Use of palliative chemotherapy in South Africa: National survey of paediatric oncologists and experience in a single unit

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Declaration

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ACRONYMS

5-FU	Fluorouracil
COJEC	Neuroblastoma first line combination chemotherapy (Cyclophosphamide, Vincristine, Carboplatin, Etoposide, Cisplatin)
COMBAT	Combined Oral Metronomic Biodifferentiating Antiangiogenic Treatment
DNR	Do not resuscitate
DSRCT	Desmoplastic Small Round Cell Tumour
EURAMOS	European and American Osteosarcoma Study Group
ICE	Combination chemotherapy: Ifosfamide/Carboplatin/Etoposide
ICU	Intensive Care Unit
IT	Intrathecal chemotherapy
IV	Intravenous
IVADo	Combination chemotherapy: Ifosfamide, Vincristine, Actinomycin, Doxorubicin
JXD	Juvenile Xanthogranulomatous Disease
HIV	Human Immunodeficiency virus
HREC	Health Sciences Research Ethics Committee
LMIC	Low or Middle Income Country
MAP	Combination chemotherapy: Methotrexate, Adriamycin, Cisplatin
MAPIE	Combination chemotherapy: Methotrexate, Adriamycin, Cisplatin, Ifosfamide, Etoposide
MIBG	123 I-meta-iodobenzylguanidine
OPEC/OJEC	Combination chemotherapy: Cyclophosphamide, Vincristine, Carboplatin, Etoposide, Cisplatin
PC	Palliative chemotherapy
PO	Per os (oral treatment)
PODC	Paediatric Oncology for Developing Countries
QOL	Quality of life
SACCSG	South African Children's Cancer Study Group
SBAH	Steve Biko Academic Hospital
SCID	Severe Combined Immunodeficiency Disease

SIOP	International Society for Paediatric Oncology
UCT	University of Cape Town
UP	University of Pretoria
USA	United States of America
VAC	Combination chemotherapy: Vincristine/Actinomycin/Cyclophosphamide
VEC	Combination chemotherapy: Vincristine/Etoposide/Carboplatin
WHO	World Health Organisation

ABSTRACT

BACKGROUND: Palliative chemotherapy is cancer-directed therapy, which aims at stopping or slowing down the progression of the malignancy even though it may not have any potential for remission or cure. In South Africa, delayed diagnosis of childhood cancer is a common problem for a variety of reasons including lack of health care facilities, transport, information about the disease and delayed presentation due to traditional healer visits or other cultural issues. In patients who present with advanced cancer, or in patients with relapsed cancer without realistic hope of cure, palliative chemotherapy can be offered in an attempt to manage symptoms, improve quality of life and prolong meaningful survival.

OBJECTIVES: This research study evaluated South African paediatric oncologists' perspectives and practices regarding the use of chemotherapy in patients with cancer with no realistic hope of cure. The second part of the study described the use of palliative chemotherapy in patients who received treatment at the Steve Biko Academic Hospital Paediatric oncology unit.

DESIGN & METHOD: An online survey was conducted among paediatric oncologists in South Africa. The main aims of the questionnaire were to assess paediatric oncologists' considerations around the use of palliative chemotherapy, and then focus on the most recent patients treated with palliative chemotherapy. For the second part of the study, a file review was done of deceased patients who died in the period from January 2012 to December 2018 and who had received palliative chemotherapy as part of their cancer management. We reviewed diagnoses, palliative chemotherapy regimens, timing of initiation and stopping palliative chemotherapy, and whether end of life decisions and discussions were documented.

RESULTS: A total of 41 participants completed the survey, giving a response rate of 89%. The majority of the paediatric oncologists were either neutral or agreed that palliative chemotherapy should be considered. The most important treatment aim was to improve quality of life of the patient (92.7% of respondents). The most important considerations when prescribing palliative chemotherapy was to minimise toxicity of the chemotherapy regimen (4.56 mean, SD=0.5 utilising a 5 point scale where 1=not important to 5=very important), and the effectiveness of the chemotherapy (4.37; SD=0.48). Only 19.5% of patients received treatment primarily because

parents requested it. According to the oncologists polled, the key considerations were largely achieved in the most recent patient treated with palliative chemotherapy. Individual opinions and preferences concerning recommending palliative chemotherapy differ between paediatric oncologists.

