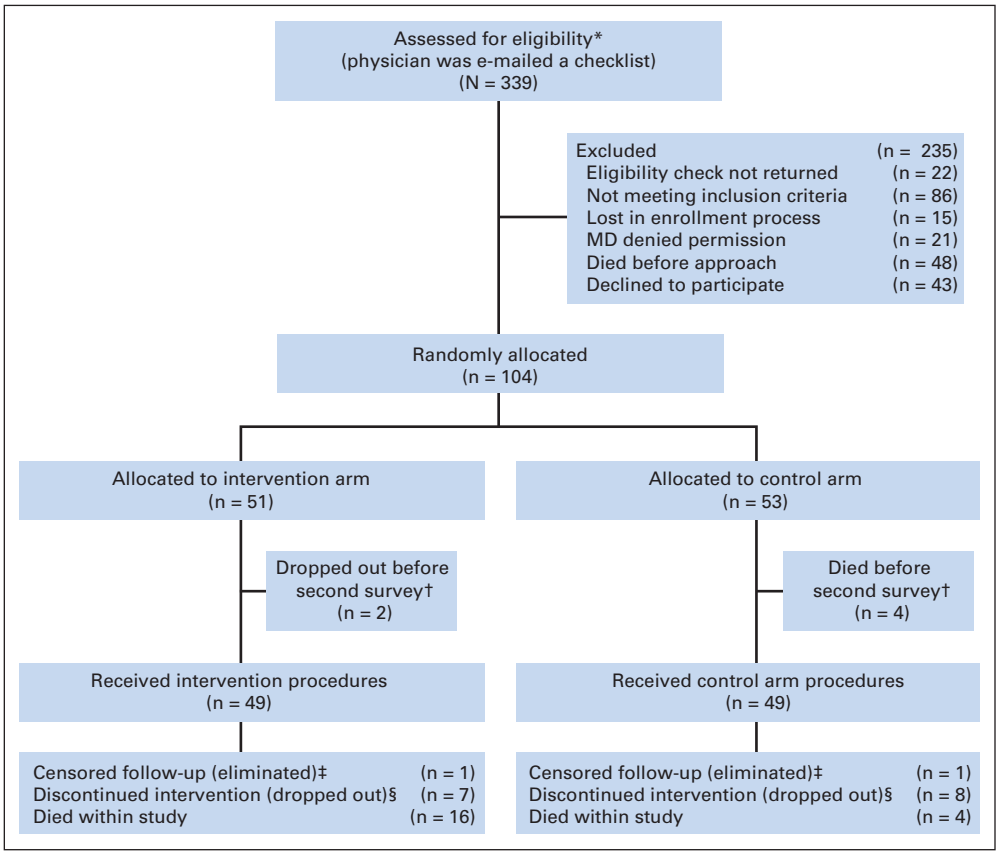

Fig 1. The Pediatric Quality of Life and Evaluation of Symptoms Technology CONSORT diagram for 9 months of follow-up. (*) One site did a preassessment of eligibility; patients from that site reported here were all eligible. (†) These patients did not receive intervention or control procedures. (‡) Children were eliminated when in remission and off treatment for more than 6 months (§) Two patients died after dropout and within the 9-month follow-up period (one patient in each study arm).

symptom distress among children with advanced cancer. Including the child's voice is critical to understand the child's symptom experience and improve pediatric cancer care during advanced stages of the illness.

With the goal of incorporating PROs into supportive care research, we developed Pediatric Quality of Life Evaluation of Symptoms Technology (PediQUEST), a computer-based system that generates printed feedback reports and e-mail alerts after collecting PROs (child-reported symptoms and HRQoL data or, when reports from children were not possible, reports from their parents). The effect of providing PediQUEST feedback to providers and families of children with advanced cancer was evaluated through a multicenter randomized controlled trial (RCT).[17] This study seeks to describe symptom distress in children with advanced cancer, one of the primary aims of the PediQUEST study. Specifically, we sought to describe symptom prevalence and distress and examine factors associated with higher symptom scores during 9 months of follow-up and at the end of life.

METHODS

Study Design

This cohort study was embedded in the PediQUEST RCT (ClinicalTrials.gov ID NCT01838564) conducted at three large pediatric cancer centers: Dana-Farber Boston Children's Hospital Cancer and Blood Disorders Center, The Children's Hospital of Philadelphia, and Seattle Children's Hospital.[17] Patients prospectively reported symptoms and HRQoL on a PediQUEST survey (PQ-Survey) administered through tablet computers. PQ-Surveys were completed at the clinic or ward on a weekly basis at the most frequent; for participants not attending clinic, PQ-Surveys were administered by phone once per month. Small incentives were provided to children and parents. Patients were followed up until death or the end of data collection. Electronic PROs were collected during 9 months for the first 29 patients; in the second year of the study, follow-up changed to 3-month enrollment periods with the option to re-enroll until study closure (December 2009). Data on cancer-directed therapy, disease status, and other relevant clinical covariates were extracted from medical records. The study was approved by the institutional review boards of participating sites.

