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Illness and end-of-life experiences of children with cancer who receive palliative care.

Erica C. Kaye, MD¹, Courtney A. Gushue, DO^{2,3}, Samantha DeMarsh, BS⁴, Jonathan Jerkins, MD^{2,3}, April Sykes, MPH¹, Zhaohua Lu, PhD¹, Jennifer M. Snaman, MD,MS^{5,6}, Lindsay Blazin, MD¹, Liza-Marie Johnson, MD,MPH,MBE¹, Deena R. Levine, MD¹, R. Ray Morrison, MD¹, and Justin N. Baker, MD,FAAHPM¹

¹St. Jude Children's Research Hospital, Memphis, TN

²Le Bonheur Children's Hospital, Memphis, TN

³University of Tennessee Health Science Center, Memphis, TN

⁴Ohio University Heritage College of Osteopathic Medicine, Cleveland, OH

⁵Dana-Farber Cancer Institute, Boston, MA

⁶Boston Children's Hospital, Boston, MA

Abstract

Background: The field of pediatric palliative oncology is newly emerging. Little is known about the characteristics and illness experiences of children with cancer who receive palliative care.

Methods: A retrospective cohort study of 321 pediatric oncology patients enrolled in palliative care who died between 2011 and 2015 was conducted at a large academic pediatric cancer center using a comprehensive standardized data extraction tool.

Results: The majority of pediatric palliative oncology patients received experimental therapy (79.4%), with 40.5% enrolled on a phase I trial. Approximately one-third received cancer-directed therapy during the last month of life (35.5%). More than half had at least one intensive care unit hospitalization (51.4%), with this subset demonstrating considerable exposure to mechanical ventilation (44.8%), invasive procedures (20%), and cardiopulmonary resuscitation (12.1%). Of the 122 patients who died in the hospital, 44.3% died in the intensive care unit. Patients with late palliative care involvement occurring less than 30 days before death had higher odds of dying in the intensive care unit over the home/hospice setting compared to those with earlier palliative care involvement (OR: 4.7, 95% CI: 2.47–8.97, P<0.0001).

Conclusions: Children with cancer who receive palliative care experience a high burden of intensive treatments and often die in inpatient intensive care settings. Delayed palliative care

Address correspondence to: Erica C. Kaye, Departments of Oncology and Palliative Care, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Mail Stop 260, Memphis, TN 38105, [erica.kaye@stjude.org], Office: 901-595-8188, Fax:.

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involvement is associated with increased odds of dying in the intensive care unit. Prospective investigation of early palliative care involvement in children with high-risk cancer is needed to better understand potential impacts on cost-effectiveness, quality of life, and delivery of goal concordant care.

Keywords

pediatric oncology; palliative care; palliative oncology; quality of life; end of life; intensive care

INTRODUCTION

Cancer is the leading cause of death by disease among children in the United States. Approximately 1 in 285 children are diagnosed with cancer each year, and despite advances in therapy, currently 1 in 5 children with cancer do not survive their illness.¹ Children with high risk cancer and their families face significant physical, psychological, social, and spiritual challenges,^{2–15} and they require expert guidance in navigating difficult decision-making and reframing hope in the face of unspeakable tragedy.^{16–25}

Over the past decade, the field of palliative oncology has developed,^{26,27} bolstered by evidence that patients with high-risk or incurable disease who receive cancer-directed care in synergy with palliative care (PC) demonstrate improved outcomes.^{28–37} Specifically in the context of pediatric cancer, the value of palliative oncology has gained traction over the past few years.^{38–42} Integration of PC principles and services into routine cancer care for children with high-risk disease has been associated with improved symptom management for patients^{5,43} and quality of life (QOL) for both children and families.^{44–47} The advent of combined training programs in pediatric oncology and hospice and palliative medicine further aim to improve delivery of care for this unique patient population.⁴⁸

As pediatric palliative oncology (PPO) develops as a field, the patients and families it serves have emerged as a distinct cohort within the pediatric patient population. Yet little is known about the characteristics, illness trajectories, and end-of-life (EOL) experiences of children with high-risk or incurable cancer who receive PC services. Even less is known about how EOL experiences are associated with timing of PC consultation for pediatric oncology patients.

To address these deficits, we conducted a retrospective cohort study of deceased children with cancer enrolled on a PC service at a large academic pediatric cancer center over a four-year period. This work builds upon a very limited literature describing pediatric PC cohorts, of which a small subset are oncology patients,⁴⁹ as well as recent cohort analyses of pediatric, adolescent, and young adult cancer patients, of which a subset received PC^{5,50} and a single study investigating goals of care and location of death for PPO patients.⁵¹ To date, the literature is sparse on this topic in part due to limited numbers of PPO patients available for investigation; this analysis aims to address this deficit by presenting data from a large cohort of 321 patients. To our knowledge, this is the first study to investigate the demographics, disease characteristics, treatments, interventions, symptom burden, and EOL experiences of a uniquely vulnerable population, with the goal of better understanding this

distinct cohort of patients and identifying potential future targets for improving their illness and EOL experiences.

METHODS

Study design

This study was conducted at St. Jude Children's Research Hospital (SJCRH). The SJCRH Institutional Review Board reviewed the study and deemed it exempt in the context of retrospective analysis of a deceased cohort.

Institutional data was mined to obtain a list of all patients with a primary cancer diagnosis who were enrolled on the PC service at SJCRH at the time of their death and whose death occurred between April 1, 2011 and March 31, 2015. This four-year window was selected for two reasons: 1) institution-wide data became available in the electronic medical record beginning on April 1, 2011, allowing for more thorough and accurate data abstraction; and 2) the characteristics of patients on the PC service and the frequency of requested PC consultations remained stable during this time period.

Upon careful review of available data, the decision was made to limit the cohort to patients with cancer who received PC as evidenced by documentation of at least one note in the medical record confirming PC or hospice involvement. This decision was predicated on the fact that 93.0% of patients who died during the study window had some degree of PC integrated into their care by the date of death; most of the small minority of patients who died without PC involvement were not followed at this institution at the time of death, resulting in limited availability of medical records. For the purpose of this investigation, deceased PPO patients served as an approximate surrogate for all patients with cancer who died during the 4-year study window. Given the very small number of patients who died without PC involvement at this institution, it was not statistically feasible to draw meaningful comparisons between patients who died with and without PC involvement.