Of the 305 patient deaths recorded in the study period, a total of 74 patients had received palliative chemotherapy and were included in the file review. The most common diagnoses were neuroblastoma (18.2%), retinoblastoma (15.6%) and osteosarcoma (14.3%). At the time of diagnosis, the median age of the patients was 6.0 years (range 0.3 to 17.6 years). In 47 patients (63.5%) the disease was deemed incurable at first diagnosis and palliative chemotherapy given from the onset of treatment, while 27 patients (36.5%) were given palliative chemotherapy at relapse. The median time from last palliative chemotherapy to death was 30 days (range 0-742 days). The main documented aim of palliative chemotherapy was to improve symptom control (97.3%) while parents' opinion played an important role in 32.9% of cases. About half of the patients (41 of 74, 55.4%) had documentation of symptomatic improvement.

CONCLUSION: Although the overall attitude towards the use of palliative chemotherapy is positive, there is great inter-individual variation between oncologists in opinions and experience. The lack of empirical data to justify recommendations about palliative chemotherapy remains a problem, and the researcher hopes that this study will spark productive discussion and planning towards more structured use of palliative chemotherapy in children with cancer in South Africa. This study shows that many decisions around end of life care and decision-making could be better researched using a quantitative, prospective, interview-based approach. Repeated measurements of the child and family's quality of life and its associations with palliative chemotherapy should be a research priority in future.

CHAPTER 1: Introduction

1.1 Background

Over the last 50 years there has been consistent improvement in survival rates of childhood cancer.(1) In high income countries the 5-year survival rates now approach 75%, with rapid advances in new areas such as cancer vaccines, immunotherapy and personalised cancer treatment.(1) In contrast to first world countries, like the United States (US) where cancer is the leading cause of non-accidental deaths in children 1-14y old,(2) South African children are still more likely to die of infectious diseases and malnutrition.(3,4) With improved control of infectious diseases as well as improved rate of diagnosis, the number of children diagnosed with cancer annually in South Africa is expected to increase.(3, 5)

Palliative care is an important research area in paediatric oncology because ultimately, despite all the recent advances in treatment, 25 – 30% of all children diagnosed with cancer in high income countries will die due to the disease.(6) In Africa the percentage of cancer-related mortality is much higher (close to 60%) due to late presentation and advanced disease.(3) Late diagnosis is common in Africa, which makes palliative care often the only management option. Reasons for late presentation include lack of health care facilities, transport, information about the disease and delayed presentation due to traditional healer visits or other cultural issues.(4) Unfortunately there are many challenges in the provision of effective palliative care in South Africa, including a lack of trained health care professionals who can offer palliative care, as well as cultural beliefs that may prevent families from seeking help for their dying child.(5)

1.2 Definition of palliative care

Palliative care is "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."(7,8) According to the World Health Organisation (WHO), **palliative care for children** is "the active total care of the child's body, mind and spirit, and also involves giving support to the family. Palliative care begins when illness is diagnosed, and continues regardless of whether or not a child receives treatment directed at the disease."(7) It

is widely believed that a patient has to be "off chemotherapy" to receive palliative care. However, the WHO clearly states that the two modalities (active chemotherapy treatment and palliative care) can and should happen simultaneously. It is possible and advisable to initiate palliative care while the patient is on disease-directed treatment, and disease-directed treatment in the form of chemotherapy may play an important role in the palliative care strategy.

When considering the diagnosis of childhood cancer, the term "life-threatening" which describes a disease for which cure is possible but may fail definitely applies. One of the crucial aims of paediatric palliative care is to prolong life of reasonable quality, but also to avoid futile treatments which may be potentially harmful.(8)

1.3 Palliative chemotherapy

Palliative chemotherapy is cancer-directed therapy which aims at stopping or slowing down the progression of the malignancy even though it may not have any potential for remission or cure.(9) Palliative chemotherapy, in broad terms, refers to the use of cytotoxic chemotherapy (oral or intravenous) for treatment of a patient without a realistic chance of cure. The focus at this stage is symptom control (reduction of common symptoms such as bleeding, dyspnoea and pain) and prolongation of life, as well as improvement of quality of life.(10) Although the disease is deemed incurable, some degree of disease control and improvement also adds symptomatic control. In a sense the use of palliative chemotherapy can be seen as a midway between all or nothing – continuing some cancer-directed therapy with the knowledge that it is unlikely to be curative, while focusing on symptom control, quality of life and minimising side-effects.(1)