Study Population

We included children age 2 years or older who were regular patients at one of the sites and had at least a 2-week history of progressive, recurrent, or nonresponsive cancer or a decision not to pursue cancer-directed therapy. The child's parents and primary oncologist were also enrolled. From December 2004 to June 2009, we identified 339 patients, of whom 231 were eligible; 147 were approached, and 104 enrolled (enrollment rate, 70.3%). Full RCT methods have been described previously.[17] Figure 1 shows the CONSORT diagram at 9 months of follow-up. All enrolled patients are included in this cohort study.

Symptom Ascertainment

The PQ-Survey included the PQ-Memorial Symptom Assessment Scale (MSAS), an adapted version of the validated MSAS[7,18,19] that assessed 24 physical and psychological symptoms and is fully described elsewhere.[17] Teenagers (age 13 years or older) answered all 24 items (PQ-MSAS 13-18), children ages 7 to 12 years answered eight items (PQ-MSAS 7-12) and their parents answered the remaining 16 items (PQ-MSAS 7-12-proxy-supplement)—this group used simplified response options[19]—and for children ages 2 to 6 years,

all items were answered by their parents (PQ-MSAS-proxy-full). When children or teens refused to answer, parents were asked to complete a PQ-MSAS-proxy-full. Whenever a child answered, we classified the survey as a self-report, even if it was a combined report from the child and parent. PQ-MSAS scores were calculated following recommendations[18,20]: PQ-MSAS individual symptom scores were the average of frequency, severity, and extent-of-bother subitems; PQ-MSAS total score was calculated as the average of all 24 PQ-MSAS symptom scores; the PQ-MSAS physical subscale averaged eight physical symptoms; and PQ-MSAS psychological subscale averaged six psychological symptoms. All scores were standardized to 0 to 100 scales (100 worst). Total and subscale scores were calculated if at least 50% of the items were answered. PQ-MSAS total score distribution was skewed and highly concentrated on low values. For descriptive purposes, individual symptom scores were dichotomized into high/low distress. The cut point scores for high/low were 44 for PQ-MSAS-7-12, and 33 for PQ-MSAS-13-18, and PQ-MSAS-proxy-full. PQ-MSAS response options, cut points, and rationale for variable dichotomization are provided in the Appendix (online only).

Disease Status

We collected changes in disease status (relapse, progression, regression, complete remission) and their dates, from first progression through the end of study. We then assigned a disease status, dichotomized as active (progressing/present) or inactive (regressing/absent), and calculated days elapsed from last recorded progression to each PQ-Survey.

Cancer-Directed Therapy

For each PQ-Survey, we collected type and date of cancer treatments or procedures that had occurred in the preceding 10 days; procedures were classified as major (bone marrow aspiration and/or biopsy, portacath or central line placement/removal, major debridement, or other) or minor (lumbar puncture, G-tube change, ventriculoperitoneal shunt valve reprogramming, or skin biopsy). Treatment and procedure information was used to define cancer therapy intensity, a time-varying variable representing treatment burden before each PQ-Survey, and categorized as mild (oral or outpatient chemotherapy or minor procedure), moderate (inpatient intravenous [IV] chemotherapy, radiation alone or with oral chemotherapy, or major procedure), or high (stem-cell transplantation conditioning, radiation therapy with IV chemotherapy, or surgery).

Other Covariates

We collected sex, race/ethnicity, age, diagnosis, date of diagnosis, and date of death, when applicable. For each PQ-Survey, we determined whether the patient had been admitted in the prior 10 days. Provider demographic information was gathered through an e-mail survey.

Statistical Analysis

All analyses were performed with SAS statistical software (version 9.2; SAS Institute). We report on outcomes from 9 months of follow-up. We assessed the association of PQ-MSAS total, physical, and psychological scores with relevant factors using linear mixed-effects models. All multivariable models incorporated the patient as a random effect and all other variables as fixed effects. Independent variables potentially related to symptom scores were selected a priori on the basis of expert opinion and existing literature.[21,22] Specifically, we included cancer treatment intensity and a marker of disease status ("days since last recorded progression") for the 10 days before PQ-Survey, as well as cancer type, sex, age, and study arm. Although the intervention did not significantly affect PQ-MSAS scores, which is why we report pooled results, we could not rule out a small intervention effect[17] and, therefore, have included study arm in the models to adjust for potential confounding. Given the skewed distribution of PQ-MSAS scores, we ran models on log-transformed scores; results were unaffected, thus we report estimates on the basis of original scores. To describe the end-of-life experience, we conducted the same analysis in the subgroup of PQ-Surveys answered in the last 12 weeks of life (n = 25).