Of note, for the target study population, provision of PC encompasses a formal PC consultation with subsequent follow-up predicated on patient and family needs. At this institution, on-site PC is provided by a subspecialty team of expert PC clinicians who see patients and families in the hospital and clinic settings and provide local home visits as needed. The institutional PC team also collaborates closely with an extensive network of community-based hospices, both locally and across the country to coordinate and guide home care for patients and families. Patients who died at home locally received frequent in-person and telephone-based support by the PC team; those who died outside of the catchment region received local hospice services with close coordination and guidance provided by the institutional PC team.

A data abstraction tool comprising 67,308 data cells was created by PPO clinicians and researchers (EK, JB, DG) based on a review of the literature.^{49,52-58} Input from a separate panel of oncology and critical care clinicians and researchers (RM, AN) was solicited to improve the abstraction form. Iterative revisions to the standardized tool were made until

general consensus was achieved. The items targeted for abstraction are summarized in Table 1.

A team of six researchers (EK, SD, CG, JJ, LP, LJ) independently abstracted data from the electronic medical record using a standardized form. The two researchers who created the form (EK, DG) provided training to the remaining research team. For certain items, secondary review of paper charts was performed to supplement electronic medical record review. Any questions raised by a team member were discussed in groups of two to four researchers to clarify the abstraction tool and achieve consensus.

Auditing process

Three independent researchers (EK, DG, LP) conducted a 10% audit of the entire database. Random sampling was performed to obtain a subset of cases for auditing. For database items relevant to all 321 patients, sampling of every tenth patient was performed. For items relevant only to select subsets of patients, random sampling was altered accordingly to ensure capture of 10% of the subset for auditing. An acceptable threshold for inter-rater reliability was established a priori at 0.85. All database items met this threshold; however, two items had inter-rater reliability scores at the lower limit of 0.85. Excluding the cases screened in the prior audit, a subsequent 15% audit was performed on these items, establishing inter-rater reliability scores of 0.90 for these data.

Statistical analysis

Demographic, disease, treatment, EOL, and QOL related characteristics of PPO patients were summarized using descriptive statistics (number and percentage or median, interquartile range, minimum, and maximum). Demographic characteristics were compared between PPO patients and all-comer patients (excluding the PPO cohort) using Chi-square tests. Multinomial logistic regression was utilized to explore the relationship between days from first PC consult to death [<30 and 30 days] and location of death [hospital pediatric intensive care unit (PICU), hospital non-PICU, and outpatient (home or hospice facility)]. Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). A two-sided significance level of $P<0.05$ was used for all statistical tests.

RESULTS

Description of the PPO patient population

A total of 321 St. Jude PPO patients died between April 2011 and March 2015. Demographic characteristics of these patients are summarized in Table 2.

The disease and treatment history of the 321 PPO patients is summarized in Table 3. Approximately one-fourth of patients had leukemia or lymphoma as their primary cancer diagnosis (24.0%), one-third had solid tumor (32.7%), and the rest had brain tumor (43.3%) as their primary cancer diagnosis. A large proportion of patients received experimental protocol therapy (79.4%) with 40.5% enrolled on a phase I protocol at some point during the course of their disease. Seventy-nine patients (24.6%) received hematopoietic stem cell transplantation, and of those, 14 (17.8%) received more than one transplant. During the last

month of life (LMOL), 35.5% of patients received cancer-directed therapy and 87.5% had evidence of disease.

Of the 321 PPO patients, 165 (51.4%) had at least one PICU hospitalization. The PICU history of these 165 patients is summarized in Table 4. Patients had a range of 1 to 8 PICU hospitalizations, with nearly half having 2 or more PICU hospitalizations (49%). The median total number of days hospitalized in the PICU was 8 days. While hospitalized in the PICU, 44.8% required ventilator support and 35.2% required cardiovascular pressor support. Thirty-three patients (20%) underwent invasive procedures such as paracentesis, thoracentesis, chest tube placement, and organ biopsies. Twenty patients (12.1%) received cardiopulmonary resuscitation during their PICU hospitalization.

QOL and EOL characteristics of the 321 deceased PPO patients are summarized in Table 5. The median time between first PC consult and death was 79 days. Approximately three-fourths of patients had PC involvement 30 days or more prior to death (73.5%). All patients had documentation of goals of care at their first PC consult; 27.1% of patients had a goal of cure, 12.8% had a goal of life prolongation with focus on cure, 40.8% had a goal of life prolongation with focus on comfort, and 19% had a goal of comfort only. The majority of patients had hospice involvement (81%). A minority had ethics involvement (2.5%). Regarding location of death, 53% of patients died at home, 3.4% in a hospice facility, and 38% in the hospital. Out of the 122 patients that died in the hospital, 44.3% died in the PICU. Advance directives were in place at the time of death for 90.4% of those patients with full EOL chart access (n = 225). Advance directives were placed a median of 23 days prior to death.

Association between Timing of PC Involvement before Death and Location of Death

The results of the multinomial logistic regression model exploring the relationship between days from first PC consult to death and location of death are shown in Table 6. Patients with PC involvement occurring less than 30 days before death had a higher odds of dying in the PICU over the home/hospice setting compared to those with PC involvement occurring 30 days or more before death (OR: 4.7, 95% CI: 2.47–8.97, $P < 0.0001$).

DISCUSSION

Cancer is the leading cause of death by disease among children in the United States, with 20% of children diagnosed with cancer succumbing to their disease.¹ The numbers of children with cancer who receive palliative or hospice care vary between institutions,^{50,59,60} and little is known about this uniquely vulnerable patient population in terms of demographic, treatment, QOL, and EOL attributes. To our knowledge, this is first study to describe the illness and EOL experiences exclusive to a large cohort of PPO patients, as well as the first study to investigate the association between timing of PC consultation and location of death for these uniquely vulnerable patients.