1.4 Metronomic chemotherapy

The word "metronomic" is derived from the word "metronome" which refers to a musical device that produces regular clicks. Metronomic chemotherapy is defined as "the chronic administration of chemotherapeutic agents at relatively low, minimally toxic doses, and with no prolonged drug-free breaks."(11–15) This produces a sustained low blood level of the chemotherapy drug without any major side effects. The target of metronomic chemotherapy is inhibition of tumour growth

through anti-angiogenic mechanisms, compared to conventional chemotherapy that treats cancer directly by killing rapidly dividing tumour cells.(11)

A wide range of conventional chemotherapy drugs including cyclophosphamide, methotrexate, etoposide and vinblastine have been shown to be cytotoxic to circulating endothelial cells. These endothelial cells are inherently less likely to develop drug resistance. For this reason significant inhibition of tumour growth can sometimes be achieved with metronomic (low dose, prolonged) chemotherapy even in tumours that are resistant to maximum tolerated doses of conventional chemotherapy.(11) Other drugs that are commonly used in addition to the above-mentioned chemotherapy drugs as part of a metronomic regimen includes celecoxib, thalidomide, retinoic acid, cholecalciferol, fenofibrate and temozolamide. These are known drugs not initially developed as anticancer agents that are "repositioned" to treat new indications, specifically targeting the tumour microenvironment (including stimulating an antitumour immune response, targeting cancer cells and targeting the tumour vasculature).

The use of metronomic chemotherapy is mostly described in the context of multiple relapsed or refractory cancer. It certainly is a very effective form of palliative chemotherapy but it could and likely will be used in the future with curative intent. It has already been used as part of curative strategy for high risk rhabdomyosarcoma.(16) So while it is not restricted to the palliative paradigm that remains the major focus of its use to date. There is a good deal of utility in using low toxicity chemotherapy strategies for palliation in the setting of relapsed and refractory malignancy. Bahl(11) described this clearly when stating "*at this crucial junction of progressive disease and limited options of chemotherapy, declining further treatment for the patient usually gives the patient and their caretakers a feeling of being abandoned. Saying yes to an alternate way of administering chemotherapy drugs may prevent impending doom and provides a ray of hope*."

1.5 Possible indications for palliative chemotherapy

Patients who present with advanced incurable cancer or patients who are refractory to conventional therapy will arrive at a point where they no longer have a reasonable chance of cure. At this stage the treating team and the parents will have to consider different options of treatment, such as

palliative care with symptom relief only, further aggressive treatments (with good symptom control included), or the "in between" option of palliative chemotherapy.(17) This is often one of the most difficult decisions facing parents and physicians in the management of a child with cancer.

It is not easy to find the balance between "cure at all costs" and deciding when to direct the focus of treatment towards symptom control, minimising suffering and maximising quality of life.(1) The philosophy of palliative care supports the belief that for some children the relief of suffering may be a more appropriate and more attainable goal than "cure at all costs".

Research has been done on the factors that affect treatment choices in paediatric palliative care.(1,2,9,17–19). From the perspective of parents, the important factors considered in making the decision between aggressive therapy and supportive care alone were found to be hope, increased survival time and the child's quality of life.(17) For health care professionals, the child's quality of life and increased survival time were the most important factors, with financial considerations also included.(17).

In these very important decisions it is suggested that health care professionals explicitly address the issues of hope, quality of life and survival during discussions with the family and patient.(17) Honest communication about what palliative chemotherapy can and cannot offer to the patient should facilitate informed decision-making in the interest of the child. It is very important that the parents understand the prognosis, as inaccurate perceptions can sometimes lead parents to make decisions to continue aggressive therapy with unrealistic expectations and false hope.(18) When families choose to go ahead with palliative chemotherapy in an attempt to prolong life, they should have an understanding of the expected trajectory of the illness.(20)

Measuring the efficacy of palliative chemotherapy would depend greatly on the patient and family's treatment goals. Some families may want to fight for a cure regardless of the odds, while other families may focus purely on quality of life. The duty of the health care provider is to help the family and patient achieve their own goals as far as possible.(19)

1.6 Benefits and potential problems associated with palliative chemotherapy

Palliative chemotherapy aims at stopping or slowing down the progression of the malignancy in order to improve or maintain the quality of life of children with incurable cancer. It often improves symptom control by controlling the underlying disease process. Palliative chemotherapy has fewer side-effects than aggressive chemotherapy and can often be administered on an outpatient basis, avoiding the need for prolonged hospital stay. One very important potential benefit of using palliative chemotherapy could be buying time for the patient and family to do the work of dying – having important conversations, coming to terms with the fact that the condition is incurable, achieving personal goals, working on a legacy, and doing anticipatory grief work.(8)

