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Impact of Specialized Pediatric Palliative Care: A Systematic Review

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Abstract

Context: Specialized pediatric palliative care (SPPC) is increasingly involved in the care of seriously ill children, yet the evidence on its impact has not been comprehensively reviewed.

Objective: To assess the effects of providing SPPC to seriously ill children on patient-, caregiver-, and systems-level outcomes.

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Contributors' Statement Page

Dr. Marcus conceptualized and designed the study, designed the data collection instruments, collected data, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

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Dr. Ciapponi conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Mr. Comandé designed and implemented the search strategy, oversaw study screening and selection, and critically reviewed the manuscript for important intellectual content.

Ms. Bilodeau collected and analyzed data and critically reviewed the manuscript for important intellectual content.

Dr. Wolfe conceptualized and designed the study, coordinated and supervised data collection, and reviewed and revised the manuscript.

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All authors have completed and submitted the Disclosure of Potential Conflict of Interests forms. KM, GS, DC, and AC indicated no potential conflicts of interest, whereas JW and VD indicated potential academic conflict of interest as they are authors of four and one of the included articles respectively. Of note, they did not participate in data extraction of papers where authorship involved potential conflict.

Methods: We performed a Systematic Review following Cochrane methods. *Data Sources:* Medline, Embase, PsycINFO, Global Health, The Cochrane Central Register of Controlled Trials, LILACS, and Web of Science were searched from January 1996 to June 2018. *Study Selection/ Data Extraction* ; We included randomized controlled, cohort, case-control, and before-after studies in which exposure to SPPC services was the intervention of interest. All outcomes reported in these studies were included. Two investigators independently selected articles, extracted data, and assessed risk of bias of included studies using standardized criteria.

Results: Twenty-four studies were included in qualitative synthesis: one non-randomized controlled trial, 16 cohort studies, and seven before-after studies. Evidence certainty was low. Twenty-one studies had 1 area with high risk of bias, most commonly selection bias, low group comparability, risk for confounding, and inadequate statistical reporting. Studies analyzed 46 domains, operationalized as 136 distinct outcomes. SPPC was associated with better child quality of life (QOL) scores in all four studies that assessed this outcome. No other outcome showed this consistency.

Conclusions: Receiving SPPC was associated with better child QOL. However, the paucity and low certainty of the evidence precluded any firm recommendations about SPPC practice. Larger collaborative networks and greater consensus regarding SPPC research standards are needed.

PROSPERO Registration Number: CRD42016049533

Keywords

Palliative care; pediatrics; outcome assessment; end of life; patient-reported outcomes; systematic review

Introduction

Specialized pediatric palliative care (SPPC) is an integrative model of care for children with life-threatening illnesses that aims to ease suffering, improve child and family quality of life (QOL), and support families in delineating their goals of care and making decisions accordingly.(1) For nearly two decades, the National Academy of Medicine and the American Academy of Pediatrics have recommended involvement of SPPC early in the illness course and concurrent with disease-directed therapies.(2,3) Recognized by the American Board of Medical Subspecialties since 2006 with subsequent formation of dedicated fellowship training programs,(4) SPPC has grown rapidly as a field over the last decade with increasing numbers of SPPC programs across the United States, particularly in academic hospital settings.(5) Nonetheless, significant heterogeneity exists between programs with regards to SPPC team composition, the spectrum of and availability of services provided, and funding.

Despite the recent growth of SPPC programs in hospitals nationwide, evidence-based research to guide standards of practice is lacking, deterring implementation of SPPC services.(6) Furthermore, there is no consensus as to which outcomes or outcome metrics should be used to evaluate the impact of SPPC. Two recent systematic reviews studied the instruments and indicators chosen to evaluate pediatric palliative care and identified substantial variability along with scarce use of valid child-reported measures.(7,8) Other

reviews have focused on a particular SPPC model or a specific outcome domain and have revealed a small number of studies representing a scarce body of evidence.(9,10) These findings are similar to what has been reported in the adult palliative care literature, in which recent systematic reviews have also demonstrated significant methodologic limitations and outcome heterogeneity, with varying evidence of effects on patient-, family-, and systems-level outcomes.(11–17) To our knowledge, no review has reported on the full spectrum of SPPC intervention studies to date, including description of the exposure and impact and a critical assessment of the existing literature.

As part of the formative research contributing to the development of a complex SPPC intervention, we sought to systematically summarize and critically evaluate the available evidence on effects of providing SPPC to children with serious illnesses and their families on patient and health system outcomes.

Methods

The methodology for this review was informed by the Cochrane Collaboration's Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist.(18) This review was registered with PROSPERO (<http://www.crd.vork.ac.uk/PROSPERO/>) under protocol registration number CRD42016049533.

Selection Criteria

We defined the following inclusion criteria: (1) **study design:** randomized controlled trials (RCTs), cohort studies, case-control studies, and before-after studies. Observational non-comparative studies (e.g., cross-sectional studies, case series) were excluded; (2) **population:** individuals eligible for SPPC care; no limitations were placed on patient age or patient diagnosis due to the heterogeneity of the population seen by SPPC teams; (3) **intervention/exposure:** receipt of SPPC services, defined as comprehensive care provided by individuals or teams that is distinct from and complementary to the services provided by the primary medical team. Thus, studies examining the impact of a singular component of pediatric palliative care (e.g., pain management) or primary palliative care interventions (e.g., advance care planning provided by clinicians not specialized in PPC), were excluded; also, studies that focused on a specific result (e.g., location of death), were excluded only if SPPC exposure was not the primary independent variable studied; (4) **control:** individuals receiving usual/standard care; (5) **setting:** inpatient, ambulatory, home, or inpatient hospice; (6) **outcomes:** although initially QOL was defined as the primary outcome, the scarcity of publications meeting this criterion led to the broadening of our search to include any type of outcome so as to better describe the range of effects represented in the literature; and (7) **publication status and language:** studies published in a peer-reviewed journal in English, Spanish, or French.

Search Strategy

We searched Medline, Embase, PsycINFO, Global Health, The Cochrane Central Register of Controlled Trials, LILACS, and Web of Science (January 1996 to June 2018). In addition,

we searched the following clinical trial registries through December 2018: ISCRTN (a registry of observational and interventional trials), clinicaltrials.gov, the WHO International Clinical Trials Registry Platform (IC-TRP), and the European registry. With input from the review team, a professional librarian (DC) formulated the search strategy and performed the search, including modification of the strategy based on initial results (see Appendix, Table A1 for complete search strategy). We manually reviewed reference lists of included studies and related systematic reviews to identify additional relevant studies.

Study Screening and Selection

For the screening and selection process we used the Early Review Organizing Software (EROS),(19) a web-based software program developed by the Cochrane Center at the Institute of Clinical Effectiveness and Health Policy in Buenos Aires, Argentina. EROS organizes the various phases of a systematic review and facilitates independent review of studies, discrepancy reconciliation, and risk of bias assessment.

Titles and abstracts were independently screened by pairs of co-authors. Two reviewers (KM and GS) independently screened full-text manuscripts of all potentially eligible references. If eligibility was unclear, we contacted study authors. Discrepancies were resolved at each stage through discussion and involvement of a third reviewer if necessary.

Data extraction

For each included article, we systematically collected the following variables using EROS: (1) study design; (2) setting; (3) study population (i.e., source, number of participants enrolled, diagnostic categories represented); (4) definitions of exposure and control; (5) outcomes and outcome measures; and (6) results.

Risk of Bias Assessment

Given that all but one of the studies generated by the search were observational studies, risk of bias was critically evaluated using an adapted version of the quality criteria outlined by Sanderson et al.,(20) including the following domains: 1) methods for selecting study participants; 2) methods for measuring exposure and outcome variables; 3) methods to control confounding; 4) statistical methods; 5) conflict of interest; and 6) comparability between groups, a domain added to better represent the risk of bias of included studies. For the single controlled trial identified, we additionally evaluated random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Regarding assessment of bias in the measurement of subjective outcomes (e.g., patient symptoms and quality of life), based on published recommendations(21) we developed a guide to evaluate risk of bias. We considered risk to be low when patient-reported outcomes were self-reported (or equivalent, depending on participant's age/developmental status) through measures with proven validity, reliability and responsiveness, and we considered risk to be high when outcomes were not self-reported and instruments had not undergone any formal validation (see Appendix, Table A2 for more details). Two reviewers (KM and GS) independently assigned risk as "low," "high," or "unclear," and a senior author (VD) reviewed all determinations and associated justifications. Disagreements were resolved through discussion with the full review team.

