Insights on palliative cares from birth to infancy in pediatric patients with neurological diseases

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Running head: Neuropalliative care in pediatric age

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Statements

Ethics approval and consent to participate

The study was approved by the Ethical Committee of the University of Catania, Italy.

All parents of the included patients gave their consent to participate to the present study.

Consent for publication
All parents of the included patients gave their consent for publication of the present data in anonymous form.

**Availability of data**

The datasets generated and/or analysed during the current study are not publicly available due to privacy policies but are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contribution**

RF, CM, LT, SM, SDM, AND GV contributed substantially to the conception and designed the work, they also acquired and interpreted data, drafted and wrote the paper and revised it for publication. FS, PP, CS contributed substantially to the conception of the paper, acquired the data, and revised it for final publication. RF, CM, GV, PP acquired the data and interpreted it, wrote the draft of the paper, revised it for final publication. PP, MR performed he bibliographic research to draft and write the paper, interpreted data and revised it for final publication. RF, MR: contributed substantially to the conception and designed the work, they also acquired and interpreted data, drafted and wrote the paper and revised it for publication.

**Ethical approval and consent to participate**

The ethics committee of the University of Catania approved the present study. All research was performed in accordance with relevant guidelines/regulations. Informed consent was obtained from all the studied patients.
Abstract

**Background:** Palliative care, in pediatric age, is a comprehensive approach to treatment that guarantees patients and their families a whole healing process from diagnosis to death. The techniques used for neurologic patients in the field of palliative care can enhance the quality of care provided to all patients with neurologic disorders and support their families.

**Objective:** Our goal was to analyze palliative care protocols in use in our departments, describing the palliative course in our clinical setting and to present a proposal that allows implementation of hospital palliative care patients with neurologic diseases with a long-term prognosis.

**Methods:** In this retrospective observational study, we present our experience in the application of palliative care for neurologic patients from birth to early infancy. We studied 34 newborns with diseases affecting the nervous system, causing impairment of the prognosis. The study was conducted from 2016 to 2020, in Neonatology Intensive Care Unit and the Pediatric Unit of the San Marco University Hospital in Catania, Sicily, Italy.

**Results:** Despite the legislative rules, no palliative care network has been activated to meet the needs of the population. In our center, given the vast number of patients with neurologic conditions requiring palliative care interventions, it can be suggested to activate a straightforward departmental unit for neurologic pediatric palliative care.

**Conclusions:** The establishment of specialized reference centers that deal with significant neurological illnesses is due to the progress of neuroscience in recent decades. Integration with specialized palliative care is sparse but now seems essential.

**Keywords:** Neonatal, Paediatric Neurology, Palliative Care.
Key message

Question: To analyze palliative care protocols in use, describing the palliative course and to propose an implementation of hospital palliative care patients with neurologic diseases.

Finding: We studied, 34 newborns with nervous system diseases, with poor prognosis.

Meaning: Despite the legislative rules, no palliative care network has been activated. Given the vast number of patients with neurologic conditions standardized guidelines and protocols should already exist for their palliative management.
Introduction

Palliative care focuses on body, mind, and spirit management of adults or children with incurable illness with no chance of healing, involving the global health of their families.\(^1\)\(^\sim\)\(^4\) The WHO has long acknowledged the differences between pediatric and adult palliative care and has importantly stated that “palliative care should be commenced when illness is diagnosed, and should continue regardless of whether a child receives treatment directed at the disease” or not.\(^5\) Within the framework of Neonatal Intensive Care Units (NICUs) various conditions are eligible to start palliative care. In case a diagnosis of a life-limiting disease is established prenatally, palliative care and family counseling is required even before birth.\(^6\) Furthermore, most neurologic diseases remain incurable, and lead to significant disability, emotional distress, pain and other physical, psychological, and spiritual sources of pain often difficult to control. Thanks to advances in research, technology and treatment, survival of preterm neonates is increasing and consequently many of these children with neurological conditions live longer, with increasing health- and care needs, such as long-term home ventilation,\(^7\) infusion therapy, partial or complete parenteral feeding or feeding via gastrostomy tubes.\(^8\) In these conditions, it is crucial that a multidisciplinary team specifically trained in palliative care and pain-therapy coordinates the therapeutic approach with the patient’s family. A pediatric palliative care (PPC) team may be able to follow up these patients listed below throughout the perinatal period: chromosomal or genetic abnormalities, organ problems, infectious diseases, immune system disorders, as well as preterm and related complications.\(^9\). A few neurological conditions are accompanied with behavioral problems, cognitive decline, and motor dysfunction. A multidisciplinary strategy is necessary for the management of these symptoms, and some skills should be used on a regular basis.