Families should be informed about the potential problems associated with palliative chemotherapy. Patients receiving palliative chemotherapy are at risk of spending precious time in hospital away from their families, receiving treatment with no or minimal benefit, being exposed to unnecessary painful procedures, experiencing unwanted side-effects, entertaining false hope of extended life (unrealistic expectations), and therefore not preparing for death and missing out on appropriate palliative care.(10,18) Patients may also die prematurely from sepsis or bleeding as a result of chemotherapy related complications. The financial burden to the family when including travelling costs, time away from work for caregivers and loss of income as a result of giving palliative chemotherapy, also need to be taken into account. It is important to make the purpose of the palliative chemotherapy clear to parents, and also to help them understand that it is reasonable to choose not to continue any cancer-directed therapy (and focus purely on symptom-directed care).(9)

1.7 Conclusion

Efficient palliative care is one of the cornerstones of cancer treatment. There are different reasons why cancer in children may be advanced and even incurable at presentation to an oncology unit. Childhood cancer is very rare and early subtle signs may be difficult to recognise on first presentation to a health service. There may be no option for cure, or attempts at cure may not be successful and the disease may relapse or progress. In these situations, palliative chemotherapy may be offered in an attempt to improve quality of life and prolong survival.

This introductory chapter provided background on the importance of palliative care research in paediatric oncology, the concept of palliative chemotherapy and its possible benefits as well as potential problems. The need for awareness around palliative chemotherapy and the usage thereof has been introduced and its merits documented. The next chapter reviews local and international literature pertaining to health care professionals as well as patients and parents' opinion on the use of palliative chemotherapy, treatment decisions around the end of life, the differences in palliative chemotherapy in children compared to adults, and the differences between palliative chemotherapy in high income countries compared to South Africa.

CHAPTER 2: Literature review

2.1 Overview

Chapter 2 presents the findings of a literature search on the use of palliative chemotherapy and treatment decisions around the end of life. There are many articles describing the goals and preferences of children who suffer from cancer and their parents when the disease trajectory moves to a point where the prognosis becomes poor. For some of these families, palliative care (management of symptoms with the focus on quality of life) takes preference, whereas other families will pursue cure at all costs even if it may mean that the child receives disease-directed treatment way beyond what is clinically advisable or even acceptable. Palliative chemotherapy is seen by some as a good compromise between these two extremes, providing symptom relief and improvement in quality of life whilst at the same time offering some disease-directed treatment. The literature findings of the general benefits of and problems with palliative chemotherapy, the opinion of health care professionals and caregivers, the role of the young patient's opinion in palliative decision-making and the differences between paediatric and adult palliative chemotherapy are discussed and an attempt made to emphasise the differences between high income countries and our context of a low-resource setting.

2.2 Literature search methodology

A literature search was done to explore the subject. The search was limited to published works in the English language after the year 2000. A Boolean search was done through Google Scholar, Medline and Pubmed using the keywords "palliative chemotherapy", "palliative care in oncology", "end of life care", cross-linked with "paediatrics" or "children". A separate search was conducted to identify articles on the oncologists' use of palliative chemotherapy. This search was done using key words "oncologist", "palliative chemotherapy", "decisions".

Key researchers in the field were identified by amount of relevant publications and all their previous publications were searched to find relevant articles.

References quoted by the two most relevant articles found were also searched to find more articles that are relevant.

2.3 The role of palliative chemotherapy at the end of life

Waldman and Wolfe(21) wrote a review article on palliative care for children with cancer in 2013, where they mention a few of the issues around palliative chemotherapy. They question the definition of palliative chemotherapy, quoted as "chemotherapy that is administered without intent to cure, for the purpose of alleviating symptoms and/or extending life", asking specifically at what point chemotherapy should be labelled to be palliative as opposed to chemotherapy given for the aim of cure. They also mention a paucity of data on the use of palliative chemotherapy in children. The difficulty of balancing the toxicities of cancer-directed therapy with the effect it has on the quality of life becomes increasingly difficult as the prognosis worsens with subsequent recurrences of disease. Towards the end of life, increased survival and quality of life often becomes two opposing goals, with toxic chemotherapy given in an (often futile) attempt to increase survival leading to rapidly worsening of quality of life.