Synthesis

We planned to conduct a meta-analysis of marginal heterogeneity of study design, outcomes, and reporting of results. If not feasible, we planned to summarize results through a qualitative synthesis focused on outcomes and risk of bias. Outcomes were grouped into conceptual categories to summarize their measurement and reported effects. We decided to show the effects reported to describe potential trends, or lack thereof, that may aid future research efforts. Risk of bias was assessed by domain; we used graphs to summarize risk of bias across studies. As recommended by the Cochrane collaboration,(22) we did not estimate composite scores by paper. For domains that had more than one element (e.g., studies with more than one outcome in the same category), we assigned the highest risk level observed across elements.

Results

Description of Studies

We identified 5412 individual articles by our search strategy and included twenty-four studies. The selection process and reasons for article exclusions are presented in Figure 1.

Characteristics of included studies are presented in Table 1. The 24 publications spanned the years 2001–2018, with 79% (19/24) published in the last five years (2013 or later).(23–41) Sample sizes and participant characteristics varied significantly across studies. Greater than half of the studies (13/24) had a sample size of fewer than 100 subjects. (24–29,32,34,38–40,42,43) Fourteen studies exclusively represented the experience of decedents.(23,24,29–31,34,36–38,40,41,44–46) Out of the 21 studies that provided diagnostic information, nine included only patients with cancer,(23,24,29,34,37,40,41,45,46) two only patients with non-oncologic diagnoses,(39,43) and ten included patients with cancer or other diagnoses.(25–27,30,31,33,36,38,42,44) Fifteen studies conducted in the United States(24–26,30–33,35–37,39,40,42,44,45) reported the experience of ten SPPC teams and one was a large database analysis; three were based in England,(23,28,43) Germany(27,34) and Canada(29,41) had two publications each, and Israel(46) and Singapore(38) one.

Notably, only one controlled trial (non-randomized) was identified in the search.(39) A majority of studies (16/24) used a cohort design: one prospective(32) and 15 retrospective; (23,24,29–31,34–38,40,41,44–46) the remaining were uncontrolled before/after studies.(25–28,33,38,42,43) One study used two designs: a retrospective cohort and an uncontrolled before/after.(38) Half of the studies were survey-based,(24,25,27–29,32,34,38,39,42,43,45) and only one of these used a patient-reported outcome; the other survey studies used outcomes reported by parents or primary caregivers.

Description of Exposure/Intervention groups

Regarding the SPPC exposure/intervention, 19 out of 24 studies evaluated the impact of single SPPC programs (characteristics described in Table 1), whereas five described the impact of SPPC from a population-based (i.e. county, state/province, national) perspective.

Descriptions of the intervention or exposure under study often emphasized different components and rarely included enough detail about team composition, the setting in which the team worked, or the team's activities and frequency, rendering comparison difficult. Only three studies thoroughly described these four characteristics, either in the methods section or as part of their results.(24,25,36,39,44) Five studies did not provide any description of the team, the setting where care was provided, or their activities or frequency; three of these were population-based studies.(29,30,34,40,41) See Appendix, Table A3 for more on description of the intervention/exposure.

Most control groups consisted of “usual care,” which was operationalized as: “late or no SPPC consultation” (controlled trial), “no receipt of SPPC” (most cohort studies), and “pre-exposure” (before/after studies). Three studies used historic cohorts to examine hospital-wide(45,46) or statewide(34) systemic effects of introducing a SPPC team.

Outcomes

Across the 24 studies, 46 outcome domains and 136 outcomes were examined, representing significant heterogeneity. For ease of discussion and synthesis, we grouped outcomes into six conceptual categories. Most studies (n=14, 58%) reported on more than one outcome category and only three(23,35,39) identified a primary outcome. Therefore, we report on and evaluate risk of bias for all outcomes with equal emphasis. Outcomes are discussed in the context of their conceptual groupings. For details about individual outcomes and reported effect sizes, please refer to Table 2.

Patient symptoms and QOL—Eight of the 24 studies reported symptom and/or QOL outcomes. Six of these studies evaluated patient symptoms using three outcome domains operationalized in seven different ways. None of the studies used validated patient-reported outcome measures (PROMs), although three used parent-report via the Survey about Caring for Children with Cancer (SCCC), which is a commonly used but not formally validated survey.(47) No clear patterns emerge with regards to effects of SPPC on patient symptoms.

Patient QOL was included as an outcome domain in four studies. Each study utilized a different outcome measure and different timeframe. One study used child-report (using the Health Utilities Index), while the rest assessed caregiver-reported QOL. All studies found that SPPC exposure was associated with better scores in at least one QOL sub-domain when compared to controls, as shown in Table 2.

Caregiver outcomes—One of the most commonly studied outcome categories, included in half of the studies, was the impact of SPPC involvement on caregivers. Studies looked at ten different domains, all measured through caregiver self-report. Only half used validated questionnaires and two studies used ad hoc survey items only. Timeframes of interest varied between studies, with some focusing on the end-of-life (EOL) period and others focusing on the time during which SPPC was involved in a child's care.

Few studies measured the same outcome, with a total of 26 outcomes reported, rendering it difficult to identify any patterns. Most studies reported at least one nonsignificant result.

Five studies reported significant results in all outcomes assessed, all in the expected direction (i.e., better caregiver outcomes in the setting of exposure to SPPC).

EOL discussions—Six studies evaluated the impact of SPPC on EOL discussions, the least frequently evaluated category. A total of 24 outcomes were used to operationalize six domains. The most frequent data source for this category was the medical record, except for two studies that used parent-report (SCCC). Each study used a different outcome measure and/or timeframe.

More consistent results were observed for discussions about hospice/palliative home care, death and dying, and prognosis, which occurred more frequently and earlier among families exposed to SPPC.

Patterns of EOL care—Eleven studies included outcomes on patterns of EOL care, with nine studies including location of death as one of the outcome domains. Over 37 different outcomes were used to operationalize 11 outcome domains, many differing in their timeframe. All studies relied on medical record or administrative database review except two, which used parent-report with SCCC.

Of the nine studies examining location of death, all but one showed that patients receiving SPPC were less likely to die in the intensive care unit and/or more likely to die at home or in the palliative care unit. In addition, SPPC exposure was more consistently associated with earlier documentation of do-not-resuscitate orders and receipt of less invasive interventions and procedures; use of pain medication was not associated with exposure to SPPC.

Healthcare utilization—Healthcare utilization was operationalized as six dimensions examined in eight studies. All studies relied on review of administrative databases or medical records. There was significant heterogeneity as to how the periods and populations of interest were defined, with 33 different outcome measures used to evaluate these domains. No substantial consistencies were observed among these results.

Utilization of supportive services—Seven studies examined whether the use of supportive services was impacted by SPPC exposure. In addition, the provision of sibling support and bereavement support were also included in this category. Five studies relied on medical record documentation and two on parent-report via SCCC. All studies focused on children who had died.

Here too, each specific outcome was examined by few studies. No consistent findings emerged with regards to the involvement of supportive services. On the other hand, the two studies that investigated sibling support reported greater support among those exposed to SPPC.

Risk of Bias Assessment—The overall quality of the studies was low. Figure 2 (a and b) graphically depicts the risk of bias assessment results for the 24 studies. Justifications for each bias domain assessment can be found in the Appendix, Table A4.

The only controlled trial identified(39) was non-randomized and also had high risk of selection bias (allocation by date of birth/admission date) and performance bias (unblinded), but low risk of attrition and selective outcome reporting bias. Other potential sources of bias for this study are reported in the following sections and in Figure 2.

Participant selection—Almost half of the studies were considered to have high risk of participant selection bias, while only a third were categorized as low risk. Most significant limitations came from the study design. Observational, retrospective cohort, and before/after studies could not control how participants were allocated to groups. Reasons for being in the exposure group (SPPC) were often not clearly delineated and seemingly subject to provider preference. In addition, response rates for survey-based studies were variable, with several studies limited by low response rates (either initially or over time, when multiple surveys were involved), and reporting of response rates was non-standardized across studies (i.e., whether response rates were based on the number of potential participants who could be contacted or all potentially eligible participants), rendering their interpretation difficult. In several survey-based studies, there was no comparison of responders to non-responders, limiting judgment of selection bias and generalizability of the findings. Furthermore, several studies of parent-reported outcomes had cohorts that were predominantly female, educated, and/or white, limiting diversity of perspectives and experiences described.

Measurement of exposure and outcome variables—Nearly all studies had clear methods for measuring exposure to the SPPC team and thus were determined to be low risk.

With regards to measurement of outcome variables, the category that contributed the most significant risk of bias was the “patient symptoms and QOL” category: one study had high risk (caregiver-report using a non-validated tool) and six unclear risk (caregiver-report using validated measures when self-report was appropriate). Caregiver outcomes carried less bias; over two thirds of the studies used self-report and validated measures. In the case of the EOL discussions and health care utilization categories, risk of bias was related to risk for misclassification, use of partially validated tools (e.g., SCCC), use of non-validated imputation methods, and limitations with estimating costs. Finally, measurement of EOL care patterns and utilization of supportive services rated low on the risk of bias spectrum.