PPO patient gender and race closely paralleled all-comer demographics in the large pediatric cancer center represented in this study. Although racial disparities related to PC access in adult cancer patients are well described,^{61,62} disparities in the context of PPO remain

understudied. Hispanic patients in this study comprised a larger proportion of the PPO population as compared to all-comers, a finding that differs from descriptions of ethnic disparities related to PC/hospice access for adults.^{63,64} However, this finding corroborates limited pediatric oncology data in which ethnicity appears not to negatively impact access to PC/hospice services for children with cancer.^{60,65} The effect of race and ethnicity on illness and EOL experiences for PPO patients requires further investigation, with a particular eye towards explaining potential discrepancies in disparities identified between pediatric and adult PC cohorts.

All subsets of neoplasms were well represented within the PPO cohort. Patients with central nervous system tumors comprised the largest subpopulation, followed by patients with solid tumors and those with hematologic malignancies. A similar hierarchy has been reflected in adult data, where patients with hematologic malignancies are less likely to receive specialized PC services and patients with brain tumors more likely to enroll in hospice.⁶⁶ However, further research is needed in the context of pediatric cancer to corroborate these findings and identify potential barriers to palliative and hospice care as stratified by neoplasm subtype. Of note, the authors' decision to limit the targeted cohort to children with high-risk cancer already enrolled in PC intentionally resulted in a study population that, as a whole, faces highly challenging treatments and poor prognoses. However, we recognize that disease-specific subpopulations are likely to experience different illness trajectories and EOL experiences. Although this detailed discussion falls beyond the scope of this manuscript, further stratified analyses of disease-specific illness experiences within subgroups of the pediatric palliative oncology population are ongoing.

Unsurprisingly, PPO patients received extensive therapies and interventions across their illness trajectory, with the majority receiving some degree of experimental treatment (i.e., phase I-III trial), nearly half enrolling on a phase I trial, nearly a quarter undergoing at least one hematopoietic stem cell transplant, and more than a third receiving cancer-directed therapy during the LMOL. More than half experienced at least one PICU hospitalization, the majority sustaining significant interventions including mechanical ventilation, cardiovascular support, invasive procedures, or cardiopulmonary resuscitation. Seminal work by Wolfe et al has shown that children with high-risk cancer experience substantial suffering across their illness trajectory and at the EOL.^{2,15,67} The goal of PC is to mitigate the extent of suffering, particularly for children with progressive or refractory disease, and although little is known about the extent of suffering experienced by PPO patients, these findings raise concerns about the potentially high levels of physical and psychosocial suffering sustained by children with cancer prior to death.

In particular, the extent of PICU burden on this patient population warrants closer attention. Prior literature suggests that one of every 3 to 4 children with cancer is hospitalized in the PICU during their illness,^{56,68} and PICU mortality for pediatric oncology patients has been shown to be 4-fold higher than overall PICU mortality.^{57,58} However, this study suggests that the risk of PICU hospitalization may be increased even further in PPO patients. This finding is unsurprising to the extent that children with progressive disease often receive extensive therapy and experience significant illness- and treatment-related complications.⁵

Importantly, these data further demonstrate that PC can and does overlap with intensive cancer-directed therapy.

Yet for the authors of this study, the high burden of PICU hospitalization in a PPO cohort provokes important questions about the extent to which intensive care in PPO patients is cost-effective, goal-concordant and/or precludes provision of quality of life related care. We believe that PICU hospitalization for PPO patients is neither inherently right nor wrong; rather, intervention fitness depends largely on clinical context in synergy with patient/family and provider goals of care. To date, goals of care remain under-documented and underreported in this vulnerable patient population, particularly as they relate to the unique experiences of children with high-risk cancer who receive intensive therapy in the PICU. Further investigation is needed to evaluate goal concordance and quality of life in this patient population.

One particularly important facet of goal-concordant care in the context of PPO centers on location of death. The majority of children with cancer die in the hospital,⁵⁰ and as this study demonstrates, a substantial number of PPO die in intensive care settings. While EOL in the PICU is not necessarily incongruous with delivery of optimal PC, these findings emphasize the critical need for further research regarding cost-effective and goal-concordant care related to location of death for PPO patients and families. Further research is also needed to investigate potential variables that may increase the odds of dying in the PICU for pediatric palliative oncology patients, as preemptive identification may afford opportunities for development and investigation of targetable interventions to enhance delivery of goal-concordant care at the EOL for children with cancer.

Of additional interest is the negligible percentage of PPO patients who died in a hospice facility, which stands in contrast to adult oncology patients who die in greater numbers in hospice facilities.⁶⁹ This finding likely speaks to a lack of hospice facilities with pediatric expertise in the U.S.^{70,71} To date, only 14% of participating hospice agencies report having formal pediatric PC services with specialized staff,⁷¹ and a number of educational, procedural, and sociocultural barriers further impede provision of community-based EOL care for children and families.⁷² Development and implementation of interventions to improve access to pediatric PC and hospice in the community is a valuable area of research that remains largely unexplored.⁷³

Importantly, three-quarters of PPO patients at this institution had PC involvement prior to the LMOL, with the median time between initial consultation and death falling at approximately 2.5 months. These findings reflect a growing acceptance of PC in the context of pediatric oncology, bolstered by gradually increasing support for integration of PC into the care of children with cancer.^{40,74} Notably, at the time of initial PC consultation, nearly half of patients identified their goal of care to involve cure. These data highlight a growing awareness on the part of patients and families and clinicians that PC is not synonymous with EOL,⁷⁵ and they speak further to the importance and acceptability of early PC integration in pediatric cancer care.^{40,74,75} Both of these points are important to emphasize, as they have the potential to initiate a meaningful culture shift within the pediatric oncology community with regards to the value of integrating PC principles and services in the care of children

with cancer and their families. We believe that PC involvement is particularly meaningful for children with high-risk cancer who maintain curative goals of care, as PC providers can help patients and families navigate decisions that balance quality of life in the context of cure-directed therapy and encourage reevaluation and evolution of goals of care in the context of illness progression, in the PICU or any other care location.