For the first time, a summary of children's palliative care advancements was included in the recently released European Association of Palliative Care (EAPC) Atlas on Palliative care in Europe 2019. Results in the Atlas show that there are still many countries in the WHO Europe Region where palliative care for children is not still available.\(^10\)-\(^11\) In our country, the Ministry of Health estimates
that over 11,000 children require pediatric palliative care. The prevalence of children eligible for such care has continuously and progressively increased in Italy to an estimated 32 cases per 10,000 minors.\textsuperscript{12} It is known that only a proportion not exceeding 15\% of eligible children have access to a PPC, despite Legislative Decree 38/2010, which defines that pediatric palliative care is a right of the child.

In this retrospective observational study, we present our experience on palliative cares of children at early infancy and pediatric neurologic patients, whose neurologic disease diagnosis was performed at birth. We aimed to analyze the way in which the palliative care is performed in a clinical setting and to present a proposal for implementation of palliative care for these neurologic patients with poor prognosis.

The aim of our study was to assess the current organization of the palliative care from birth to early infancy in our NICU and Pediatric Unit and the consequence support provided to patients and their families. The analyzed data were gathered from the medical files and register where the records of palliative decision were documented.

We analyzed the data for a period of 4 years because no explicit record related to palliative care was recorded in previous folders.

**Materials and Methods**

In this retrospective observational study, we analyzed the data of 34 patients, including 20 males and 14 females, born between January 1, 2016, and December 31, 2020, admitted to our NICU and/or Pediatric Ward for severe neurologic diseases with poor prognosis. Diagnosis of severe neurologic diseases was performed within the patients’ first 28 days of life.

All patients with experience of physical pain, social, spiritual, and emotional pain underwent to palliative cares. Decisions on palliative care were defined according to the needs of patients and their families when setting and revisiting goals of care. A multidisciplinary team assisted in the management and treatment of infants, children, with a serious neurological condition included in our study.
After diagnosis, the following patients were deemed eligible for palliative care: those who were born on the verge of viability or who are vulnerable due to their neurological disease, those who had birth anomalies that might endanger vital functions, and those whose intensive care had been applied appropriately but who were now subjected to interventions that were no longer deemed beneficial but had instead become burdensome, inappropriate, or both.

In our study, we excluded those patients with neurologic diseases secondary to other systemic pathologies such as tumours, neurologic coma or hepatic failure (these children were then referred to those Operative Units responsible for treatment and care of their primary disease); patients whose data in their clinical files were incomplete; patients with an incomplete checklist of all received palliative cares during hospitalization.

For each patient we collected the following data: demographic data; anthropometrical and clinical data; diagnosis of the disease causing a poor prognosis; age at diagnosis; age of onset of palliative care; all procedures that were performed to sustain the vital functions of these children (breathing support, feeding support, pain treatment); the quality of palliative cares provided (Timing, setting and healthcare professionals involved in communicating to the family the patient’s state of incurability and opportunity to start palliative care); health professionals involved in palliative cares; type of palliative cares needed by the included patients; causes and setting of death.

The research was performed in accordance with the Declaration of Helsinki guidelines. All methods were carried out in accordance with relevant guidelines and regulations.