Confounding control—In only nine of the 24 studies, authors adequately controlled for potential confounding through multivariate analysis or regression modeling. In half of the studies, authors did not perform (or performed an incomplete) multivariate analysis, leading to a high risk for confounding bias. Three studies were assigned an unclear risk given that it was not possible to rule out confounding bias due to either small sample or a strict exploratory nature.

Comparability between groups—In eleven studies, the risk of bias due to poor comparability between SPPC and non-SPPC groups was high and related to important baseline differences, >20% attrition between baseline and follow-up, and changes in SPPC utilization over time that were not accounted for in analysis. In six studies, the risk of comparability bias was unclear due to lack of description of group differences, very small samples, and inability to account for secular trends in two of the historic cohorts.

Statistical methods—Only nine studies were considered to have low potential for bias introduced by the statistical methods used. Studies with high or unclear risk frequently had more than one limitation. Most did not report uncertainty measures (e.g., confidence intervals). Other problems identified included small samples, high attrition, multiple testing, no report on effect sizes, failure to use appropriate methods, and lack of description of statistical methods.

Discussion

The aim of this review was to summarize and critically assess the available evidence about the effects of SPPC exposure on children with serious illnesses and their families, regarding a broad spectrum of outcomes. Due to the variability of study design and study populations, the inconsistency in timing and characteristics of the SPPC exposure, and the heterogeneity of outcomes assessed, meta-analysis across studies was not feasible and any conclusions drawn from the data are limited. Nonetheless, the findings of this review provide a comprehensive assessment of the current state of the field and identify several important lessons to guide future SPPC research.

The need for high-quality intervention research in SPPC has long been identified as a national priority.(2) However, no published or completed RCTs or large prospective observational or multisite studies specifically evaluating the impact of SPPC were identified by this review. Except for two, all included studies were retrospective or uncontrolled before/after studies with strong methodological limitations; many had a poor description of the exposure and unclear or high risk for selection and confounding bias. Non-randomized designs, especially retrospective ones, are attractive because they are relatively feasible and involve lower costs. However, the ability to draw definitive conclusions from such studies is very limited. These designs are prone to different sources of bias, one of the most salient being the impossibility of balancing the distribution of known and, more importantly, unknown potential confounders among groups.(48) Only a few of the studies included in this review used bias amelioration strategies, such as prospective design, a concurrent control group, or adjustment by baseline factors and confounders during analysis. To move the field forward, we need to focus our efforts on the design and conduct of studies that provide evidence of a high level of certainty.

In recent years, palliative care studies among seriously ill adults have included a growing number of RCTs that, despite some methodological limitations, are bridging the knowledge gap.(49) Unfortunately, this experience cannot be directly applied to pediatrics. Children in need of SPPC are a small and heterogeneous population,(50,51) limiting the viability of single site RCTs. In addition, SPPC services are highly diverse,(5) research funding continues to be scarce,(52) and there seems to be a limited number of trained scientists.(53) Given this context, cluster randomized trials emerge as an ideal design to study SPPC interventions. However, because a high number of clusters are required to reach an effective sample size,(54) costs may be prohibitive. Instead, well-designed multisite parallel RCTs, Sequential Multiple Assignment Randomized Trial (SMART) trials,(55) or large multisite prospective observational studies may still help generate the evidence the field needs.(56,57) These studies will only be possible through research collaboratives and strong

interdisciplinary work that incorporates statisticians and social scientists. Two such networks have been developed and have published foundational work.(58–60)

This analysis also highlights the need for authors to thoroughly describe the intervention/exposure under scrutiny. The Equator Network CONSORT (Consolidated Standards of Reporting Trials) and STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statements(61,62) call for providing a detailed depiction of interventions/exposures, including their main characteristics and “dose,” to allow studies to be replicable. A clear majority of the studies included in this review did not provide information pertaining to the team’s composition, let alone types of activities or frequencies. Even when there may be wide variation among teams, or perhaps because of this, it is crucial to provide a detailed account of what SPPC encompasses, as it can help identify core subspecialty components that may be worth replicating.

We also confirmed another key challenge identified by prior systematic reviews,(7,8), that is the heterogeneity and low consensus around outcome measurement. Results from this review raise several questions regarding which outcomes are being measured and how. First, the finding that caregiver factors and patterns of EOL care were the most frequent outcomes reported led us to wonder about the main drivers of outcome selection. Based on the studies included, it seems that outcome choice is influenced by feasibility and accessibility over relevance or responsiveness. In support of this hypothesis, we observed that while alleviation of suffering and improvement of QOL are considered the essence of SPPC,(1) only one third of identified studies used these as measures of effectiveness, and only one study used PROMs. Interestingly, even with all the methodological limitations described, child QOL was one of the few outcomes to show potential responsiveness to SPPC exposure. The infrequent use of symptoms, suffering, and QOL as endpoints can be explained by the challenges related to eliciting these outcomes directly from pediatric patients, including ethical concerns about burdening a vulnerable population (50) and the paucity of valid, reliable, responsive, and age-adapted outcome measures,(63) among others. An additional barrier to more generalized use of PROMs in research studies lies in the fact that these outcomes are still under scrutiny and are often considered to have a “high risk of bias,”(48) even when there has been a call to consider PROMs “reliable outcomes.”(21) Over the past 20 years, due to growing awareness of the importance of self-report and limitations of parent and clinician proxy-reports,(63) along with an increasing number of validated tools in children,(8) approaches are gradually changing, raising hope for incorporating the child’s voice as part of routine care and research.(58,64) In addition, the methods used in this paper to appraise the risk of bias of PROMs may further encourage the use of such outcomes. Notably, caregiver experience and EOL care patterns remain meaningful outcomes in SPPC research. However, the palette of outcomes should be chosen a priori based on the target of the intervention or exposure under study.

Another salient consideration pertains to the types of outcomes we are measuring. For example, is it correct to consider the outcomes from the “EOL discussions” domain as endpoints, i.e. the result of SPPC delivery? Alternatively, should they more correctly be considered processes or intermediate measures, i.e. tasks that are inherent to SPPC delivery? In this review, none of the papers provided this distinction. If used as process measures, the

link to an expected endpoint should be demonstrated,(65) such as what has been reported for “planning location of death” or “early awareness about a child’s unrealistic chance of cure.” These have been associated with outcomes such as parental reports of feeling prepared for and comfortable with the place of death, lower intubation rates, and less use of cancer-directed therapy, among others.(66,67) The explicit description of the type of outcomes chosen will increase rigor and provide more ground to develop a theoretical framework of SPPC delivery.

Finally, many of the outcomes reported focused on the EOL period, which makes sense from a historical perspective given how the subspecialty developed.(47,68) However, as the scope of SPPC is changing and is being integrated earlier into care, it is important to develop outcomes that can account for the impact of early SPPC on seriously ill children and their families.

Limitations and Strengths

One limitation was that we were unable to perform a meta-analysis due the heterogeneity mentioned above. Also, our search strategy did not exhaustively look for grey literature, resulting in a risk for publication bias and the possibility that some studies may have been missed. Importantly, no abstracts were excluded because of language, suggesting that the risk for language restrictions is low. Recent systematic reviews that were similar in scope(7,8) did not capture any other papers that would have been included in this review. Moreover, given that we did not identify any completed clinical trials in existing trial databases, it seems unlikely that, even if we missed studies, the results of the review would change significantly.

On the other hand, this is one of the first systematic reviews to evaluate the existing evidence about the impact of SPPC and thoroughly assess its risk of bias using standardized criteria. (20) As such, we hope that these results will assist the design and conduct of future palliative care research in seriously ill children and their families.