Despite the fact that nearly half of PPO patients and families identified cure-oriented goals at the time of initial PC consultation, the majority of PPO patients had advance directives in place at the time of death, with median documentation occurring more than three weeks prior to death. This finding is powerfully reflective of the journey to reframe hope in the context of goals of care,⁷⁶ and more research is needed to better understand how the extent and timing of PC involvement potentially impacts the gradual evolution of goals from cure to comfort.

These findings also demonstrate an important association between timing of PC consultation and location of death that deserves further exploration. Specifically, those PPO patients who first received PC services in the LMOL had higher odds of dying in the PICU. Although the nature of this finding is associative rather than causal, it highlights the need for prospective investigation of the impact of earlier PC involvement on goal-concordant care around location of death. Institution-specific automatic PC consultation for select high-risk patient subpopulations is one potential strategy to facilitate earlier PC involvement,⁴¹ and our center is currently investigating the feasibility and effect of “trigger-based” PC consults for all children who undergo hematopoietic stem cell transplantation. A significant barrier to this model centers on oncologist resistance to the concept of a “trigger,” which intrinsically connotes a “forced” or “imposed” intervention;^{41,77} at our institution, we have found it to be helpful to reframe the concept of a “trigger” as simply an “institutional standard of care” for a prior-identified high-risk subgroups. Automatic PC involvement in the context of PICU hospitalization has not been well-described in the context of pediatric oncology, and we hope that these data may serve as a foundation upon which to begin a dialogue about the possible benefits of routine standardized PC integration for children with high-risk cancer and their families.

This study has a number of limitations. First, it represents the experience of a single large academic cancer center that treats patients from across the country and internationally, with a potential selection bias for higher risk patients and families seeking more aggressive therapies. However, we hypothesize that children with high-risk cancer enrolled on a PC service do not reflect the average pediatric oncology population, regardless of institution. Based on our single-center findings, we believe that this population is a uniquely vulnerable sub-cohort that faces significant challenges irrespective of the treating center, and we advocate for the development of multi-site studies to investigate the illness and EOL experiences specific to PPO patients across the country and globally. Second, retrospective data abstraction relies on precise clinical documentation. Although incomplete or missing data was minimal in this study, we cannot be certain that missing data occurred randomly. Third, retrospective cohort design limits our ability to make conclusions about chronology or causality; rather, we have identified consequential associations that warrant further investigation through prospective study. Fourth, for the minority of patients who left the

institution, it is not possible to parse out the influence of institution-provided PC versus local care. For those patients who died outside of our catchment area, we rarely have access to documentation from local centers or hospices. In our experience, however, the vast majority of patients and families who opt to go home at the EOL (whether locally or to other regions) do so with advance directives in place, such that we would expect patients who die at home to have similar EOL trajectories with regards to the metrics that we queried (i.e., receipt of aggressive interventions, hospitalizations, advance directives, etc), regardless of whether they were followed by our PC team or by a local hospice. Our PC team also provides close guidance via telephone to local hospices, so care recommendations are fairly standardized regardless of where the patient is located at the EOL. For the very small minority of PPO patients who go elsewhere to seek further cancer-directed therapy, however, we have limited information regarding their illness and EOL experiences, inhibiting examination of influences of institutional PC as compared to local cancer care.

CONCLUSION

Children with high-risk cancer who receive PC often experience a high burden of intensive treatments during the illness course and at EOL, and a substantial number of PPO patients die in the PICU setting. PC involvement occurring less than a month prior to death is associated with increased risk of dying in the PICU for PPO patients. Further prospective investigation is needed to better understand how early PC involvement in children with high-risk cancer impacts both goal concordance and cost-effectiveness of care in the context of QOL and EOL.

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Abbreviations Key:

PC	Palliative care
PPO	Pediatric palliative oncology
QOL	Quality of life
EOL	End of life
PICU	Pediatric intensive care unit

References

1. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin* 2014;64(2):83–103. [PubMed: 24488779]