RESULTS

Baseline Characteristics and Follow-Up Information

Full cohort. Of 104 patients enrolled, 49.0% were female, a majority were non-Hispanic white, and nearly half were ≥ age 13 years

Table 1. Baseline Characteristics of Children Enrolled Onto the PediQUEST Study: Full Cohort (9 months of follow-up) and the Subgroup of Children Who Died and Had Completed End-of-Life PQ-Surveys (last 12 weeks of life)

Characteristic	Full Cohort (N = 104)		Subgroup of Children With End-of-Life PQ-Surveys (n = 25)	
	No.	%	No.	%
Intervention arm	51	49.0	16	64.0
Site				
1	24	23.1	6	24.0
2	59	56.7	11	44.0
3	21	20.2	8	32.0
Female sex	51	49.0	12	48.0
Non-Hispanic white	93	89.4	22	88.0
Older than age 12 years	50	48.1	13	52.0
Diagnosis				
Hematologic malignancy	36	34.6	11	44.0
Brain tumor	10	9.6	1	4.0
Solid tumor	58	55.8	13	52.0
Time from diagnosis to enrollment, months				
Median	27		29	
IQR	(17-51)		(21-35)	
Time from last progression to enrollment, months				
Median	5.9		4.2	
IQR	(3.4-9.4)		(3.2-5.6)	

Abbreviations: IQR, interquartile range; PediQUEST, Pediatric Quality of Life and Evaluation of Symptoms Technology; PQ-Survey, PediQUEST survey.

(Table 1). Most children (55.8%) had solid tumors. At enrollment, median duration of disease was 27 months, and median time since most recent progression was 6 months. Twenty-six children (25.0%) died during the follow-up period.

A total of 920 PQ-Surveys were answered by 9 months of follow-up, with a median of eight administrations per child (Table 2). Most (89%) were answered in the outpatient clinic. Of 708 potential child administrations (ie, PQ-Surveys for children ≥ age 7 years), 694 (98%) were self-reports (teenagers, 456 [99% self-report], and combined child-parent reports of children ages 7 to 12 years, 238 [96%]), and 14 were parent-reports; the remaining 212 surveys were answered by parents of children ages 2 to 6 years. Sixty-four oncologists (64.1% females) were enrolled—89.1% physicians, and 10.9% nurse practitioners, with a median experience of 7 years. On average, oncologists had 1.6 patients enrolled onto the study (range, 1 to 6).

Table 2 summarizes child disease status and cancer-directed therapy in the 10 days before a PQ-Survey. Approximately two thirds of the PQ-Surveys corresponded to children with active disease, and in one quarter of the children, progression had occurred within the preceding 10 days. For only 10.8% of the administrations, the children had been treated as inpatients. In 53.0% of PQ-Surveys, children had received cancer-directed therapy, mostly chemotherapy alone; in addition, 5.9% had undergone a major procedure and 3.0% a minor one. All told, in 43.6% of PQ-Surveys, children had received neither cancer treatment nor procedure; 38.3% were preceded by mild therapy, 14.1% by moderate therapy, and 3.6% by high-intensity therapy.

Subgroup of children with end-of-life PQ-Surveys. Twenty-five children completed at least one PQ-Survey in the last 12 weeks of life (Table 2; total, 73 PQ-Surveys; median, 2 surveys per child). Children with brain tumors were underrepresented in this subgroup (n = 1). In 80.8% of administered PQ-Surveys, children had active disease, and 47.9% had experienced disease progression in the preceding 10 days. In 46.6% of PQ-Surveys, children had received treatment within the prior 10 days, most frequently outpatient IV chemotherapy, followed by oral chemotherapy or radiation alone or with oral chemotherapy; in 20.5% of PQ-Surveys, children had undergone a major procedure and in 5.5% a minor one. Overall, in 54.9% of PQ-Surveys, children had received some sort of cancer-directed therapy in the prior 10 days, mostly of mild (28.8%) or moderate (24.7%) intensity.

Symptoms and Distress

Full cohort. Overall, a median of 5.0 (interquartile range [IQR], 3.0-8.0) symptoms were reported per survey, and a median of 3.0 (IQR, 1.0-6.0) were reported with high distress. Specific symptom prevalence and associated distress reported during the 9-month period are delineated in Figure 2A. Common physical symptoms included pain (47.7%), fatigue (46.2%), and drowsiness (39.4%); the most frequently reported psychological symptoms were irritability (37.2%) and sleep disturbances (29.0%). Approximately, one quarter of the surveys reported nervousness or sadness. When a symptom was present, scores usually denoted high distress. Median PQ-MSAS total score was 8.5 (IQR, 4.3-14.0), physical subscale score was 11.5 (IQR, 4.1-20.7), and psychological subscale score was 7.3 (IQR, 0-16.8; Fig 3A). Of note, no clear trajectories in symptom scores over time were apparent.

Subgroup of children with end-of-life PQ-Surveys. In the last 12 weeks of life, a median of 5.0 (IQR, 2.0-10.0) symptoms were reported per PQ-Survey, 3.0 (IQR, 1.0-9.0) with high distress. Figure 2B shows that the most frequently reported symptoms were pain (61.6%), drowsiness (50.0%), and fatigue (49.3%); other physical symptoms like nausea, anorexia, diarrhea, vomiting, dry mouth, and irritability were particularly prevalent at the end of life. High distress was also prevalent in this subgroup. Median PQ-MSAS total score was 9.3 (IQR, 4.2-20.8), physical subscale score was 14.6 (IQR, 5.5-31.1), and psychological subscale score was 5.5 (IQR, 0-16.7; Fig 3B).