Conclusions

Given the existing evidence is scarce and provides a low level of certainty, no firm recommendations can be made about the impact of SPPC in the care of seriously ill children. However, child QOL seems to emerge as a promising outcome. To overcome barriers to conducting high quality research, we need to strengthen and broaden existing collaborative research networks, conduct multicentered prospective studies, and reach greater consensus regarding meaningful and measurable outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

DNR	do-not-resuscitate
EOL	end of life
EROS	Early Review Organizing Software
ICU	intensive care unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMs	patient-reported outcome measures
RCT	randomized controlled trial
SCCC	The Survey about Caring for Children with Cancer
SPPC	specialized pediatric palliative care
QOL	quality of life

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Figure 1: Flow Diagram of Study Selection Process

Figure 2: Risk of Bias Graphs of the 24 Included Studies
A. Risk of bias summary by study; B. Risk of bias summary by assessed item.
Abbreviations: EOL - end of life; **HC** - healthcare; **Pt** - patient; **QOL** - quality of life

Study Characteristics

Table 1:

Author (Year)	Country	Study Design	Source Population	Participants		Diagnostic Categories	SPPC Characteristics	Outcomes					
				Sample Size	Characteristics			Pt Symptoms, QOL	Caregiver	EOL Discussions	EOL Care Patterns	HC Utilization	Supportive Services
Chong (2018)	Singapore	RCoh	Hospital-based	N=138 (SPPC: 71; non-PPC: 67)	Pts diagnosed 1 month-19 years of age who died between 2012–2015 at home or hospital AND had received care at participating hospitals (SPPC group included 7 pts that were referred from non-participating hospitals)	Cancer (43%), Other (57%)	Home-based SPPC service consisting of 1 SPPC MD, 4 pediatric nurses, 2 social workers, and 1 administrative executive; provide home and inpatient consults; 24/7 support provided by a mixed adult-pediatric service			X		X	
								X	X				
Fraser (2013)	England	RCoh	Population-based (county level)	N=443 (SPPC: 132; non-PPC: 311)	Pts 0–19 years old diagnosed between 1990–2009 (identified via cancer registry), who died prior to 08/2011 and who could be linked to hospital episode statistics data	Cancer (100%)	Hospice-based SPPC service; full-time SPPC consultant appointed in 2004; 24/7 on-call medical service; provide home visits and inpatient care					X	
Friedrichsdorf (2015)	US	RCoh	Hospital-based	N=60 (SPPC: 30; non-PPC: 30)	Bereaved parents of pts 0–17 years old who died between 2002–2008	Cancer (100%)	Palliative home care and/or home hospice care; visits by SPPC nurses, social workers, child life specialists, chaplaincy, SPPC physician; providing SPPC in community, outpatient clinic,	X	X		X		

Author (Year)	Country	Study Design	Source Population	Participants		Diagnostic Categories	SPPC Characteristics	Outcomes					
				Sample Size	Characteristics			Pt Symptoms, QOL	Caregiver	EOL Discussions	EOL Care Patterns	HC Utilization	Supportive Services
Gans (2015)	US	Ub/a	Population-based (county level)	N=93	Primary caregivers of pts <21 years old who enrolled in SPPC program between 2010–2012, who were deemed likely to be hospitalized for >30 days in next year	Neurologic/neuromuscular (44%), respiratory failure (12%), transplant-related complications (12%), cancer (13%), other (19%)	SPPC program contracting with nurses and social workers at multiple hospice and home health agencies across 11 counties; access to 24/7 on-call nurse		X				
Golan (2008)	Israel	RCoh	Hospital-based	N=246 (historic cohort: 144; intervention cohort: 102)	Historic cohort: pts who died of cancer between 1990–1999 and received care at the participating pediatric oncology department Intervention cohort: pts who died of cancer between 1999–2005 and received care at the participating pediatric oncology department	Cancer (100%)	Oncology-based SPPC team: full-time SPPC nurses; provide ambulatory and inpatient care (SPPC unit), home visits, and bereavement follow-up; they work with interdisciplinary oncology staff which includes oncologists, social workers, psychologists, creative art/child life specialists, nutritionists, physical therapists, and spiritual advisor. Not all pts in intervention cohort were necessarily exposed to SPPC			X			
Goldhagen (2016)	US	Ub/a	SPPC Program-based	N=40	Pts 0–18 years old enrolled in SPPC who had documented hospital admissions during 2 years prior to and first 2 quarters after enrollment	Neurologic (27%), congenital anomalies (27%), neoplasms (13%), symptoms/signs unspecified (9%), circulatory system (6%), injury/poisoning	Community-based SPPC program providing medical, nursing, social work, child life, spiritual, and volunteer services					X	

Author (Year)	Country	Study Design	Source Population	Participants		Diagnostic Categories	SPPC Characteristics	Outcomes					
				Sample Size	Characteristics			Pt Symptoms, QOL	Caregiver	EOL Discussions	EOL Care Patterns	HC Utilization	Supportive Services
Groh (2013)	Germany	Ub/a	SPPC Program-based	N=40	Primary caregivers of pts newly admitted to SPPC service between 2011–2012	Neurologic (33%), cancer (25%), congenital anomalies (20%), metabolic (18%), cardiovascular (5%)	Home-based SPPC consisting of 3 pediatricians, 2 nurses, social worker, chaplain, all trained in SPPC; 24/7 on-call service	X	X				
Gupta (2013)	England	Ub/a	SPPC Program-based	N=23	Parents of pts referred to SPPC program between 2005–2007	Unknown - authors present diagnostic categories for all referrals, not subset comprising study cohort	Community-based SPPC program consisting of nurses, clinical psychology, palliative care support workers, cultural development worker, bereavement support worker		X				
Hancock(2018)	US	RCT	Hospital-based	N=40 (intervention arm: 18; control arm: 20)	Mothers of neonates with single-ventricle heart disease admitted for first-stage palliative surgery referred during pregnancy to pediatric cardiology between 04–2013 and 08–2015	Single ventricle heart disease (100%)	Hospital-based SPPC consisting of 1 physician, nurse practitioner, nurse, and social worker all trained and certified in SPPC		X				
Hays (2006)	US	Ub/a	Hospital-based	N=41	Parents of pts 0–21 years old with severe illness that might result in death within 24 months and who were referred to SPPC program over 2-year period	Neurologic (44%), cancer (34%), congenital anomalies (10%), metabolic (5%), cardiovascular (5%), respiratory (2%)	Hospital-based multidisciplinary team (consisting of physicians, advanced practice nurses, social worker, benefits coordinator) that implemented 3 major program components; 1) clinical decision-	X	X				

Author (Year)	Country	Study Design	Source Population	Participants		Diagnostic Categories	SPPC Characteristics	Pt Symptoms, QOL	Caregiver	Outcomes				
				Sample Size	Characteristics					EOL Discussions	EOL Care Patterns	HC Utilization	Supportive Services	
								making; 2) provider education on pain and symptom management, EOL care, and ethical decision-making; and 3) flexible administration of benefits and co-case management						
Horrocks (2002)	England	Ub/a	SPPC Program-based	N=16	Parents of pts who were referred to SPPC service 5 months after service was established, excluded parents of pts who were "close to death" at time of referral	Degenerative (38%), neurologic (25%), circulatory (13%) congenital anomalies (13%), metabolic (6%), other (6%)	Community-based service consisting of 3 community pediatric nurses and 2 part-time child psychologists, supported by hospital-based consultants and senior nurse managers		X					
Kassam (2015)	Canada	RCoh	Hospital-based	N=75 (SPPC: 42; non-PPC: 33)	Parents of pts who died between 2005–2011, with death occurring >4 weeks after diagnosis	Cancer (100%)	Hospital-based SPPC team, no further details provided. Exposure defined based on parent report and confirmed through medical record review		X	X				X
Keele (2013)	US	RCoh	Population-based (national level)	N=24,342 (SPPC: 919; non-PPC: 23,423)	Pts <18 years old who died >5 days after admission between 2001–2011 from 40+ children's hospitals comprising Children's Hospital Association (secondary analysis of Pediatric Health Information System data)	Neonatal (41%), respiratory (14%), circulatory (11%), lymphatic/hematopoietic/malignancy (6%), gastrointestinal (6%), infectious disease (5%), other (11%), 85% classified as complex chronic	Hospital-based SPPC characteristics vary by site. Exposure defined by ICD-9 code for SPPC services during final hospital admission				X	X		

Author (Year)	Country	Study Design	Source Population	Participants		Diagnostic Categories	SPPC Characteristics	Outcomes					
				Sample Size	Characteristics			Pt Symptoms, QOL	Caregiver	EOL Discussions	EOL Care Patterns	HC Utilization	Supportive Services
Osenga (2016)	US	RCoh	Hospital-based	N=114 (SPPC: 28; non-PPC: 86)	Pts 0–18 years old who were treated for >24 hours prior to death and who died while inpatient between 2012–2013	Neonatal (50%), trauma/other (27%), cardiovascular (15%), hematology/oncology (8%)	Hospital-based SPPC (same as Friedrichsdorf (2015))	X			X		X
Petteys (2015)	US	PCoh	Hospital-based	N=22 (SPPC: 6; non-PPC: 16)	Parents of pts in NICU who had anticipated stay of >2 weeks	Unknown	Hospital-based SPPC service consisting of advanced practice nurse and registered nurse with extensive NICU experience, both trained in SPPC; additional medical support as needed		X				
Pierucci (2001)	US	RCoh	Hospital-based	N=196 (SPPC: 25; non-PPC: 171)	Pts <1 year old at time of death and who died while inpatient between 1994–1997	Cardiovascular (39%), trauma (11%), congenital anomalies (10%), gastrointestinal (7%), neonatal (7%), infectious disease (6%), genetic/chromosomal (5%), myopathy (3%), metabolic (2%), dehydration (1%)	Hospital-based SPPC consultation service consisting of 2 clinical nurse specialists and a physician medical director				X	X	X
Postier (2014)	US	Ub/a	SPPC Program-based	N=425	Pts 1–21 years old who initiated home- or hospice-based SPPC service between 2000–2010	Cancer (47%), non-cancer (53%)	Hospital-based SPPC (same as Friedrichsdorf (2015))					X	
Schmidt (2015)	Germany	RCoh	Population-based (state/province level)	N=96 (historic cohort: 48; intervention cohort: 48)	Historic cohort: parents of pts who died of cancer between 1999–2000 and were seen at a participating	Cancer (100%)	No details provided on specific SPPC state teams. Authors describe a series of national initiatives	X	X	X	X		X