2. Wolfe J, Orellana L, Ullrich C, et al. Symptoms and Distress in Children With Advanced Cancer: Prospective Patient-Reported Outcomes From the PediQUEST Study. *J Clin Oncol* 2015;33(17): 1928–35. [PubMed: 25918277]
3. Ullrich CK, Dussel V, Hilden JM, Sheaffer JW, Lehmann L, Wolfe J. End-of-life experience of children undergoing stem cell transplantation for malignancy: parent and provider perspectives and patterns of care. *Blood* 2010;115(19):3879–85. [PubMed: 20228275]
4. Bona K, Dussel V, Orellana L, et al. Economic impact of advanced pediatric cancer on families. *J Pain Symptom Manage* 2014;47(3):594–603. [PubMed: 23870843]
5. Snaman JM, Kaye EC, Lu JJ, Sykes A, Baker JN. Palliative Care Involvement Is Associated with Less Intensive End-of-Life Care in Adolescent and Young Adult Oncology Patients. *J Palliat Med* 2017;jpm.2016.0451.
6. Johnson L- M, Snaman JM, Cupit MC, Baker JN. End-of-Life Care for Hospitalized Children. *Pediatr Clin North Am* 2014;61(4):835–54. [PubMed: 25084727]
7. Elkin TD, Jensen SA, McNeil L, Gilbert ME, Pullen J, McComb L. Religiosity and coping in mothers of children diagnosed with cancer: an exploratory analysis. *J Pediatr Oncol Nurs* 24(5): 274–8. [PubMed: 17827493]
8. Goldman A, Christie D. Children with cancer talk about their own death with their families. *Pediatr Hematol Oncol* 10(3):223–31. [PubMed: 8217537]
9. Lima NNR, do Nascimento VB, de Carvalho SMF, et al. Spirituality in childhood cancer care. *Neuropsychiatr Dis Treat* 2013;9:1539–44. [PubMed: 24133371]
10. Klopfenstein KJ, Hutchison C, Clark C, Young D, Ruymann FB. Variables influencing end-of-life care in children and adolescents with cancer. *J Pediatr Hematol Oncol* 2001;23(8):481–6. [PubMed: 11878774]
11. Bemis H, Yarboi J, Gerhardt CA, et al. Childhood Cancer in Context: Sociodemographic Factors, Stress, and Psychological Distress Among Mothers and Children. *J Pediatr Psychol* 2015;40(8): 733–43. [PubMed: 25840446]
12. Kamper R, Van Cleve L, Savedra M. Children with advanced cancer: responses to a spiritual quality of life interview. *J Spec Pediatr Nurs* 2010;15(4):301–6. [PubMed: 20880278]
13. Freyer DR. Children with cancer: special considerations in the discontinuation of life-sustaining treatment. *Med Pediatr Oncol* 1992;20(2):136–42. [PubMed: 1370855]
14. Ishibashi A The needs of children and adolescents with cancer for information and social support. *Cancer Nurs* 2001;24(1):61–7. [PubMed: 11219424]
15. Wolfe J, Grier HE, Klar N, et al. Symptoms and suffering at the end of life in children with cancer. *N Engl J Med* 2000;342(5):326–33. [PubMed: 10655532]
16. Mack JW, Cook EF, Wolfe J, Grier HE, Cleary PD, Weeks JC. Understanding of prognosis among parents of children with cancer: parental optimism and the parent-physician interaction. *J Clin Oncol* 2007;25(11):1357–62. [PubMed: 17416854]
17. Mack JW, Wolfe J, Cook EF, Grier HE, Cleary PD, Weeks JC. Hope and prognostic disclosure. *J Clin Oncol* 2007;25(35):5636–42. [PubMed: 18065734]
18. Mack JW, Joffe S, Hilden JM, et al. Parents' views of cancer-directed therapy for children with no realistic chance for cure. *J Clin Oncol* 2008;26(29):4759–64. [PubMed: 18779605]
19. Mack JW, Cronin A, Taback N, et al. End-of-life care discussions among patients with advanced cancer: a cohort study. *Ann Intern Med* 2012;156(3):204–10. [PubMed: 22312140]
20. Mack JW, Wolfe J, Grier HE, Cleary PD, Weeks JC. Communication about prognosis between parents and physicians of children with cancer: parent preferences and the impact of prognostic information. *J Clin Oncol* 2006;24(33):5265–70. [PubMed: 17114660]
21. Waldman ED, Levine JM. The Day Two Talk: Early Integration of Palliative Care Principles in Pediatric Oncology. *J Clin Oncol* 2016;34(34):4068–70. [PubMed: 27646941]
22. Hill DL, Miller V, Walter JK, et al. Regoaling: a conceptual model of how parents of children with serious illness change medical care goals. *BMC Palliat Care* 2014;13(1):9. [PubMed: 24625345]
23. Wolfe L Should parents speak with a dying child about impending death? *N Engl J Med* 2004;351(12):1251–3. [PubMed: 15371583]

24. Hurwitz CA, Duncan J, Wolfe J. Caring for the child with cancer at the close of life: “there are people who make it, and I’m hoping I’m one of them”. *JAMA* 2004;292(17):2141–9. [PubMed: 15523075]
25. Rosenberg AR, Postier A, Osenga K, et al. Long-Term Psychosocial Outcomes Among Bereaved Siblings of Children With Cancer. *J Pain Symptom Manage* 2014;
26. Hui D, Finlay E, Buss MK, Prommer EE, Bruera E. Palliative Oncologists: Specialists in the Science and Art of Patient Care. *J Clin Oncol* 2015;33(20):2314–7. [PubMed: 25918292]
27. Tanco K, Rhondali W, Perez-Cruz P, et al. Patient Perception of Physician Compassion After a More Optimistic vs a Less Optimistic Message: A Randomized Clinical Trial. *JAMA Oncol* 2015;1(2):176–83. [PubMed: 26181019]
28. Zhukovsky DS, Herzog CE, Kaur G, Palmer JL, Bruera E. The impact of palliative care consultation on symptom assessment, communication needs, and palliative interventions in pediatric patients with cancer. *J Palliat Med* 2009;12(4):343–9. [PubMed: 19327071]
29. Ferris FD, Bruera E, Cherny N, et al. Palliative cancer care a decade later: accomplishments, the need, next steps -- from the American Society of Clinical Oncology. *J Clin Oncol* 2009;27(18):3052–8. [PubMed: 19451437]
30. Bruera E, Hui D. Integrating supportive and palliative care in the trajectory of cancer: establishing goals and models of care. *J Clin Oncol* 2010;28(25):4013–7. [PubMed: 20660825]
31. Fadul N, Elsayem A, Palmer JL, et al. Supportive versus palliative care: what’s in a name?: a survey of medical oncologists and midlevel providers at a comprehensive cancer center. *Cancer* 2009;115(9):2013–21. [PubMed: 19235253]
32. Hui D, Bruera E. Models of integration of oncology and palliative care. *Ann Palliat Med* 2015;4(3):89–98. [PubMed: 26231806]
33. Dhillon N, Kopetz S, Pei BL, Fabbro E Del, Zhang T, Bruera E. Clinical findings of a palliative care consultation team at a comprehensive cancer center. *J Palliat Med* 2008;11(2):191–7. [PubMed: 18333733]
34. Parikh RB, Kirch RA, Smith TJ, Temel JS. Early specialty palliative care--translating data in oncology into practice. *N Engl J Med* 2013;369(24):2347–51. [PubMed: 24328469]
35. Berendt J, Stiel S, Simon ST, et al. Integrating Palliative Care Into Comprehensive Cancer Centers: Consensus-Based Development of Best Practice Recommendations. *Oncologist* 2016;21(10):1241–9. [PubMed: 27440065]
36. Smith TJ, Temin S, Alesi ER, et al. American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. *J Clin Oncol* 2012;30(8):880–7. [PubMed: 22312101]
37. 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* 2016;34:1–17. [PubMed: 26578609]
38. Weaver MS, Heinze KE, Bell CJ, et al. Establishing psychosocial palliative care standards for children and adolescents with cancer and their families: An integrative review. *Palliat Med* 2015;
39. Wolfe J, Friebert S, Hilden J. Caring for children with advanced cancer integrating palliative care. *Pediatr Clin North Am* 2002;49(5):1043–62. [PubMed: 12430625]
40. Kaye EC, Friebert S, Baker JN. Early Integration of Palliative Care for Children with High-Risk Cancer and Their Families. *Pediatr Blood Cancer* 2016;63(4):593–7. [PubMed: 26579997]
41. Kaye EC, Rubenstein J, Levine D, Baker JN, Dabbs D, Friebert SE. Pediatric palliative care in the community. *CA Cancer J Clin* 2015;65(4):315–33.
42. Waldman E, Wolfe J. Palliative care for children with cancer. *Nat Rev Clin Oncol* 2013;10(2):100–7. [PubMed: 23337915]
43. Schmidt P, Otto M, Hechler T, Metzger S, Wolfe J, Zernikow B. Did increased availability of pediatric palliative care lead to improved palliative care outcomes in children with cancer? *J Palliat Med* 2013;16(9):1034–9. [PubMed: 23901834]
44. Vollenbroich R, Duroux A, Grasser M, Brandstätter M, Borasio GD, Führer M. Effectiveness of a pediatric palliative home care team as experienced by parents and health care professionals. *J Palliat Med* 2012;15(3):294–300. [PubMed: 22216782]