**Results**

We analyzed the data of 34 patients born at the Neonatal Intensive Care Unit, San Marco University Hospital of Catania, Italy, who were diagnosed with pathologies involving the central nervous system with poor prognosis. Three patients suffering from extreme prematurity, six with severe metabolic encephalopathies, eight with genetic encephalopathies, seven with neuromuscular diseases, nine with hypoxic–ischemic encephalopathy and one patient suffering from surgically treated posthemorrhagic hydrocephalus were included in the analysis. The extreme premature patients were born at 23, 24 and
27 weeks of gestation, respectively. The six patients with severe metabolic encephalopathies were affected by: MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes), MERRF (Myoclonus Epilepsy with Ragged Red Fibers), Niemann-Pick C disease. The other three patients were suffering from neurodegenerative diseases such as: Krabbe disease, X-linked adrenoleukodystrophy and metachromatic leukodystrophy. Regarding the genetic encephalopathies found in our patients, the specific diagnoses are: West syndrome, Dravet syndrome, SCN2A gene mutation, Rasmussen syndrome, GABRB3 gene mutation, 7q31.32 partial duplication, ATP1A3-related disorder and PRRT2 gene variant. Finally, with regard to the seven patients affected by neuromuscular diseases, the specific diagnoses are the following: Duchenne muscular dystrophy, spinal muscular atrophies (type zero and type one) and congenital myopathies. Diagnosis was performed by genetic tests (including Array-CGH and Next Sequencing Generation) and neuroimaging exams.

This category accounts for 0.8% of those born annually in our hospital. Our data were confined to a subgroup of neonatal population who were candidates for palliative care, considering that in Sicily 42,072 children are born every year, and among them 11,640 were born in Catania.

All the included patients had a predicted end of life given since birth, given the severity of the neurological disease on which the palliative supports depended. All patients eligible for palliative care were started at palliation at a medium age of 7.1 months.

Palliative care interventions performed on included patients
In our patients, diagnosis of a neurologic disease with poor prognosis was performed at 3.8 weeks of life. These patients then underwent to intensive care interventions when their disease worsen and they had to start palliative cares to support their vital functions, at a medium age of 7.1 months.

All patients underwent to palliative cares for ventilatory support, nutritional support, and pain therapy.
As far as the ventilator support is concerned, all patients underwent a tracheostomy. Invasive ventilation was then maintained for 5 patients, while Non-Invasive Ventilation (NIV) was started for 19 patients (20% with nasal goggles and 80% without). Non-Invasive ventilation was performed in B Level mode (IPAP 12-24 mmHg and EPAP 4-7 mmHg).

The nutritional support was mainly assured by PEG placements in 85% of patients, after 1 month of oro-gastric tube feeding, while 15% of patients underwent a Nielsen Surgery. Among these last, 20% developed a Dumping Syndrome. The efficacy of nutrition was analyzed by the changes on auxologic parameters, and in our patients 20% showed a growth failure and their weight was under 15th percentile. 70% of patients had a normal weight and 10% overweight.

Pain therapy was started with paracetamol in all patients, and at the end of life was the continued with tramadol and morphine as add on therapy. Five patients (14.79%) underwent end-of-life sedation procedures with opioids. Not all patients were guarantee respiratory physiotherapy due to the lack of specialized professional figures permanently present on the ward (Tables 1 and 2).

1.0 Timing, setting and healthcare professionals involved in communicating to the family the patient’s state of incurability and opportunity to start palliative care

Between 3 and 50 days after birth, these patients' need to begin a support/palliation course was communicated. The neonatologists on duty conducted this conversation with 9 patients, while the head of the operating room conducted it with 31 patients. A psychologist then initiated conversation. Two families were given access to a weekly psychological support session hosted at the S. Marco Hospital's NICU operating room. There are no certified neonatal-pediatric experts, such as psychologists or spiritual helpers, in our university hospital.