Administering chemotherapy in the last 30 days of life in patients with poor prognosis, with palliative intent, has been used as a marker for "aggressiveness of cancer care" as well as an indicator of quality care near the end of life.(22) In multiple articles from adult oncology settings it has been shown that treatment near death is becoming increasingly aggressive,(23,24) clinicians consistently tend to overestimate survival,(25) and that the use of palliative care in conjunction with disease-directed chemotherapy nearing the end of life reduces the use of futile anticancer chemotherapy in the last 30 days of life.(22,24,26) These articles report that between 9 and 43% of patients received chemotherapy in the last 30 days of life.

Wolfe et al(27) looked at the symptoms and suffering at the end of life in children with cancer in the US. Out of 103 children whose parents were interviewed after their child's death, 56% reported that their child received cancer-directed treatment in the last month of life. These children had received an average of 3.7 different regimens of cancer-directed treatment and 23% of them were enrolled in a phase I trial. A total of 49% of them died in hospital, and half of these in-hospital deaths happened in the intensive care unit. This study emphasises again that when long-term survival chances are low, cancer-directed therapy (in other words palliative chemotherapy) should not be offered without concurrent attention to palliative care principles.

Browner et al wrote in a 2005 review article on chemotherapy(28) that the treatment modalities for advanced cancer may include palliative (hospice) care, palliative chemotherapy as well as phase I trials. The article discusses the importance of allowing palliative care from the time of diagnosis, having a continuum of care starting from aggressive care and moving on to comfort care, and allowing these aspects of care to happen simultaneously.

2.4 When "palliative" chemotherapy gets in the way of good palliative care

A recurrent concern in the literature is summarised by Randén(10) in a 2013 article discussing treatment decisions and discontinuation of palliative chemotherapy near the end of life, namely that giving chemotherapy (disease-directed, even though the aim may be palliative) may lead to false hopes that life will be prolonged. The big concern in this situation is that the patient's opportunities to do the "work of dying" and prepare for death may be hampered. In the same way, the disease-directed treatment may prevent or delay access to good palliative care.

In 2014, Harrington(26) also published a discussion on the difficult issues around chemotherapy at the end of life. This discussion (using an adult patient case as an example) stressed the importance of defining clear and appropriate goals of chemotherapy use, and of distinguishing curative from palliative chemotherapy in discussion with patients and families. This article also states that for oncologists, giving third or fourth line chemotherapy may be an easier option than having the difficult discussion about hospice care. This uncertainty about goals of treatment may cause the family and the patient to be unprepared for what the final weeks may bring.

Chan et al (2016),(29) adds the following to the list of potential problems with palliative chemotherapy. Firstly, the toxicity of chemotherapy may lead to prolonged hospitalisation for various possible reasons including nausea, vomiting and diarrhoea, bone marrow suppression, febrile neutropaenia and septicaemia. All these complications will impair quality of life (QOL) significantly and may even shorten survival. Secondly, these patients may delay entering hospice care. In many countries hospice requires a do not resuscitate (DNR) order to be in place, which may be difficult to accept for patients still on active disease-directed treatment. Another potential issue is the cost of palliative chemotherapy, which includes also the costs of supportive care needed

when receiving chemotherapy (laboratory tests, imaging, blood products, clinic and hospital visits). A great concern raised in this article agrees with the one of Harrington(26) (see above) that in clinics where physicians work under pressure and time is precious, it may be easier just to prescribe chemotherapy rather than to spend the hours required to break bad news to a patient or family and come up with an acceptable palliative care plan (which may or may not include chemotherapy). The importance of effective communication is stressed repeatedly in this and many other articles.

2.5 Health care professionals' opinion on palliative chemotherapy

In 1998, the American Society of Clinical Oncology did a survey on the attitudes and practices among paediatric oncologists regarding end-of-life care. This survey was published by Hilden et al(30) and included questions on training in palliative care, current practice in end-of-life care, barriers to the delivery of end-of-life care, decision making and individual experiences with terminal patients. The questionnaire was completed by 228 oncologists. This survey did not specifically address palliative chemotherapy but provided important information on areas that need improvement in end-of-life care delivery, including the need for specific and formal education in paediatric palliative care, the need for a multidisciplinary approach to the care of the dying child and the need for thorough communication with patients, and the ability to initiate a discussion on advance directives and end-of-life care.