45. Groh G, Vyhnaek B, Feddersen B, Führer M, Borasio GD. Effectiveness of a specialized outpatient palliative care service as experienced by patients and caregivers. *J Palliat Med* 2013;16(8):848–56. [PubMed: 23678854]
46. Groh G, Borasio GD, Nickolay C, Bender H-U, von Lüttichau I, Führer M. Specialized pediatric palliative home care: a prospective evaluation. *J Palliat Med* 2013;16(12):1588–94. [PubMed: 24168349]
47. Gans D, Kominski GF, Roby DH, et al. Better outcomes, lower costs: palliative care program reduces stress, costs of care for children with life-threatening conditions. *Policy Brief UCLA Cent Health Policy Res* 2012;(PB2012–3):1–8.
48. Snaman JM, Kaye EC, Levine DR, et al. Pediatric Palliative Oncology: A New Training Model for an Emerging Field. *J Clin Oncol* 2016;34(3):288–9. [PubMed: 26598743]
49. Feudtner C, Kang TI, Hexem KR, et al. Pediatric palliative care patients: a prospective multicenter cohort study. *Pediatrics* 2011;127(6):1094–101. [PubMed: 21555495]
50. Brock KE, Steineck A, Twist CJ. Trends in End-of-Life Care in Pediatric Hematology, Oncology, and Stem Cell Transplant Patients. *Pediatr Blood Cancer* 2016;63(3):516–22. [PubMed: 26513237]
51. Levine DR, Johnson L- M, Snyder A, et al. Integrating Palliative Care in Pediatric Oncology: Evidence for an Evolving Paradigm for Comprehensive Cancer Care. *J Natl Compr Canc Netw* 2016;14(6):741–8. [PubMed: 27283167]
52. Feudtner C, DiGiuseppe DL, Neff JM. Hospital care for children and young adults in the last year of life: a population-based study. *BMC Med* 2003;1:3. [PubMed: 14690540]
53. Feudtner C, Feinstein JA, Satchell M, Zhao H, Kang TI. Shifting place of death among children with complex chronic conditions in the United States, 1989–2003. *JAMA* 2007;297(24):2725–32. [PubMed: 17595273]
54. Gemke RJ, van Vught JA. Scoring systems in pediatric intensive care: PRISM III versus PIM. *Intensive Care Med* 2002;28(2):204–7. [PubMed: 11907665]
55. Gonçalves J- P, Severo M, Rocha C, Jardim J, Mota T, Ribeiro A. Performance of PRISM III and PELOD-2 scores in a pediatric intensive care unit. *Eur J Pediatr* 2015;174(10):1305–10. [PubMed: 25875250]
56. Heying R, Schneider DT, Körholz D, Stannigel H, Lemburg P, Göbel U. Efficacy and outcome of intensive care in pediatric oncologic patients. *Crit Care Med* 2001;29(12):2276–80. [PubMed: 11801824]
57. Dursun O, Hazar V, Karasu GT, Uygun V, Tosun O, Yesilipek A. Prognostic factors in pediatric cancer patients admitted to the pediatric intensive care unit. *J Pediatr Hematol Oncol* 2009;31(7):481–4. [PubMed: 19564740]
58. van Veen A, Karstens A, van der Hoek AC, Tibboel D, Hählen K, van der Voort E. The prognosis of oncologic patients in the pediatric intensive care unit. *Intensive Care Med* 1996;22(3):237–41. [PubMed: 8727438]
59. Snaman JM, Kaye EC, Lu JJ, Sykes A, Baker JN. Palliative Care Involvement Is Associated with Less Intensive End-of-Life Care in Adolescent and Young Adult Oncology Patients. *J Palliat Med* 2017;jpm.2016.0451.
60. Thienprayoon R, Lee SC, Leonard D, Winick N. Racial and ethnic differences in hospice enrollment among children with cancer. *Pediatr Blood Cancer* 2013;60(10):1662–6. [PubMed: 23733549]
61. Loggers ET, Maciejewski PK, Paulk E, et al. Racial Differences in Predictors of Intensive End-of-Life Care in Patients With Advanced Cancer. *J Clin Oncol* 2009;27(33):5559–64. [PubMed: 19805675]
62. Johnson KS. Racial and Ethnic Disparities in Palliative Care. *J Palliat Med* 2013;16(11):1329–34. [PubMed: 24073685]
63. Connor S, Elwert F, Spence C, Christakis N. Racial disparity in hospice use in the United States in 2002. *Palliat Med* 2008;22(3):205–13. [PubMed: 18477714]
64. Sharma RK, Cameron KA, Chmiel JS, et al. Racial/Ethnic Differences in Inpatient Palliative Care Consultation for Patients With Advanced Cancer. *J Clin Oncol* 2015;33(32):3802–8. [PubMed: 26324373]