The conversation took place within the hospital ward in the medical room, in the chamber of the head of the operational unit, which cannot be isolated from the surrounding settings, because there were no suitable rooms available for counseling.
1.1 The environment in which PPCs were carried out

Of the 34 patients included in the study, 28 (82.35%) were transferred to the Pediatric Unit of our hospital after reaching a mean age of 50 days and 10 (35.71%) were subsequently discharged home. Of these 10 children, 3/10 (30%) were referred to the Pediatric Hospice of the Garibaldi-Nesima Hospital, 4/10 (40%) to the Integrated Home Care Service (ADI) and 3 were referred to the Center for Metabolic Diseases in our University Hospital. As for the remaining 12 children, 3/12 (35%) of them remained in the NICU awaiting transfer and 9/12 (75%) died.

1.2 Professionals who were actively involved in the palliative care and therapeutic interventions

Health practitioners' inadequate understanding of Law 38/2010 and what was codified as a right of children to palliative care is one reason why the current situation is so urgent. During hospitalization both in Neonatology and in the Pediatric Unit, nutritional interventions were performed (feeding through gavage, partial and total parenteral nutritional therapy), ventilatory support was guaranteed (non-invasive and invasive ventilations), and pharmacological treatments suitable for the type of pathology were performed (antibiotic therapy, antifungal, caffeine, anticonvulsant). All of the infants received oro-gastric tube feeding and 33 of the 34 patients underwent PEG placement surgery. Five patients underwent tracheostomy and subsequently received assisted ventilation. In only one case, the family refused the tracheostomy procedure. The placement of an umbilical venous catheter was reported in 20 patients in the neonatal intensive care unit. None of the patients received analgetic therapy of any kind for procedures such as blood draws, intubation, or central venous catheter placement. Five patients underwent end-of-life sedation procedures with Fentanyl. Not all patients were guarantee respiratory physiotherapy due to the lack of specialized professional figures permanently present on the ward (Tables 1 and 2).

1.3 Causes and setting of death
Nine (26.47%) out 34 patients are alive today and followed up at the Centre for Metabolic Diseases. Of the 25 patients who died, 4/25 (16%) were admitted to hospice; 15/25 (60%) to neonatal intensive care unit and pediatric wards, and 6/25 (24%) to the pediatric intensive care unit. One of the enrolled patients died in the delivery room. The causes of death of these patients were: extreme prematurity; cardiac arrest; disseminated intravascular coagulation, and shock.

The average age of death in our cohort was of 23.9 months of life.

**Discussion**

In our study, those patients eligible for palliative care due to severe neurologic diseases with poor prognosis represent 0.8% of the babies born yearly in our facility. It seems that palliative cares in patients with by neurologic diseases show different features than those performed on oncologic patients. In fact, our study shows that the end-of-life expectation of children with neurologic diseases seems longer than oncologic patients. As a matter of fact, these lasts are usually initiated to palliative cares when their end-of-life is already expected, according to international cancer protocols for diagnosis and treatment. There is no clear end-of-life expectation, instead, for patients with severe neurologic diseases; in fact, these patients are not able to move or speak properly, and their vital functions at the end-of-life are often related to the appropriate support of machines such as ventilator or feeding supports. Moreover, in our cohort, 9 (26.47%) patients who were expected to die, survived after palliative care onset, this underlying the need to clarify what are the right criteria to initiate palliation in these patients.

Another important finding is that neurologic patients often need an external machinery support to maintain their vital functions (mechanical ventilation, machinery feeding). In fact, in our study ventilator and feeding support were the most representative cares needed by the enrolled patients. Thus, while palliative cares in oncologic patients are “pain-centered”, in order to alleviate pain deriving from their main disease, palliative care in neurologic patients is mainly related to the use of
proper machinery support. This might explain the longer life expectance of neurologic patients that is strictly related to the proper functioning of external supports.