Factors Associated With Higher Symptom Scores

Full cohort. Being female, having a brain tumor, experiencing disease progression in the prior 10 days, and receiving cancer therapy of moderate or high intensity in the past 10 days were associated with increases in one or more PQ-MSAS summary scores in univariable analyses. All these variables remained significantly associated with symptom scores in the multivariable analyses after controlling for age and study arm (Table 3). Higher PQ-MSAS total and psychological scores were reported in girls compared with boys (2.28 [95% CI, 0.14 to 4.42] and 4.13 [95% CI, 0.49 to 7.76], respectively); among children with brain tumors psychological scores were on average 10.65 (95% CI, 2.65 to 18.8) points higher than those of children with hematologic malignancies. PQ-MSAS scores were significantly higher for surveys completed close to disease progression (1 to 10 days) compared with those completed more than 120 days after last progression date. Finally, all three PQ-MSAS scores reported for children receiving moderate or high-intensity therapy were significantly higher than those reported for children receiving no therapy; high-intensity treatments were associated with substantial increases for total and physical scores (12.09 [95% CI, 7.54 to 16.64] and 20.54 [95% CI, 14.78 to 26.30] respectively).

Subgroup of children with end-of-life PQ-Surveys. The same multivariable analysis was fitted for surveys in the last 12 weeks of life. The pattern of associations was similar to those described for the full cohort, although most results did not reach statistical significance. Meaningful results included higher reported total and physical PQ-MSAS scores in girls compared with boys (10.00 [95% CI, 3.77 to 16.24] and 13.23 [95% CI, 5.64 to 20.82] points higher, respectively). Disease progression in the prior 10 days was associated with higher PQ-MSAS physical scores compared with progression more than 60 days before (11.82; 95% CI, 0.46 to 23.18). In contrast, children who received mild cancer therapy at the end of life had lower (better) PQ-MSAS psychological scores (−9.27; 95% CI, −17.04 to −1.49) compared with those receiving no therapy.

DISCUSSION

To date, this is the largest cohort study to prospectively describe PROs in children with advanced cancer and explore determinants of symptom distress. According to primarily their own perspective, children experience high physical and psychological symptom distress. High distress stems from common symptoms including pain, fatigue, drowsiness, and irritability. Indeed, during a 9-month period, nearly 50% of the time, children with advanced cancer experienced substantial suffering from pain that is known to be treatable.[23] Unfortunately, physical symptom prevalence and distress appears to worsen in the last 12 weeks of life, with pain again being the most common highly distressing symptom.

Although results were similar to prior proxy reports,[3-8] the strength of this report lies in the particularly high rate of child self-reporting. In other words, study results reflect to the greatest extent

Table 2. Follow-Up Information of Children Enrolled Onto the PediQUEST Study: Full Cohort (9 months of follow-up) and the Subgroup of Children Who Died and Had Completed End-of-Life PQ-Surveys (last 12 weeks of life)

Follow-Up Data	Full Cohort (N = 104; 920 surveys)*		Subgroup of Children With End-of-Life PQ-Surveys (n = 25; 73 surveys)†	
	No.	%	No.	%
No. of surveys per child				
Median	8		2	
IQR	4-12		2-4	
Disease status in 10 days prior to PQ-Survey				
Active disease				
No	325	35.3	10	13.7
Yes	590	64.1	59	80.8
Missing	5	0.5	4	5.5
Time since last recorded progression date, days				
0-10	238	25.9	35	47.9
11-30	222	24.1	16	21.9
31-60	160	17.4	8	11.0
61-120	194	21.1	11	15.1
> 120	106	11.5	3	4.1
Inpatient in 10 days prior to PQ-Survey				
No	806	87.6	59	80.8
Yes	99	10.8	8	11.0
Missing	15	1.6	6	8.2
Cancer-directed therapy in 10 days prior to PQ-Survey				
Cancer-directed treatment				
SCT conditioning	9	1.0	0	0.0
Surgery	11	1.2	1	1.4
Radiation and IV chemotherapy	13	1.4	0	0.0
Radiation alone or in combination with oral chemotherapy	21	2.3	6	8.2
Chemotherapy only	433	47.1	27	37.0
Inpatient IV	73		3	
Outpatient IV	248		15	
IM or IT or SQ	21		3	
Oral	88		6	
Missing	3		0	
None	429	46.6	35	47.9
Missing	4	0.4	4	5.5
Procedures				
Major‡	54	5.9	15	20.5
Bone marrow aspiration and/or biopsy	31		10	
Portacath or central line placement/removal	15		3	
Major debridement	6		4	
Other (apheresis, cardiac catheterization)	7		1	
Minor	28	3.0	4	5.5
Lumbar puncture (with or without IT)	23		2	
Other (G-tube change, VPS reprogramming, or skin biopsy)	5		2	
None	835	90.8	54	74.0
Missing	3	0.3	0	0.0
Cancer therapy intensity				
No treatment	401	43.6	29	39.7
Mild (chemotherapy only [oral or any outpatient] or minor procedures)	352	38.3	21	28.8
Moderate (chemotherapy only [inpatient IV], radiation alone or with oral chemotherapy, or major procedure)	130	14.1	18	24.7
High (SCT conditioning, radiation therapy with IV chemotherapy, surgery)	33	3.6	1	1.4
Missing	4	0.4	4	5.5