65. Baker JN, Rai S, Liu W, et al. Race Does Not Influence Do-Not-Resuscitate Status or the Number or Timing of End-of-Life Care Discussions at a Pediatric Oncology Referral Center. *J Palliat Med* 2009;12(1):71–6. [PubMed: 19284266]
66. Adersen M, Thygesen LC, Jensen AB, Neergaard MA, Sjøgren P, Groenvold M. Is admittance to specialised palliative care among cancer patients related to sex, age and cancer diagnosis? A nation-wide study from the Danish Palliative Care Database (DPD). *BMC Palliat Care* 2017;16(1):21. [PubMed: 28330507]
67. Wolfe J, Hammel JF, Edwards KE, et al. Easing of suffering in children with cancer at the end of life: is care changing? *J Clin Oncol* 2008;26(10):1717–23. [PubMed: 18375901]
68. Rosenman MB, Vik T, Hui SL, Breitfeld PP. Hospital resource utilization in childhood cancer. *J Pediatr Hematol Oncol* 2005;27(6):295–300. [PubMed: 15956880]
69. O'Dowd EL, McKeever TM, Baldwin DR, Hubbard RB. Place of Death in Patients with Lung Cancer: A Retrospective Cohort Study from 2004–2013. *PLoS One* 2016;11(8):e0161399. [PubMed: 27551922]
70. National Hospice and Palliative Care Organization. ChiPPS White Paper: A call for change: recommendations to improve the care of children living with life-threatening conditions. 2001.
71. Friebert SE, Williams C. National Hospice and Palliative Care Organization's Facts and Figures: Pediatric Palliative & Hospice Care in America 2015.
72. Varela AMS, Deal AM, Hanson LC, Blatt J, Gold S, Dellon EP. Barriers to hospice for children as perceived by hospice organizations in North Carolina. *Am J Hosp Palliat Care* 2012;29(3):171–6. [PubMed: 21712308]
73. Baker JN, Levine DR, Hinds PS, et al. Research Priorities in Pediatric Palliative Care. *J Pediatr* 2015;167(2):467–470.e3. [PubMed: 26028284]
74. Hilden J It is Time to Let in Pediatric Palliative Care. *Pediatr Blood Cancer* 2016;63(4):583–4. [PubMed: 26797913]
75. Levine DR, Mandrell BN, Sykes A, et al. Patients' and Parents' Needs, Attitudes, and Perceptions About Early Palliative Care Integration in Pediatric Oncology. *JAMA Oncol* 2017;
76. Feudtner C The breadth of hopes. *N Engl J Med* 2009;361(24):2306–7. [PubMed: 20007559]
77. Wentlandt K, Krzyzanowska MK, Swami N, et al. Referral practices of pediatric oncologists to specialized palliative care. *Support Care Cancer* 2014;22(9):2315–22. [PubMed: 24671435]

TABLE 1

Pediatric palliative oncology deceased cohort data abstraction items

Category	Subcategory
Demographic attributes	<ul style="list-style-type: none"> Gender Race Ethnicity Geographic affiliation
Disease attributes	<ul style="list-style-type: none"> Primary cancer diagnosis Secondary cancer diagnosis (if applicable) Date of diagnosis(es) Age at diagnosis(es)
Treatment attributes	<ul style="list-style-type: none"> Standard vs. experimental chemotherapy Phase I trial participation Hematopoietic stem cell transplant: type and number Relapse or progression during disease course Evidence of cancer in the last month of life Cancer-directed therapy in the last month of life
PICU history	<ul style="list-style-type: none"> Admissions: number of hospitalizations and days spent in PICU Morbidity and mortality scores: PIM2/3, PELOD, PRISM III Intubation/ventilator history Pressor requirements Dialysis requirements Invasive procedures: liver biopsy, paracentesis, peritoneal drain placement, thoracentesis, chest tube placement Cardiopulmonary resuscitation
EOL attributes	<ul style="list-style-type: none"> Age at death Date of death Location of death For patients who died in the hospital <ul style="list-style-type: none"> Admission circumstances Intubation/ventilator history Pressor requirements Cardiopulmonary resuscitation For all patients, regardless of location of death <ul style="list-style-type: none"> Dialysis requirements Invasive procedures: liver biopsy, paracentesis, peritoneal drain placement, thoracentesis, chest tube placement
PC involvement	<ul style="list-style-type: none"> Date of first PC meeting Time between diagnosis and first meeting Time between first meeting and death

Category	Subcategory
	<ul style="list-style-type: none">• Total number of documented PC visits• Documentation of goals of care at first consult• Documentation and timing of advance directives

Abbreviations: PICU, pediatric intensive care unit; EOL, end-of-life; PC, palliative care.

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TABLE 2

Demographics of pediatric palliative oncology (PPO) patients

Characteristics	PPO (N=321)	All-comers ^a (N=2058)	P ^b
Gender			0.205
Male	187 (58.3%)	1121 (54.5%)	
Female	134 (41.7%)	937 (45.5%)	
Race			0.031
Unknown	5 (1.6%)	18 (0.9%)	
White	217 (67.6%)	1473 (71.6%)	
Black/African American	60 (18.7%)	406 (19.7%)	
Other	39 (12.1%)	161 (7.8%)	
Ethnicity			<0.0001
Unknown	0	75 (3.6%)	
Hispanic/Latino	58 (18.1%)	153 (7.4%)	
Non-Hispanic	263 (81.9%)	1830 (88.9%)	
Religious affiliation			
Unknown/Unaffiliated	27 (8.4%)		
Christian/Catholic	284 (88.4%)		
Other	10 (3.1%)		
Geographic affiliation			
Northeast	17 (5.3%)		
Midwest	53 (16.5%)		
South	215 (67%)		
West	11 (3.4%)		
International	25 (7.8%)		

^a All-comers excludes the 321 PPO patients.^b p-value is calculated excluding the “unknown” category.