Author (Year)	Country	Study Design	Source Population	Participants		Diagnostic Categories	SPPC Characteristics	Outcomes					
				Sample Size	Characteristics			Pt Symptoms, QOL	Caregiver	EOL Discussions	EOL Care Patterns	HC Utilization	Supportive Services
					oncology department Intervention cohort: parents of pts who died of cancer between 2005–2006 and were seen at a participating oncology department		(policies, laws, academic/educational, SPPC service standards) that helped increase the provision of SPPC nationwide (>pediatric oncology departments offering SPPC, >SPPC home care programs). These changes took place in the early 2000s, between historic and intervention cohorts. Not all patients in intervention cohort were necessarily exposed to SPPC						
Smith (2015)	US	RCoh	Hospital-based	N=902 (SPPC: 86; non-PPC: 816)	Pts discharged in 2010 who represent top decile of inpatient costs	Unknown	Hospital-based SPPC service consisting of medical director, advanced practice nurse, registered nurse, social worker, interfaith chaplain					X	
Shaman (2017)	US	RCoh	Hospital-based	N=69 (SPPC: 50; non-PPC: 19)	Adolescents and young adults with cancer who died at the hospital between 2008–2014	Cancer(100%)	Hospital-based SPPC team, no further details provided. SPPC exposure defined based on medical record data	X			X	X	
Ullrich (2016)	US	RCoh	Hospital-based	N=147 (SPPC: 37; non-PPC: 110)	Pts who underwent stem cell transplant for any indication and died between 2004–2012	Hematologic malignancy (65%), solid/brain tumor (15%), non-malignancy (20%)	Hospital-based SPPC team, no further details provided (same as Wolfe, 2008)			X	X		X
Vern-Gross (2015)	US	RCoh	Hospital-based	N=191 (historic)	Historic cohort: pts <21 years	Cancer (100%)	Hospital-based SPPC program			X	X		X

Author (Year)	Country	Study Design	Source Population	Participants		Diagnostic Categories	SPPC Characteristics	Outcomes					
				Sample Size	Characteristics			Pt Symptoms, QOL	Caregiver	EOL Discussions	EOL Care Patterns	HC Utilization	Supportive Services
				cohort: 134; intervention cohort: 57)	old who died between 2001–2005, prior to establishment of SPPC service Intervention cohort: pts <21 years old who died between 2007–2012 and received SPPC consultation prior to death		began as pilot program in 2007, expanded into institution-wide program available to all pts beginning in 2008; provide inpatient consultations and ongoing SPPC and hospice support for pts and families if transferred to home institutions						
Widger (2017)	Canada	RCoh	Population-based (state/province level)	N=572 (SPPC: 166; PPC: 100; non-PPC: 306)	Nested cohort of a deceased cohort of children with cancer diagnosed at <15 years old who died between 2000 and 2012 <18 years. Patients were included if they received care at institutions with SPPC and died at a time when a clinical SPPC database was available	Cancer (100%)	Hospital-based SPPC, no further details provided about teams. Exposure levels: SPPC: patients registered in one of the SPPC databases; PPC: patients with 2 physician billing or inpatient diagnostic codes compatible with PC provision (no need of PC training); in both cases first PC contact had to occur > 30 days prior to death			X	X	X	
Wolfe (2008)	US	RCoh	Hospital-based	N=221 (historic cohort: 102; intervention cohort: 119)	Historic cohort: parents of pts who died between 1990–1997, prior to establishment of SPPC service Intervention cohort: parents of pts who died between 1997–2004, following establishment of SPPC service	Cancer(100%)	Hospital-based SPPC team providing inpatient, outpatient, and home-based consultations and ongoing education about SPPC to pediatric oncology practitioners; team consists of physician, nurse, social worker. Not all pts in	X	X	X	X		X

Author (Year)	Country	Study Design	Source Population	Participants		Diagnostic Categories	SPPC Characteristics	Outcomes						
				Sample Size	Characteristics			Pt Symptoms, QOL	Caregiver	EOL Discussions	EOL Care Patterns	HC Utilization	Supportive Services	
							intervention cohort received SPPC consultation (approximately half)							

Abbreviations: **EOL** - end of life; **HC** - healthcare; **Pt(s)** - patient(s); **QOL** - quality of life; **SPPC** - specialized pediatric palliative care; **PPC** - general pediatric palliative care provision; **non-PPC** - no pediatric palliative care; **NICU** - neonatal intensive care unit; **ICD-9** - International Classification of Diseases, Ninth Revision; **US** - United States; **PCoh** - prospective cohort; **RCoh** - retrospective cohort; **Ub/a** - uncontrolled before/after; **RCT** - randomized control trial.

Table 2:

Outcomes Reported and Summary of Findings

Outcome Categories	Specific Outcome	Study	Outcome Measurement	Effect Size (SPPC vs. comparison group or post-exposure to SPPC vs. pre-exposure to SPPC; arrow indicates direction of significant results)
Pt Symptoms/QOL				
Prevalence of symptoms at EOL	Symptom prevalence during LMOL	Friedrichsdorf (2015)	SCCC	Most symptoms NS; ↑ Constipation: 70% vs. 36%, p=0.01
		Schmidt (2013)	SCCC (German)	Most symptoms NS; ↑ Nausea: 65% vs. 42%, p=0.024
		Wolfe (2008)	SCCC	NS
	During LMOL, number of documented: 1) Symptoms 2) Refractory symptoms 3) Physical symptoms 4) Psychosocial symptoms	Snaman (2017)	Medical record review	1) NS 2) NS 3) NS 4) NS
Prevalence of suffering at EOL	Documentation of symptom prevalence in last 3 days of life	Osenga (2016)	Medical record review	NS
	“A great deal/a lot” of suffering due to [symptoms] during LMOL	Friedrichsdorf (2015)	SCCC	Most symptoms NS; ↑ Energy loss/fatigue: 93% vs. 63%, p=0.007
		Schmidt (2013)	SCCC (German)	Most symptoms NS; ↑ Fatigue: 50% vs. 25%, p=0.01
		Wolfe (2008)	SCCC	Most symptoms NS; ↓ Pain: RD 19%, p=0.018; Dyspnea: RD 21%, p=0.020
Perceived success of symptom management	“A great deal/a lot” of overall suffering during LMOL	Friedrichsdorf (2015)	SCCC	NS
	Perceived success of treatment of [symptoms] in LMOL	Friedrichsdorf (2015)	SCCC	NS
	Perceived success of symptom control, measured during first week of SPPC referral and at 6 months (presented as median score)	Schmidt (2013)	SCCC (German)	NS
		Groh (2013)	Ad hoc parent survey items (1–10 numeric rating scale)	↑ 9.0 (IQR 2) vs. 5.0 (IQR 3), p<0.000056
PtQOL	1) Report of child having had “some” to “a great deal” of fun during LMOL 2) Report of child having experienced an event that added meaning to his/her life during LMOL	Friedrichsdorf (2015)	SCCC	1) ↑ 70% vs. 45%, p=0.03 2) ↑ 89% vs. 63%, p=0.02
	Health-related QOL measured at study baseline, 3, 6, and 12 months	Chong (2018)	Health Utilities Index (self-report)	Most attributes NS; ↑ Pain-free at 3 months: OR 2.58 (95% CI: 1.12, 5.95)