Abbreviations: G-tube, gastrostomy tube; IM, intramuscular; IQR, interquartile range; IT, intrathecal; IV, intravenous; MSAS, Memorial Symptom Assessment Scale; PediQUEST, Pediatric Quality of Life and Evaluation of Symptoms Technology; PQ-Survey, PediQUEST survey; SCT, stem-cell transplantation; SQ, subcutaneous; VPS, ventriculoperitoneal shunt.

*No. of PQ-Surveys completed during 9 months of follow-up;

†No. of PQ-Surveys completed during last 12 weeks of life.

‡Some children had multiple procedures.

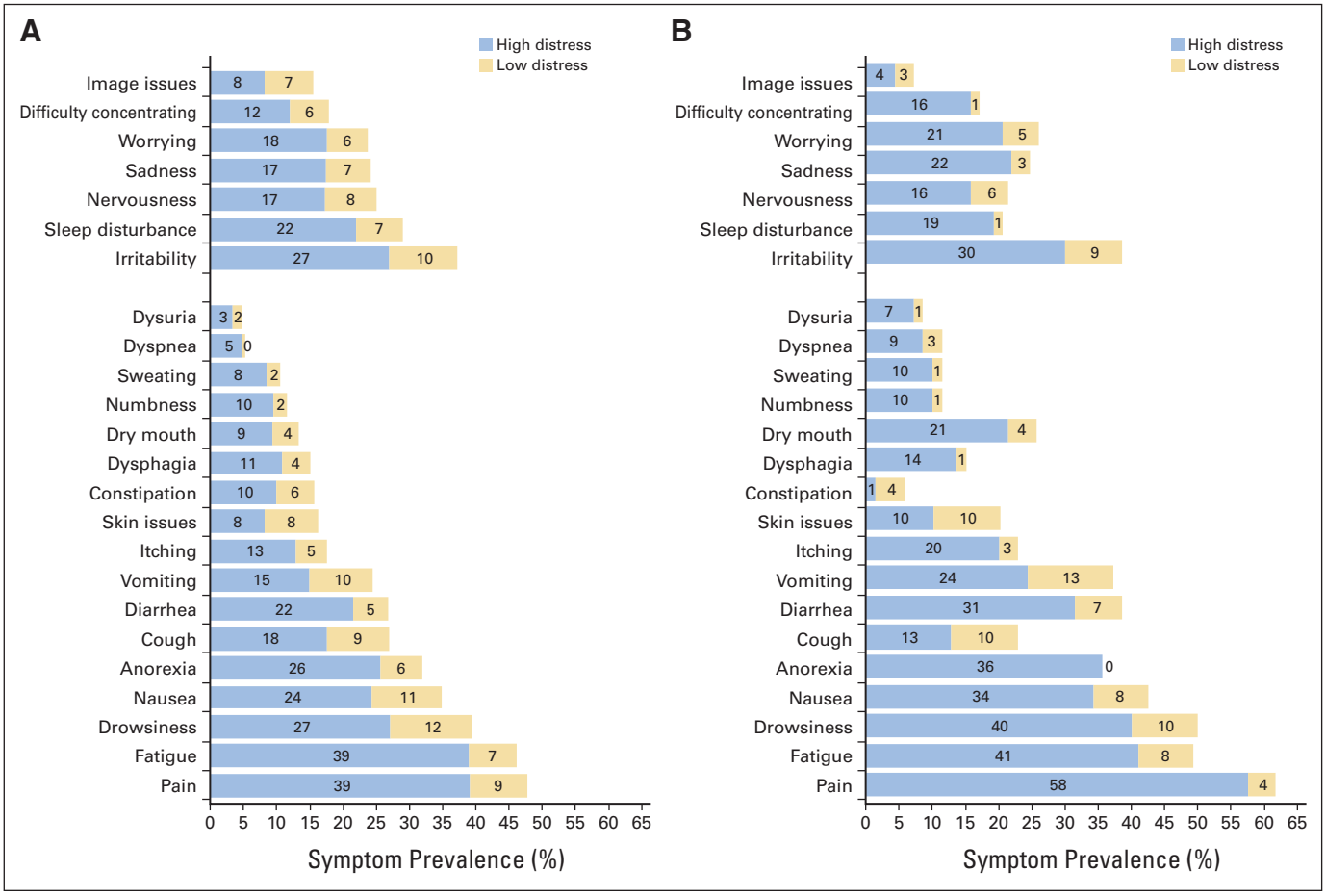

Fig 2. Symptom prevalence and distress observed in the full cohort of children with advanced cancer enrolled in the Pediatric Quality of Life and Evaluation of Symptoms Technology (PediQUEST) study and in the subgroup of children who died and had completed end-of-life PediQUEST surveys (PQ-Surveys). (A) Prevalence (full bar) and level of distress (high/low) reported in (A) the full cohort of 920 PQ-Surveys completed during 9 months of follow-up (N = 104) and (B) the subgroup of 73 PQ-Surveys completed in the last 12 weeks of life (n = 25 children).