TABLE 3

Disease and treatment history of pediatric palliative oncology patients

Characteristics	n=321
Primary cancer diagnosis	
Brain Tumor	139 (43.3%)
Leukemia/Lymphoma	77 (24%)
Solid Tumor	105 (32.7%)
Age at diagnosis, years	
0–5	148 (46.1%)
6–12	93 (29%)
13	80 (24.9%)
Median (range)	6.8 (0–21.5)
Secondary cancer diagnosis	
No	303 (94.4%)
Yes	18 (5.6%)
Leukemia/ Lymphoma	5 (27.8%)
Solid Tumor	5 (27.8%)
Brain Tumor	8 (44.4%)
Treatment plan	
Unknown	11 (3.4%)
Standard therapy ^a	54 (16.8%)
Experimental protocol therapy ^b	255 (79.4%)
No treatment	1 (0.3%)
Received HSCT	
No	242 (75.4%)
Yes	79 (24.6%)
No. of transplants	
1	65 (82.3%)
2	13 (16.5%)
3	1 (1.3%)
Median (IQR) [range]	1 (1–1) [1–3]
Relapse/disease progression during disease course	
Unknown	2 (0.6%)
No	7 (2.2%)
Yes	312 (97.2%)
Evidence of disease during the last month of life	
Unknown	29 (9%)
No	11 (3.4%)
Yes	281 (87.5%)
Enrollment/participation in a Phase I protocol	
Unknown	6 (1.9%)
No	185 (57.6%)

Characteristics	n=321
Yes	130 (40.5%)
Received cancer-directed therapy during the LMOL	
Unknown	61 (19%)
No	146 (45.5%)
Yes	114 (35.5%)

Abbreviations: IQR, interquartile range; HSCT, hematopoietic stem cell Transplantation; LMOL, last month of life.

^aRefers to patients who received standard therapy exclusively.

^bRefers to patients who received experimental therapy at any point during their illness trajectory.

TABLE 4

PICU history of pediatric palliative oncology patients

Characteristics	
<i>No. of patients with at least one PICU hospitalization</i>	<i>165</i>
Total no. of PICU hospitalizations	
1	84 (50.9%)
2	47 (28.5%)
3	34 (20.6%)
Median (IQR) [range]	1 (1–2) [1–8]
Total no. of days in PICU ^a , Median (IQR) [range]	8 (4–17) [1–128]
Required ventilator support	
No	91 (55.2%)
Yes	74 (44.8%)
Total no. of days on ventilator support	
7	39 (52.7%)
>7	35 (47.3%)
Median (IQR) [range]	6.5 (2–17) [1–161]
Required HFOV support	
No	149 (90.3%)
Yes	16 (9.7%)
Total no. of days on HFOV support, Median (IQR) [range]	4 (1–9) [1–26]
Had tracheostomies placed	
Unknown	1 (0.6%)
No	154 (93.9%)
Yes	9 (5.5%)
Required pressor support	
No	107 (64.8%)
Yes	58 (35.2%)
Total no. of days on pressor support, Median (IQR) [range]	5 (2–9) [1–54]
Required CVVHD or CRRT	
Unknown	1 (0.6%)
No	153 (92.7%)
Yes	11 (6.7%)
Total no. of days of CVVHD or CRRT, Median (IQR) [range]	3 (2–15) [2–33]
Underwent invasive procedures ^b	
Unknown	1 (0.6%)
No	131 (79.4%)
Yes	33 (20%)
Underwent CPR ^c	
Unknown	1 (0.6%)
No	144 (87.3%)

Characteristics	
Yes	20 (12.1%)
Total no. of CPRs, Median (IQR) [range]	1 (1–1) [1–4]

Abbreviations: PICU, pediatric intensive care unit; IQR, interquartile range; HFOV, high frequency oscillatory ventilation; CVVHD, continuous veno-venous hemodialysis; CRRT, continuous renal replacement therapy; CPR, cardiopulmonary resuscitation.

^aNumber of days in PICU is underestimated for 2 patients on their last PICU hospitalization because dates were poorly documented.

^binvasive procedures are defined as paracentesis, thoracentesis, chest tube placement, and organ biopsies.

^cCPR is inclusive of chest compressions, administration of cardiac medications, and/or shock therapy.

TABLE 5

Quality of life and end-of-life characteristics of pediatric palliative oncology patients

Characteristics	N=321
Time from diagnosis to first PC consultation (days)	
Median (IQR) [range]	453 (207–1062) [1–7319]
Documentation of goals of care at first PC consult	321 (100%)
Types of goals of care documented at first PC consult	
Cure	87 (27.1%)
Life prolongation with focus on cure	41 (12.8%)
Life prolongation with focus on comfort	131 (40.8%)
Comfort only	61 (19%)
Undecided	1 (0.3%)
Time from first PC consultation to death (days)	
<30 days	85 (26.5%)
30 days	236 (73.5%)
Median (IQR) [range]	79 (27–184) [0–2075]
No. of PC clinical notes	
Median (IQR) [range]	7 (4–13) [0–81]
Ethics involvement	
No	313 (97.5%)
Yes	8 (2.5%)
Community-based hospice involvement	
Unknown	2 (0.6%)
No	59 (18.4%)
Yes	260 (81%)
Location of death	
Unknown	18 (5.6%)
Hospital, ICU ^a	54 (16.8%)
Hospital, Non-ICU	68 (21.2%)
Home/St. Jude Residence	170 (53%)
Hospice	11 (3.4%)
Age at death, years	
0–5	92 (28.7%)
6–12	117 (36.4%)
13	112 (34.9%)
Median (range)	9.9 (0.2–30.1)
Advance directive order in place	
Unknown	72 (22.4%)
No	24 (7.5%)
Yes	225 (70.1%)
Days from advance directive to death	
7	58 (25.8%)

Characteristics	N=321
>7	167 (74.2%)
Median (IQR) [range]	23 (6–60) [0–677]

Abbreviations: PC, palliative care; IQR, interquartile range; ICU, intensive care unit.

^aIncludes four patients who died in the emergency department.

TABLE 6

Multinomial logistic regression modeling of the association between days from first PC consult to death and location of death

	Hospital PICU ^a		Hospital Non-ICU	
	OR (95% CI)	P	OR (95% CI)	P
Days from first PC consult to death				
30	Reference		Reference	
<30	4.7 (2.47–8.97)	<0.0001	1.07 (0.54–2.09)	0.855

Abbreviations: PC, palliative care.

Model is based on a sample size of 303. The reference category is the outpatient setting.

^aIncludes four patients who died in the emergency department.