The need to be able to acknowledge impending death was identified as an important issue, and discussions around this in the survey indicated that oncologists often recommend continued active treatment (chemotherapy) for patients who have had multiple relapses. The importance of offering concurrent palliative care with the active treatment is stressed in the summary of these survey findings.

Behl et al(31) reported in 2010 on a semi qualitative survey done on adult oncologists, asking the question "What do oncologists say about chemotherapy at the very end of life?" The survey was completed by 61 oncologists, and concluded that it is a very complex question in which oncologists should be collaborating with palliative care providers. Knowing that this survey was done with

oncologists treating adult patients, the themes may be somewhat different as what will be expected from paediatric oncologists. However, important issues that were identified included:

- Decisions on chemotherapy at the end of life are often patient (or family) driven
- Even a small chance of benefit for the patient may justify the use of chemotherapy at the end of life
- The practice of using chemotherapy at the end of life may be detrimental as it often prevents or delays the initiation of hospice services
- These decisions are complicated and revolve around society values, the oncologist alone cannot claim responsibility
- There are many barriers to end-of-life discussions.

A study done by Wusthoff et al in 2005(19) used two identical case histories in interviews with 48 paediatric oncologists working in San Francisco in the US to look at differences in estimates of curability and treatment recommendations. Both case histories were of patients with advanced cancer, and the literature including prognostic data, were included. The results demonstrated a large variability in treatment goals, perceived chances for cure as well as the degree to which further curative intervention would be considered desirable for each patient. Physicians and families are influenced by their own values when considering treatment goals, this may to some extent explain the wide variation found in this study. However, the study recommends that "the duty of the physician is to help the patient and family achieve the goals that are most closely aligned with the family's own values." The importance of recognising their own bias in communication, discussing difficult cases with colleagues and offering a second opinion is clear in these very difficult advanced cancer patients.

Kang et al(2) did an email survey on 422 paediatric oncologists practicing in the US in 2010. This survey described the oncologists' general treatment considerations when prescribing palliative chemotherapy, and also asked some questions about treatment considerations around their most recent patient treated with palliative chemotherapy. In general, this survey revealed that the three most common considerations when prescribing palliative chemotherapy were toxicity, family preference and potential to relieve symptoms. However, when looking at the most recent patient

treated, a worrying finding was that their aims were often not achieved, and that 40.8% of oncologists reported prescribing the palliative chemotherapy mainly for parental wishes. Another important finding in this study is that most oncologists (87.5%) felt that their preferences around the use of palliative chemotherapy often differed from those of their colleagues.

No matter what the opinion of the treating oncologist is, it will have a great impact on the eventual decision of the family whether to consider palliative chemotherapy for their child with incurable cancer.

2.6 Parents' opinions on palliative chemotherapy

For families, the choice between palliative chemotherapy and supportive care alone may be one of the most difficult decisions in the childhood cancer journey.(9,18,32,33) Understanding the issues surrounding this choice is a difficult topic to study and is better approached in qualitative interview-based studies. Quite a few such studies looked at parents' approaches to treatment when standard therapy has failed to cure their child's cancer. This literature review will attempt to summarise the important findings in a selection of the more recent publications.

Mack et al(18) did a retrospective survey in 2008 among a group of bereaved parents. Of the 141 parents included, 53 (38%) had children who died after receiving cancer-directed therapy for palliation (in a situation where cure was no longer possible). Parents were asked whether they perceived any benefit or suffering related to the treatment given after recognising that cure was no longer realistic. The majority of these parents felt that their child had experienced some suffering from the therapy with little or no benefit. More importantly, many of these families would not recommend treatment for incurable cancer to other families even if they had chosen treatment for their own child.(18) An important limitation in this study was the quantitative nature of the questionnaire. It was a vignette-based questionnaire and did not have open-ended questions. In these types of situations so much of the individual patient and family situation, and even the similarity to the vignette, may influence the parents' answers. This type of study design cannot assess and sufficiently comment on those complicated personal issues surrounding the eventual choices and opinions that parents report as a yes/no answer on a questionnaire.

Another study done in Germany by Hechler et al(34) in 2008 with a group of bereaved parents used a semi-structured interview to discuss distressing symptoms and quality of life in their children during the end-of-life period. A total of 48 parents were interviewed. Thirty-six patients (75%) died of progression of disease, and of this group, 50% received cancer-directed therapy at the end of life. Twenty-three of the children (48%) died at home and the remainder in hospital. Of the 18 patients who received cancer-directed therapy, only four children clearly benefited from the therapy according to their parents. The majority of these children suffered from several side effects related to the therapy, and most parents rated the therapy not as effective but as troublesome for their children.