possible the voices of children and teenagers with advanced cancer, including the end-of-life period. Because the study was conducted at highly specialized cancer centers where most children with cancer receive care and included a wide range of ages, prognoses, diagnoses, and treatments, results are largely generalizable. On the other hand, the study does not permit conclusions regarding specific age subgroups or non-English speaking families. In addition, because of sample heterogeneity and the pragmatic approach used to collect PRO data, which resulted in an unbalanced design,[17] longitudinal patterns of symptoms, if they exist, may have been veiled.

However, the study makes it evident that there is considerable room for improvement in easing distress in children with advanced cancer. Children experienced substantial suffering from pain throughout the course of the illness and especially at the end of life. Results also highlight the need for further research on complex symptoms such as fatigue, drowsiness, and loss of appetite, for which the level of evidence for available treatments is still low.[13] Importantly, this study took place during a period of increasing awareness of pediatric palliative care, which focuses on the alleviation of suffering,[24,25] yet symptom distress remained high and likely still does.

We found that PQ-MSAS total and psychological scores were higher for girls than for boys, even after adjusting by intensity of therapy and disease status. Similar sex differences in children and adolescents with cancer have previously been reported for both pain intensity[26] and quality of life.[27] Although more research is needed to better understand these differences, biologic, family, and sociocultural factors have been proposed as possible explanatory factors.[28] In addition, and consistent with existing literature,[29] children with brain tumors reported worse psychological PQ-MSAS scores, which calls for enhanced emotional support in these children.

Both experiencing recent disease progression and receiving moderate or intense cancer therapy resulted in significantly worse scores across all domains. These results are not unexpected. As cancer is controlled and intensity of treatment is lower, so too is symptom distress. Importantly, outcomes can be good; indeed, more than 70% of children in our cohort were alive at 9 months of follow-up. The challenge, of course, is the inability to know whether cancer-directed therapy will be effective and disease control achieved. In fact, providers and families of children with advanced cancer live with considerable prognostic uncertainty; whereas overall prognoses for many types of pediatric cancers are known,[30] the outcome for an individual child is not readily predictable. As such, implications from these findings are not necessarily to decrease the amount or intensity of cancer-directed therapy offered but rather to increase efforts to ameliorate symptom distress.

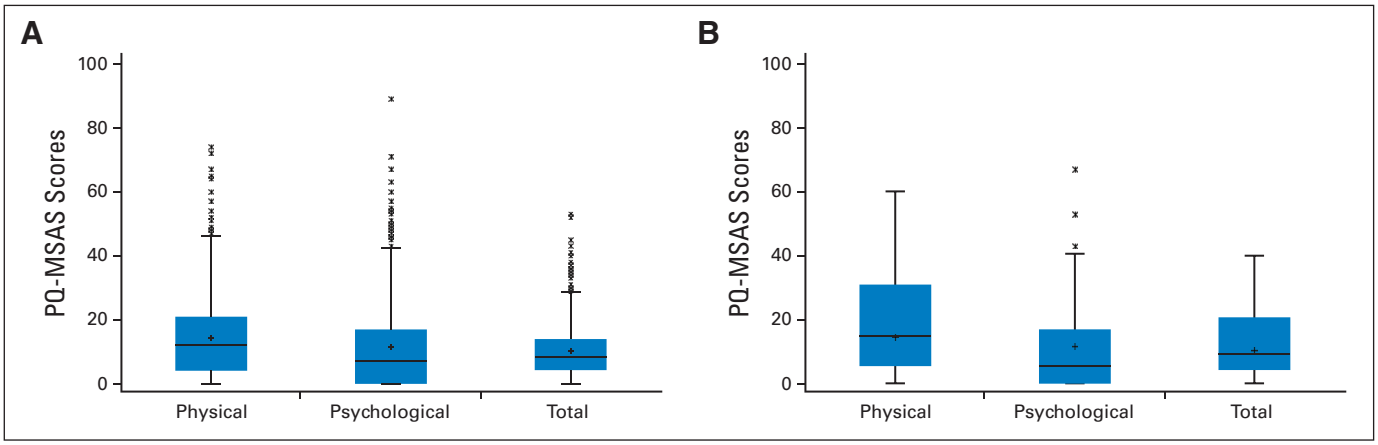

Fig 3. Boxplot of Pediatric Quality of Life and Evaluation of Symptoms Technology (PediQUEST) study Memorial Symptom Assessment Scale (PQ-MSAS) scores observed in the full cohort of children with advanced cancer enrolled in the PediQUEST study and in the subgroup of children who died and had completed end-of-life PediQUEST surveys (PQ-Surveys). Boxplots of PQ-MSAS physical and psychological subscale scores as well as PQ-MSAS total scores in (A) the 920 PQ-Surveys completed by the full cohort during 9 months of follow-up (N = 104 children) and (B) the subgroup of 73 PQ-Surveys completed in the last 12 weeks of life (n = 25 children).