To our knowledge, to date in the literature, there are no data on pediatric palliative assistance service for patients with neurologic diseases. This service would require specially trained professionals, including not only doctors but also psychologists, psychotherapists, palliative doctors, nutritionists, and physiotherapists. Numerous factors contribute to this, including the complexity of the issue given the patient health characteristics, the involved pathologies, and the difficulties related to the fact that health professionals lack specialized training in this area, cultural and social considerations, organizational challenges, and financial challenges. Despite considerable improvements in the identification and treatment of neurologic illnesses, little has been done to help families of these children navigate the difficult decisions that result in grave consequences for the body and mind. Moreover, there is a shortage of palliative care specialists, especially for children affected by neurologic diseases. It is therefore necessary to formulate standards for primary palliative care education for neurologists, but also to increase access to palliative care education to neurologic pediatric patients for all healthcare providers involved.\textsuperscript{14) As seen by the absence of focus on effective pain management, we also require common treatment pathways to be used in patients designated for palliative care. Every individual has a fundamental right to early pain treatment, which is regarded as the lowest degree of care.

The network of palliative care is constantly expanding in Italy. Unfortunately, pediatric palliative care is now only available to a small percentage of eligible children and only for very brief periods of time. It is also confined to isolated and highly heterogeneous patient groups. Additionally, help is typically given to these individuals in hospitals, frequently in critical care units.

Residential care dedicated to palliative care is considered as an improvement and more adequate response to the needs of the advanced and / or terminal stage of the disease. Even in Sicily, the implementation of palliative care services is continuously developing. The organizational model of the pediatric palliative care network was primarily developed on a regional basis, with the aim of
integrating various levels of assistance to provide real support to the minors and families in charge.

On February 12, 2015, a decree was issued by the Health Department for the organization and development of the local palliative care network focusing on three types of care settings including hospitals, domiciles, and hospices through counseling.\textsuperscript{15-17} Criteria for hospice eligibility are well developed for patients affected by oncologic diseases, but tend to be less appropriate or absent for chronic neurodegenerative diseases. Evidence-based hospice criteria for pediatric neurologic illnesses are needed.\textsuperscript{18} A Family-Centered Developmentally Focused Care in NICU and in the Pediatric Wards should improve the palliative care support for the child-family system, with a coordinator and the rest of the care team to work closely together to design a customized and early care program for the infant. Finally, it is crucial to consider that a child is always evolving and their needs and preferences vary frequently. This leads to the necessity for moral duty on the part of the family and the medical team to support the needs of these children with an incurable condition.

Limitations of the study

To our knowledge, no studies on palliative care to neurologic children have been conducted to date in children with neurologic diseases diagnosed at birth. We could deduce from the presented patient population what is required to implement this therapeutic approach on a larger scale if we take into account that our data are restricted only to a portion of the neonatal population, who are candidates for palliative care for neurologic patients, and to those born in a single local hospital. Our study has some limitations, including a four-year observation duration and the fact that it is a monocentric study with a small sample of patients. To support our findings, prospective multicenter trials with a sizable patient sample are required.

What this study adds: The majority of the literature on palliative care up to this point has been on non-neurologic palliative care. Only adult patients have received descriptions of palliative care for neurologic patients up to this point. But it's crucial to note that 25% of diseases requiring palliative care result from severe neonatal circumstances, and 25% are caused by severe congenital
abnormalities and/or chromosomal and complicated disorders. This means that about half of all
diseases requiring such treatment frequently strike newborns. Tumors, neurological diseases, in
particular degenerative and metabolic diseases, contribute to determine the majority of the remaining
cases. As already stated in the survey published by Cavicchiolo et al., which describes that in Italy
there is no national consensus on palliative cares in the perinatal period, it emerges also from our
study that there is no univocal therapeutic approach for patients who are introduced to a palliative
care path by the healthcare personnel. In this study, we sought to pay particular attention to how
palliative care for neurologic patients has been delivered in our area. We discovered that no palliative
care network has been established to serve the requirements of the people, notwithstanding the
statutory provisions. The skills necessary for efficient symptom management, communication, and
advance care planning must be mastered by all neurologists. Knowing the course of the disease can
help identify patient and family requirements quickly and make educated decisions easier.