Outcome Categories	Specific Outcome	Study	Outcome Measurement	Effect Size (SPPC vs. comparison group or post-exposure to SPPC vs. pre-exposure to SPPC; arrow indicates direction of significant results)
	HRQOL, measured at SPPC enrollment and 3 months later: 1) Total score 2) Emotional score 3) Physical score 4) Social score 5) School score 6) Psychosocial health summary score (average of emotional, social, and school functioning scores) (presented as mean scores)	Hays (2006)	PedsQL™ 4.0, parent version (items transformed to a 0–100 scale)	1) NS 2) ↑ 62.73 vs. 52.52 (mean difference +10.21), effect size 0.60, p=0.021 3) NS 4) NS 5) NS 6) NS
	Child QOL, measured at first week of SPPC and 6 months (presented as median score)	Groh (2013)	Ad hoc parent survey items (1–10 numeric rating scale)	↑ 4.0 (IQR 4) vs. 2.5 (IQR 2), p<0.000056
Caregiver Outcomes				
Caregiver worry	Worry about ability to manage child's health (5-point Likert-type response option), measured at SPPC enrollment and at 6 and 12 months (presented as change [in points] from one timepoint to the next)	Gans (2015)	Ad hoc parent survey item	↓ −0.26 (95% CI: −0.05, −0.47), p<0.05
Caregiver stress	Stress (5-point Likert-type response option), measured at SPPC enrollment and at 6 and 12 months (presented as change [in points] from one timepoint to the next)	Gans (2015)	Ad hoc parent survey item	↓ −0.26 (95% CI: −0.04, −0.48), p<0.05
	Stress, measured at SPPC enrollment and 12 months later	Gupta (2013)	PSI-SF	NS
	Stress, measured at study enrollment, 2 weeks after enrollment, at discharge	Petteys (2015)	PSS-NICU	NS
Caregiver anxiety/depression	Diagnosis of clinical or subclinical acute stress disorder, measured at study enrollment, 2 weeks after enrollment, at discharge	Petteys (2015)	SASRQ	NS
	Anxiety and depression, measured at first week of SPPC and 6 months (presented as median score)	Groh (2013)	HADS	↓ 19.0 (IQR 6) vs. 28.0 (IQR 8.5), p<0.001
	Measured at baseline and after discharge or 30 days after first stage palliative surgery: 1) Maternal depression (mean change) 2) Maternal anxiety (mean change)	Hancock(2018)	1) Beck Depression Inventory-II 2) State-Trait Anxiety Index	1) NS 2) ↓ −7.6 vs. 0.3, p=0.02
Caregiver burden	Anxiety, measured at enrollment in SPPC and 6 months later	Horrocks (2002)	State-Trait Anxiety Index	NS
	Caregiver burden, measured at study baseline and at 3, 6 and 12 months (presented as mean score difference compared to baseline)	Chong (2018)	Zarit Burden Interview	3 months: ↓ 3.4 (95% CI 1.0 – 5.9); 6 months: ↓ 4.0 (95% CI 0.5 – 7.5); 12 months: NS
	Caregiver burden, measured at first week of SPPC and 6 months (presented as median score)	Groh (2013)	HPS	↓ 14.5 (IQR 8.8) vs. 20.0 (IQR 10.5), p<0.001

Outcome Categories	Specific Outcome	Study	Outcome Measurement	Effect Size (SPPC vs. comparison group or post-exposure to SPPC vs. pre-exposure to SPPC; arrow indicates direction of significant results)
Caregiver coping	Maternal coping, measured at baseline and after discharge or 30 days after first stage palliative surgery 1) Adaptive coping (mean scores) 2) Problematic coping (mean scores)	Hancock(2018)	Brief Cope Inventory	1) ↑ 6.3 (±1.4) vs. 4.9 (±2.0), p=0.03 (for positive reframing subscale) 2) NS
Caregiver psychological wellbeing	Psychological wellbeing, measured at SPPC enrollment and 12 months later	Gupta (2013)	GHQ12	NS
Caregiver QOL	QOL, measured at first week of SPPC and 6 months later (presented as median score)	Groh (2013)	QOLTLF	↑ 7.1 (IQR 1.3) vs. 5.8 (IQR 1), p<0.001
	Parent-reported HRQOL (measured at baseline and after discharge or 30 days after first stage palliative surgery (mean ± standard deviation): 1) Physical functioning 2) Emotional functioning 3) Social functioning 4) Cognitive functioning 5) Communication 6)Worry Parent-reported family functioning: 7) Daily activities 8) Family relationships	Hancock(2018)	PedsQL Family Impact Module	1) NS 2) NS 3) NS 4) NS 5) ↑ 11.3 (± 16.9) vs. 1.0 (± 23.7), effect size: 0.46 6) NS 7) NS 8) ↑ 5.0 (± 17.2) vs. -2.6 (± 17.5), effect size: 0.41
	Four domains of QOL, measured at SPPC enrollment and 6 months later: 1) Mental role limitation 2) Mental health 3) Energy/vitality 4) Health perceptions (presented as mean score, higher score=better QOL)	Horrocks (2002)	SF-36	1) ↑ 51.6 vs. 31.2, mean difference 20.3 (95% CI: -4.0, -36.6), p=0.02 2) NS 3) NS 4) NS
	Satisfaction with various domains of care, measured at first week of SPPC and at 6 months	Groh (2013)	Ad hoc parent survey items (1–10 numeric rating scale)	↑ Differences between median scores (from before to after) for items reaching significance range +1.0 to +8.0, p values range p<0.002778 to p<0.000056
Caregiver satisfaction with care	Satisfaction with various domains of care, measured at SPPC enrollment and 3 months later	Hays (2006)	Ad hoc parent survey items	↑ Mean differences (from before to after) for items reaching significance range +0.43 to +1.42, p values range 0.000–0.048
	Satisfaction with care, measured at discharge	Petteys (2015)	Ad hoc parent survey item	Statistical comparison not feasible due to low response rate
	Satisfaction with child's EOL care	Schmidt (2013)	SCCC (German)	NS
Caregiver preparedness at EOL	Whether healthcare team prepared parents for medical aspects surrounding death	Kassam (2015)	SCCC + ad hoc items	↑ 63% vs. 36%, p=0.02
	1) Parents felt "very prepared" for EOL medical problems 2) Parents felt "very prepared" for circumstances at time of death	Wolfe (2008)	SCCC	1) ↑ 56% (95% CI: 54, 57) vs. 27% (95% CI: 26, 28), p<0.001 2) ↑ 49% (95% CI: 49, 51) vs. 25% (95% CI: 24, 26), p=0.002

Outcome Categories	Specific Outcome	Study	Outcome Measurement	Effect Size (SPPC vs. comparison group or post-exposure to SPPC vs. pre-exposure to SPPC; arrow indicates direction of significant results)
Caregiver ability to plan location of death	Parent able to plan child's location of death	Friedrichsdorf (2015)	SCCC	NS
	Parent control over location of death	Kassam (2015)	SCCC + ad hoc items	NS
EOL Discussions				
Frequency/timing of discussion regarding ACP	Proportion of patients who had an ACP in place or an ACP discussion	Chong (2018)	Medical record review	↑ OR = 5.51 (95% CI: 1.55, 19.67)
Frequency/timing of discussion regarding prognosis	1) Documented discussion regarding prognosis 2) Median number of days between discussion regarding prognosis and death	Ullrich (2016)	Medical record review	1) ↑ 97% vs. 83%, p=0.04 2) ↑ 8 days (IQR 4–26) vs. 2 days (IQR 1–13), p<0.001
	1) Median number of EOL discussions per pt 2) Median number of days between first EOL discussion and enrollment in hospice 3) Median number of days between first EOL discussion and DNR order 4) Median number of days between first EOL discussion and death 5) Median number of EOL discussions (before/after analysis among subset who received SPPC)	Vern-Gross (2015)	Medical record review	1) ↑ 12 (IQR 7.5–15.5) vs. 3 (IQR 2–4), p<0.001 2) ↑ 225 (IQR 36–442) vs. 18 (IQR 2–98), p<0.001 3) ↑ 195 (IQR 20–421) vs. 2 (IQR 0–35), p<0.001 4) ↑ 268 (IQR 57–474) vs. 64 (IQR 11–164), p<0.001 5) ↑ 1 (IQR 0–2) vs. 0 (IQR 0–1), p=0.026
	1) Documented discussion about no realistic chance for cure 2) Number of days between discussion about no realistic chance for cure and death	Wolfe (2008)	Medical record review	1) NS 2) NS
	1) Whether family was informed about possibility of palliative home care 2) Whether family perceived that timing of information was appropriate	Schmidt (2013)	SCCC (German)	1) ↑ 79% vs. 33%, p=0.003 2) ↑ 81% vs. 42%, p=0.042
	Median number of discussions about transition to home/hospice (before/after analysis among subset who received SPPC)	Vern-Gross (2015)	Medical record review	↑ 2 (IQR 1–4) vs. 1 (IQR 0–1), p=0.001
Frequency/timing of discussion about hospice or palliative home care	1) Hospice discussion documented 2) Number of days between discussion about hospice and death (outcome presented as geometric mean)	Wolfe (2008)	Medical record review	1) ↑ 76% (95% CI: 73, 79) vs. 54% (95% CI: 51, 57), p<0.001 2) ↑ 52 days (95% CI: 41, 65) vs. 28 days (95% CI: 21, 38), p=0.002
Frequency/timing of discussion regarding resuscitation status	Discussion of “no CPR” order with parents by healthcare team	Kassam (2015)	SCCC + ad hoc items	NS
	1) Discussions regarding resuscitation status 2) Median number of days between discussion regarding resuscitation status and death	Ullrich (2016)	Medical record review	1) ↑ 88% vs. 58%, p=0.002 2) ↑ 7 (IQR 3–18) vs. 2 (IQR 1–5), p<0.001
	DNR discussion documented	Wolfe (2008)	Medical record review	NS
Frequency/timing of discussion regarding death and dying	1) Discussion of death and dying with parents by healthcare team	Kassam (2015)	SCCC + ad hoc items	1) ↑ 85% vs. 46%, p<0.01 2) ↑ 61% vs. 4%, p<0.01