Interestingly, in the last 12 weeks of life, the receipt of mild cancer treatment was associated with improved child psychological well-being. Prior research underscores the need for parents to leave no stone unturned.[31] Providers often think of cancer-directed therapy as mutually exclusive from intensive symptom control in advanced cancer care.[32,33] This need not be the case. Indeed, parents favor[34] and, as suggested in this study, children may benefit from blended goals of care including continued efforts at disease control, albeit with mild cancer therapy, together with intensive symptom control. This strategy might be better embraced by providers.

Children with advanced cancer experience high suffering according to their own reports. Cancer-directed therapy contributes substantially to this suffering, but this suffering diminishes with time as the disease is controlled. Because of prognostic uncertainty among children with advanced cancer and frequency of continued cancer-directed therapy, interventions aimed at intensive symptom management are indicated.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Collection and assembly of data: Liliana Orellana, Christina Ullrich, E. Francis Cook, Tammy I. Kang, Abby Rosenberg, Russ Geyer, Chris Feudtner, Veronica Dussel

Table 3. Full Cohort Multivariable Analysis of Factors Associated With PQ-MSAS Scores (N = 104; 920 surveys)

	PQ-MSAS Total Score			PQ-MSAS Physical Score			PQ-MSAS Psychological Score		
Multivariable Model	Estimate (95% CI)*	*P*	Global *P*	Estimate (95% CI)*	*P*	Global *P*	Estimate (95% CI)*	*P*	Global *P*
Female sex	2.28 (0.14 to 4.42)	.042		2.29 (−0.64 to 5.23)	.129		4.13 (0.49 to 7.76)	.029	
Diagnosis (reference: hematologic malignancy)									
Brain tumor	1.92 (−1.48 to 5.33)	.268	.506	−0.32 (−5.62 to 4.98)	.906	.993	10.65 (2.50 to 18.8)	.010	.054
Solid tumor	−0.07 (−2.47 to 2.33)	.954		0.01 (−3.1 to 3.12)	.995		2.05 (−1.73 to 5.83)	.287	
Time since last recorded progression, days (reference: > 120)									
0-10	2.57 (0.92 to 4.21)	.002	.031	3.55 (0.47 to 6.63)	.024	.066	2.93 (0.2 to 5.66)	.035	.015
11-30	1.45 (−0.17 to 3.07)	.080		3.15 (−0.06 to 6.35)	.054		−0.03 (−2.45 to 2.4)	.983	
31-60	1.25 (−0.45 to 2.95)	.151		1.46 (−1.58 to 4.5)	.348		0.77 (−2.27 to 3.82)	.618	
61-120	0.27 (−1.1 to 1.63)	.702		−0.13 (−2.79 to 2.53)	.924		−0.24 (−2.8 to 2.31)	.853	
Cancer therapy intensity in prior 10 days (reference: no therapy)									
High	12.09 (7.54 to 16.64)	< .001	.001	20.54 (14.78 to 26.30)	< .001	.002	6.24 (0.6 to 11.89)	.030	.016
Moderate	2.92 (1.07 to 4.76)	.002		4.34 (1.28 to 7.39)	.005		3 (0.12 to 5.89)	.041	
Mild	−0.19 (−1.14 to 0.77)	.700		1.09 (−0.92 to 3.09)	.289		−1.24 (−2.8 to 0.33)	.121	

Abbreviation: PQ-MSAS, Pediatric Quality of Life and Evaluation of Symptoms Technology Memorial Symptom Assessment Scale.
*Coefficients, CIs, and *P* values obtained under a generalized linear model including the child as a random effect; arm group, age, and all other factors as fixed effects.

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GLOSSARY TERM

patient-reported outcomes: questionnaires used in a clinical setting to systemically collect information directly from the patient.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Symptoms and Distress in Children With Advanced Cancer: Prospective Patient-Reported Outcomes From the PediQUEST Study

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Appendix

Further description of PediQUEST–Memorial Symptom Assessment Scale. The Pediatric Quality of Life and Evaluation of Symptoms Technology (PediQUEST) study Memorial Symptom Assessment Scale (PQ-MSAS) questionnaires were included in the PediQUEST surveys (PQ-Surveys) and administered through PediQUEST technology, which consisted of a handheld computer device containing software allowing the selection of a user-specific survey. PQ-Surveys assessed symptoms, health-related quality of life (HRQoL), and overall sickness. The instruments used in PQ-Surveys were selected after an extensive literature review and also included the Pediatric Quality of Life Inventory (PedsQL 4.0; Varni JW, et al: Cancer 94:2090-2106, 2002), an HRQoL tool with extensive validation, the Faces Pain Scale-Revised (Bieri D, et al: 41:139-150, 1990), used to measure current pain and not included in this analysis, and a Sickness question, a single-item score, developed de novo for the study.