Our research also demonstrates the need for comfort zones where the family's privacy can be assured
in a sensitive and painful situation, as well as the need for regionally uniform protocols and guidelines
that are understood by all medical professionals who care for the newborn with an incurable disease.
It is necessary to do research on health care disparities in Italy in order to identify the underlying
causes and take action to eradicate them. To promote evidence-based treatment, it might also be
helpful to evaluate the effectiveness of palliative and palliative care therapies for neurologic patients.
Pediatric Palliative Care is a child's right that is still too much disregarded and should be implemented
in all its aspects to guarantee a better quality of life for our patients.

Conclusion

The issue of palliative care for neurologic patients in neonatal and pediatric age is complex and the
subject of increasing attention by healthcare personnel. It poses important questions of an ethical
and also managerial nature, as it emerged from data already available in the literature. The
majority of the literature on palliative care up to this point has been on non-neurologic palliative care.
There are large gaps in the provision of palliative care for people with neurologic conditions. We intended to concentrate on how the palliative care course is taught in our area in this study. Despite the legal requirements, Sicily does not have a palliative care network in place to serve the needs of the populace. Therefore, in the lack of common and established procedures, the treatment of pediatric palliative care is now handled by medical professionals working in pediatrics or by doctors handling palliative care for adults. It is clear that this service has to be organized, and that a vast network must be built to ensure that such care is provided. Given the large number of kids at our facility who require palliative care treatments due to neurologic diseases, the creation of a straightforward departmental unit devoted to pediatric palliative care for neurologic patients should be suggested. As soon as the kid need it, palliative care can be introduced to neurologic patients. This allows for a prompt assessment and treatment of pain and other problems, which could lead to less aggressive care and better results at the end of life. To provide a higher quality of life for our tiny children, palliative care is a right that is still far too often disregarded.
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References


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Table 1 Basic characteristics of the patients in the study.

<table>
<thead>
<tr>
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<th>Description</th>
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<tbody>
<tr>
<td><strong>Age of birth (weeks)</strong></td>
<td>36 median; 35.3 average</td>
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<tr>
<td><strong>Gender</strong></td>
<td>20 M; 14F</td>
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<tr>
<td><strong>Birth Weight (gr)</strong></td>
<td>2.6 median; 2,389.4 average</td>
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<tr>
<td><strong>Pregnancy Status'</strong></td>
<td>24/34 Did not report any pathologies</td>
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<td></td>
<td>10/34 Threat of preterm birth</td>
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<tr>
<td><strong>Childbirth mode</strong></td>
<td>18/34 Caesarean section</td>
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<td></td>
<td>16/34 Spontaneous birth</td>
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<tr>
<td><strong>Diagnosis</strong></td>
<td>3/34 extreme prematurity (23, 24 and 27 weeks of gestation)</td>
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<td>6/34 severe metabolic encephalopathies [MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes), MERRF (Myoclonus Epilepsy with Ragged Red Fibers), Niemann-Pick C disease, Krabbe disease, X-linked adrenoleukodystrophy and metachromatic leukodystrophy].</td>
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<td>8/34 genetic encephalopathies (West syndrome, Dravet syndrome, SCN2A gene mutation, Rasmussen syndrome, GABRB3 gene mutation, 7q31.32 partial duplication, ATP1A3-related disorder and PRRT2 gene variant.)</td>
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<td></td>
<td>7/34 neuromuscular diseases [Duchenne muscular dystrophy, spinal muscular atrophies (type zero and type one) and congenital myopathies]</td>
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<td>9/34 hypoxic–ischemic encephalopathy</td>
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<td>1/34 posthemorrhagic hydrocephalus</td>
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Table 2: Nature and content of the palliative treatment received by the subjects in the study.

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<thead>
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<th>Nature and content of the palliative treatment received by the subjects in the study.</th>
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<td><strong>Average age at diagnosis</strong></td>
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<td><strong>Average age at start of PPC</strong></td>
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<td><strong>Average age at death</strong></td>
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<tr>
<td><strong>Ventilatory support</strong></td>
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<td><strong>Nutritional support</strong></td>
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<td><strong>Pain therapy</strong></td>
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