Outcome Categories	Specific Outcome	Study	Outcome Measurement	Effect Size (SPPC vs. comparison group or post-exposure to SPPC vs. pre-exposure to SPPC; arrow indicates direction of significant results)
	2) Discussion of death and dying with child by healthcare team when appropriate			3) ↑ 62% vs. 13%, p<0.01
	3) Provision of guidance to parents on how to talk to child about death and dying when appropriate			
	Median number of discussions focused on the “high likelihood of death” (before/after analysis among subset who received SPPC)	Vern-Gross (2015)	Medical record review	↓ 1 (IQR 1–3) vs. 2.5 (IQR 1.5–4), p=0.003
	Median number of discussions regarding transition of care/withdrawal of life support (before/after analysis among subset who received SPPC)	Vern-Gross (2015)	Medical record review	NS
Patterns of EOL Care				
Location of death	Home death	Friedrichsdorf (2015)	SCCC	↑ 93% vs. 20%, p<0.001
		Schmidt (2013)	SCCC (German)	NS
	1) Pediatric ward death	Golan (2008)	Administrative database and medical record review	↓ 4% vs. 40%, p<0.001
	2) Oncology ward death			↓ 8% vs. 26%, p<0.001
	3) ICU death			NS
	4) Home death			↓ 16% vs. 28%, p<0.003
	5) Palliative care unit death			66% (post PPC)
	ICU death	Keele (2013)	Administrative database review	↓ 60% vs. 88%, RR 0.67 (95% CI: 0.64, 0.72)
		Pierucci (2001)	Medical record review	↓ 68% vs. 97%, p<0.001
		Snaman (2017)	Medical record review	↓ 19 (38%) vs. 13 (68%), p=0.024
		Schmidt (2013)	SCCC(German)	NS
Procedures/interventions at EOL (including CPR, intubation, blood draws, imaging, fluids, etc.)		Ullrich (2016)	Medical record review	↓ 58% vs. 80%, p=0.03
	ICU or outside hospital death	Wolfe (2008)	Medical record review (missing values [n=5] imputed using parental report)	↓ 22% (95% CI: 19, 26) vs. 38% (95% CI: 35, 42), p=0.024
	In-hospital death	Widge (2018)	Pediatric Oncology Group of Ontario Networked Information System (POGONIS)	↓ OR 0.3 (0.2 to 0.4), p<0.001
	Various interventions during final admission before death	Keele (2013)	Administrative database review	↑/↓ RR ranged 0.14–2.8 (non-invasive ventilation and intracranial pressure monitoring or extraventricular device more common in

Outcome Categories	Specific Outcome	Study	Outcome Measurement	Effect Size (SPPC vs. comparison group or post-exposure to SPPC vs. pre-exposure to SPPC; arrow indicates direction of significant results)
Medication use at EOL	1) Documentation of 1 diagnostic or monitoring procedure in last 48 hours of life 2) Documentation of various interventions in last 48 hours of life	Osenga (2016)	Medical record review	1) ↓ 61% vs. 92%, OR 0.16 (95% CI: 0.04, 0.61) 2) ↓ OR ranged 0.07–0.18 for significant findings; several procedures/interventions were NS
	Various interventions in last 48 hours of life	Pierucci (2001)	Medical record review	↓ p<0.001 for significant findings; several procedures/interventions were NS
	During LMOL: 1) MV (reported as n (%)) 2) Number of medical procedures (presented as median) 3) Other interventions: CPR, dialysis	Snaman (2017)	Medical record review	1) ↓ 17 (34%) vs. 12 (63%), p=0.028 2) ↓ 1 (IQR 0–3) vs. 3 (IQR 2–4), p=0.009 3) NS
	1) Intubation in last 24 hours of life 2) CPR attempted at EOL	Ullrich (2016)	Medical record review	1) ↓ 42% vs. 66%, p=0.02 2) ↓ 3% vs. 20%, p=0.03
	Various interventions between time of DNR order and death	Vern-Gross (2015)	Medical record review	↑ Fluids: 75% vs. 40%, p=0.001; other interventions NS
	1) MV within 14 days of death 2) High intensity EOL care	Widger (2018)	Pediatric Oncology Group of Ontario Networked Information System	1) ↓ OR 0.2 (0.1–0.5), p<0.001 2) ↓ OR 0.2 (0.1 – 0.3), p<0.001
	Intubation in last 24 hours of life	Wolfe (2008)	Medical record review	NS
	Use of various medications in last 4 days of life	Keele (2013)	Administrative database review	↓ RR ranged 0.15–0.53 for analgesics, sedatives, paralytics, antibiotics, and inotropics
	Orders placed for various medications in last 3 days of life	Osenga (2016)	Medical record review	NS
	Use of various medications in last 48 hours of life	Pierucci (2001)	Medical record review	↓ Paralytics: 8% vs. 41%, p<0.001; other medications NS
Integrative medicine therapies at EOL	During LMOL: 1) Use of chemotherapy 2) Opioids 3) Benzodiazepines	Snaman (2017)	Medical record review	1) NS 2) NS 3) NS
	Use of various medications between DNR order and death	Vern-Gross (2015)	Medical record review	↑ Antibiotics: 69% vs. 43%, p=0.008; steroids: 63% vs. 22%, p=0.001; anti-convulsants: 40% vs. 6%, p=0.001; other medications NS
	Orders placed for integrative medicine therapies in last 3 days of life	Osenga (2016)	Medical record review	NS
Actions to manage specific	Documentation of specific action to manage 1) pain and 2) non-pain symptoms in last 3 days of life	Osenga (2016)	Medical record review	1) ↑ OR ranged 3.14 (95% CI: 1.08, 9.16) to 6.51 (95% CI: 1.92, 22.12)

Outcome Categories	Specific Outcome	Study	Outcome Measurement	Effect Size (SPPC vs. comparison group or post-exposure to SPPC vs. pre-exposure to SPPC; arrow indicates direction of significant results)
symptoms at EOL	Receipt of treatment for various symptoms in LMOL	Schmidt (2013)	SCCC (German)	↑ Anxiety: 36% vs. 9%, p=0.035; other symptoms NS
Pain assessments at EOL	Documentation of pain assessments in final 3 days of life (measured in 12-hour increments)	Osenga (2016)	Medical record review	↑ RR 1.57 (95% CI: 1.16, 2.10) for last 12–24 hours of life; other 12-hour increments NS
Frequency/timing of documentation of resuscitation status	DNR documented prior to death	Osenga (2016)		↑ 79% vs. 53%, OR 7.92 (95% CI: 2.02, 31.12)
		Pierucci (2001)		NS
		Snaman (2017)	Medical record review	NS
		Ullrich (2016)		↑ 97% vs. 68%, p=0.002
		Vern-Gross (2015)		↑ 84% vs. 47%, p<0.0001
		Wolfe (2008)		NS
Withdrawal of life-sustaining therapies or nutritional support	Days between DNR order and death	Snaman (2017)	Medical record review	↑ 6 (IQR 2–21) vs. 2 (IQR 1–4), p = 0.008 (median)
		Wolfe (2008)		↑ 18 (95% CI: 13, 25) vs. 12 (95% CI: 9, 15), p=0.031 (geometric mean)
	1) Documentation of life-sustaining therapy withdrawn 2) Documentation of nutritional support withdrawn	Osenga (2016)	Medical record review	1) NS 2) NS
	Withdrawal of vasopressors, feedings, intravenous fluids, mechanical ventilation	Pierucci (2001)	Medical record review	NS
	Withholding of vasopressors, feedings, intravenous fluids, mechanical ventilation	Pierucci (2001)	Medical record review	↑ Withholding of vasopressors: 56% vs. 13%, p<0.001; withholding of mechanical ventilation: 28% vs. 4%, p<0.001; others NS
	Time before death that cancer-directed therapy was discontinued	Wolfe (2008)	Medical record review	NS
Documentation of pt/family emotional status prior to death	Documentation of emotional status of families by physicians and nurses	Pierucci (2001)	Medical record review	NS
Healthcare Utilization				
Hospital admissions	Hospital admissions over 12 months (mean difference)	Chong (2018)	Medical record review	↓ 2.46 (95% 0:0.43, 4.48)
	Between referral to SPPC and death (or proxy date and death for control group): 1) Total hospital admissions (“main outcome”) 2) Unplanned hospital admissions 3) Planned hospital admissions	Fraser (2013)	Review of linked databases for hospital episode statistics	1) NS 2) NS 3) ↓ IRR 0.60 (95% CI: 0.43, 0.85)
	Hospital admissions in 12 months preceding SPPC enrollment vs. 12 months following SPPC enrollment	Postier (2014)	Administrative database review	NS