The PQ-MSAS was adapted from the previously validated MSAS child[18,19] and proxy[7] versions. Details of the adaptation and piloting process are reported elsewhere.[17] When the PediQUEST study was initiated, the MSAS was the only multidimensional and multiple symptom instrument that had been adapted and validated for use in children. There are two validated child versions: MSAS 10-18[18] and MSAS 7-12.[19] A proxy version had been developed for report by nurses.[7] MSAS 10-18 and MSAS proxy contain 31 items, whereas MSAS 7-12 is shorter with only eight items.

The PQ-MSAS consists of three 24-item versions: PQ-MSAS 13-18 (adapted from MSAS 10-18), PQ-MSAS 7-12 (comprising PQ-MSAS 7-12 [eight items for self-report] and PQ-MSAS proxy-supplemental for the 16 remaining items), and PQ-MSAS proxy-full (adapted from the MSAS proxy, 24 items). The three versions of PQ-MSAS allowed for assessment of severity, frequency, and distress of each of the 24 physical and psychological symptoms across the age range of the study. The PQ-MSAS proxy-full was used by parents of children ages 2 to 6 years and when the child did not want to self-report. The PQ-MSAS proxy-supplemental was administered to parents of children ages 7 to 12 years to assess the 16 symptoms not included in the PQ-MSAS 7 to 12. Items and time frame of proxy versions (originally the MSAS proxy asked about symptoms during the last day of life of the patient) were modified to match PQ-MSAS 13-18, which asks about symptoms during the past week. Necessary wording changes were introduced so that the questions addressed parents appropriately (given that the questions were originally developed for nurses).

Conceptual equivalence and score equivalence between the three PQ-MSAS versions (7-12, 13-18, and proxy-full) is assumed. Permission for all changes and use of the scale was obtained from the author (J.J. Collins, personal communication, April 2003).

MSAS Response Options

For each symptom, The PQ-MSAS includes three items (frequency, severity, and extent of bother). Item response options use categorical scales (5-point scales for parental and teenager questionnaires and 4-point scales for children ages 7 to 12 years [child and parent]). Appendix Tables A1 and A2 show the response options and the scores assigned to each option.

MSAS Scoring

In its original form, the MSAS uses a 0 to 3 scale for young children and a 0 to 4 scale for older children and proxy versions.[18] PQ-MSAS scores were standardized to 0 to 100 scales (100 worst) to increase comparability across age groups and with HRQoL scores. As recommended by the authors,[18] the following average scores were calculated: individual symptom scores (average of the three subquestions for each symptom [frequency, severity, distress]), MSAS total score (average of all symptom scores), MSAS physical subscale (average of eight physical symptoms), and MSAS psychological subscale (average of six psychological symptoms). Denominators are based on the number of questions answered. Total and subscale scores were calculated if at least 50% of the items were not missing.

High/Low Symptom Distress

Individual symptom scores were dichotomized to simplify the report of the level of distress produced by a given symptom. The cut points were established on the basis of the potential combinations of answers for a given symptom. For all MSAS versions and all respondents, the chosen cut points (33 for PQ-MSAS 13-18 and PQ-MSAS proxy-full, or 44 for PQ-MSAS 7-12 child and proxy-supplemental versions) corresponded to responses that denoted at least moderate distress (scores of 50, 66, 75, or 100) in one or more of the three symptom domains of frequency, severity, and extent of bother. Considering that once a child reported a symptom as present, frequency and severity cannot score 0, individual symptom scores of 33 or 44 correspond to have provided, for example, a score of 100 on one of the subitems, a score of 50 or 66 in two subitems, or a score of 50 or 66 in one subitem and the other two with scores of 25 or 33.

Table A1. Response Options and Scoring for PQ-MSAS 7-12 (child and proxy supplement)

Item	0	33	66	100
Frequency		A very short time	A medium amount	Almost all the time
Severity		A little	A medium amount	A lot
Extent of bother	Not at all	A little	A medium amount	Very much

Abbreviations: PQ-MSAS, PediQUEST Memorial Symptom Assessment Scale; PediQUEST, Pediatric Quality of Life and Evaluation of Symptoms Technology.

Table A2. Response Options and Scoring for PQ-MSAS 13-18 and PQ-MSAS Proxy-Full

Item	0	25	50	75	100
Frequency		Almost never	Sometimes	A lot	Almost always
Severity		Slight	Moderate	Severe	Very severe
Extent of bother	Not at all	A little bit	Somewhat	Quite a bit	Very much

Abbreviations: PQ-MSAS, PediQUEST Memorial Symptom Assessment Scale; PediQUEST, Pediatric Quality of Life and Evaluation of Symptoms Technology.