Outcome Categories	Specific Outcome	Study	Outcome Measurement	Effect Size (SPPC vs. comparison group or post-exposure to SPPC vs. pre-exposure to SPPC; arrow indicates direction of significant results)
Hospital length of stay	Hospital admissions among: 1) Those who died within 2 years of 2010 discharge 2) Those who survived 2 years following 2010 discharge	Smith (2015)	Administrative database review	1) ↓ RR 0.5 (95% CI: 0.28, 0.91) 2) ↑ RR 2.1 (95% CI: 1.3, 3.4)
	1-year cumulative length-of-stay (mean difference)	Chong (2018)	Medical record review	↓ 52.3 days (95% CI: 25.44, 79.17)
	Hospital length of stay: quarterly means calculated from Quarters 3 and 4 of 2005 and Quarters 1–4 of 2006 before and after enrollment in SPPC	Goldhagen (2016)	Administrative database review	↓ 1.22 days/quarter (SE 0.39) vs. 2.92 days/quarter (SE 0.94), p<0.05
	Mean length of stay (days) in 12 months preceding SPPC enrollment vs. 12 months following SPPC enrollment	Postier (2014)	Administrative database review	↓ 19 (± 34) vs. 34 (± 60), Z = -6.175, p<0.001
ED Visits	Median length of stay (days) for: 1) 2010 (all pts) 2) Those who died during 2010 admission 3) Those who died within 2 years of 2010 discharge 4) Those who survived 2 years following 2010 discharge	Smith (2015)	Administrative database review	1) ↑ 37 vs. 26, p=0.002 2) NS 3) ↓ 0 (IQR 0–26.1) vs. 11.9 (IQR 3.6–61.2), p=0.010 4) ↑ 9.1 (IQR 0–31.4) vs. 0 (IQR 0–6.0), p<0.001
	Number of Emergency Department (ED) visits	Chong (2018)	Medical record review	NS
	Admission to ICU	Keele (2013)	Administrative database review	↓ RR 0.29 (95% CI: 0.26, 0.32)
ICU admissions	PICU admissions for: 1) 2010 (all pts) 2) Those who died within 2 years of 2010 discharge 3) Those who survived 2 years following 2010 discharge	Smith (2015)	Administrative database review	1) ↑ OR 4.8 (95% CI: 0.1.7, 13.5) 2) NS 3) ↑ 47% vs. 17%, p<0.001
	ICU admission within 30 days of death	Widger (2018)	Pediatric Oncology Group of Ontario Networked Information System (POGONIS)	↓ OR 0.2 (0.1–0.4), p<0.001
Days spent in ICU	Days spent in ICU during final admission before death	Pierucci (2001)	Medical record review	↓ 6 days (± 8) vs. 14 days (± 28), p=0.01
Hospital costs	Difference in healthcare expenditure between patients who received PPC and those on standard care (reported as mean incremental cost) in their final year of life at: 1) 1 month prior to death 2) 3 months prior to death 3) 6 months prior to death 4) 12 months prior to death	Chong (2018)	Medical record review	1) ↓ -\$72K (95% CI: -\$76K, -\$69K) 2) ↓ -\$116K (95% CI: -\$121K, -\$111K) 3) ↓ -\$151K (95% CI: -\$159K, -\$143K) 4) ↓ -\$175K (95% CI: -\$186K, -\$164K)
	1) Total charges and 2) diagnostic charges: quarterly means calculated from Quarters 3 and 4 of 2005 and Quarters 1–4 of 2006 before and after enrollment in SPPC	Goldhagen (2016)	Administrative database review	1) NS 2) NS
	Average total charges in 12 months preceding SPPC enrollment vs. 12 months following SPPC enrollment	Postier (2014)	Administrative database review	↓ 10.91 (± 21.3) vs. 20.97 (± 43.3), Z = -6.581, p<0.001 (\$10,000 per unit)

Outcome Categories	Specific Outcome	Study	Outcome Measurement	Effect Size (SPPC vs. comparison group or post-exposure to SPPC vs. pre-exposure to SPPC; arrow indicates direction of significant results)
	Median inpatient cost/cost-per-day for: 1) 2010 (all pts) 2) Those who died within 2 years of 2010 admission 3) Those who survived 2 years following 2010 discharge 4) Those who received SPPC (before/after analysis; secondary outcome)	Smith (2015)	Administrative database review	1) ↑ Total cost: \$138, 168 vs. \$90,791, p=0.000; Cost/day: \$3,755 vs. \$3,404, p=0.035 2) Total cost: NS; ↓ Cost/day: \$4,260 (IQR 3,071–5,663) vs. \$5,945 (IQR 4,735–8,940), p=0.001 3) Total cost: NS; Cost/day: NS 4) Total cost: NS; ↑ Cost/day: \$2,965 (IQR 0–4,295) vs. \$0 (IQR 0–2,956), p<0.001 5) ↓ Cost/day: \$3,625 vs. \$4,732, p<0.0001
Involvement of Supportive Services				
Pain team consultation	Pain team involvement at EOL	Wolfe (2008)	Medical record review	NS
Social work	Involvement of a religious or spiritual mentor for: 1) Parent 2) Child, when appropriate	Kassam (2015)	SCCC + ad hoc items	1) NS 2) NS
	Referral during EOL period	Osenga (2016) Pierucci (2001)	Medical record review	↓ 71% vs. 99%, OR 0.04 (95% CI: 0.01, 0.36) ↑ 80% vs. 30%, p<0.001
Spiritual support	Involvement of a religious or spiritual mentor for: 1) Parent 2) Child, when appropriate	Kassam (2015)	SCCC + ad hoc items	1) NS 2) NS
	Chaplaincy consultation during EOL period	Osenga (2016) Pierucci (2001)	Medical record review	NS ↑ 64% vs. 23%, p<0.001
Ethics committee	Ethics consultation during EOL period	Osenga (2016)	Medical record review	NS
Psychology	Psychology consultation during EOL period	Osenga (2016)	Medical record review	NS
Home care Hospice	Whether child received palliative home care Frequency of hospice involvement	Schmidt (2013) Ullrich (2016) Vern-Gross (2015)	SCCC (German) Medical record review	↑ 65% vs. 33%, p=0.007 NS ↑ 71% vs. 46%, p=0.002
	Time between hospice enrollment and death	Vern-Gross (2015)	Medical record review	NS
Sibling support	Receipt of sibling support	Kassam (2015) Vern-Gross (2015)	SCCC + ad hoc items Medical record review	↑ 58% vs. 26%, p=0.01 ↑ 50% vs. 16%, p<0.0001
Bereavement support	Receipt of bereavement support	Vern-Gross (2015)	Medical record review	↑ 96% vs. 50%, p<0.0001

Abbreviations: ACP - advanced care planning; CPR - cardiopulmonary resuscitation; DNR - do-not-resuscitate order; EOL - end of life; GHQ 12 - General Health Questionnaire Short Version (parent-report); HADS - Hospital Anxiety and Depression Scale (parent-report); HPS - Hausliche Pflegeskala (home care scale) (parent-report); HUI - Health Utilities Index II and III (child/teen self-report); ICU - intensive care unit; IQR - interquartile range; IRR - incidence rate ratio; NS - non-significant; OR - odds ratio; PedsQL™ 4.0 - Pediatric Quality of Life Inventory™, Version 4.0 (parent-report); PICU - pediatric intensive care unit; PSI-SF - Parenting Stress Index, Short Form (parent-report); PSS/NICU - Parental Stressor Scale: NICU (parent-report); Pt(s) - patient(s); QOL - quality of life; QOLIT-F -