Using a different semi-structured interview approach, Bluebond-Langner et al(9) did a prospective study of parents in 2010 whose children had disease that recurred and had a less than 30% chance of cure. Important findings in this study were that parents viewed cancer-directed and symptom-directed treatment as a continuum of care, not as mutually exclusive approaches, and that parents will discuss and negotiate care rather than being constrained by what the oncologist offers. A total of 34 children were enrolled and their courses of treatment, including treatment decisions by their parents, were prospectively studied. In 28 of the 34 patients (82.4%), parents chose to continue with cancer-directed therapy. This included phase I/II trials, second-line (palliative) chemotherapy, newer interventions (metronomic type therapy including anti-angiogenesis drugs) or more aggressive therapies (high-dose chemotherapy with stem cell rescue). Of the 25 children who died during the study period, 11 children (44%) received some cancer-directed therapy in the last month of life. One important finding in this study, in contrast to the study by Mack et al(18), was that parents valued more time with their children, and were not regretting making choices that included giving palliative chemotherapy. A strong palliative care presence in Bluebond-Langner's institution could explain this difference.

Another interview-based prospective study by Tomlinson et al(32) in 2011 included 77 parents of children who had been diagnosed with terminal cancer, but who were not yet at the point of decision-making regarding end of life care plans. This study primarily looked at the differences between parents' and health care professionals' opinion on palliative chemotherapy versus

supportive care alone. The findings were impressive – significantly more parents (42/77, 54.5%) than health care professionals (20/128, 15.6%) were in favour of palliative chemotherapy. Although they reported similar considerations during decision-making in the two groups, hope was a much more important factor for parents. In fact, parents reported that hope for a cure was so great that they may choose chemotherapy even it reduced the child's QOL and survival time.

It is clear from these studies that decision making around palliative chemotherapy for their children is a complicated situation for parents, with many different contributing factors. It is interesting that the prospective studies(9,32) (with parents whose children were still alive at the start of the study) reported a much more positive attitude towards palliative chemotherapy, whilst a lot of the bereaved parents(18,34) felt that they should not have agreed to chemotherapy.

As a final statement, it is the opinion of the researcher that one of the most important caveats with palliative chemotherapy is that it must not prevent the parents from doing the emotional preparation for the death of their child. Parents' expectations of palliative chemotherapy need to be carefully and continually guided towards the goals of symptom control, improvement in QOL, and "buying extra time" for the patient and family to do the "work of dying".(35)

2.7 The role of the sick child in end of life care decision making

Older children and adolescents frequently prefer to be included in end of life discussions.(8) Even younger children, especially when they have been exposed to an oncology ward or setting for a prolonged period, may express their desire to be involved in hearing what the doctors discuss with their parents. Most health care professionals agree that children should be informed about their prognosis, as well as changes in the treatment plan and disease trajectory.(36) This type of disclosure will facilitate communication between the child and parents, and will most likely improve the family's experience of the end of life journey.

Matsuyama et al(37) published a review in 2006 of studies done on adult patients who chose palliative chemotherapy. In this review, multiple studies showed that adult patients are willing to undergo treatment for smaller benefit than their health providers, and for a small chance of

survival. No similar studies have been done in children and will be almost impossible to do. However, the stark contrast between bereaved parents' opinions in Mack et al(18) and adult patients' opinions in Matsuyama et al(37) creates the question of what paediatric patients would choose for themselves if they were allowed to choose.

In contrast with the impressive amount of studies focusing on clinicians and parents' preferences around end of life care and palliative chemotherapy, there are very few articles looking primarily at the opinion of the child at the end of life. Hinds et al(38) published a study in 2006 in which they interviewed 20 children with cancer between the ages of 10 and 20 and asked specific questions about their care and decision making. These children all had terminal cancer and had been part of an end-of-life discussion in the week preceding the interview. What they found was that these children understood the nature of the discussion, the eventual consequences of their decisions, and that they were able to participate in this very complex multi-faceted decision-making process. As a conclusion, the study supported the ability of children between 10 and 20 years old to take active part in the end-of-life decision-making process. A 2016 narrative systematic review by Bluebond-Langner et al(39) looked at defining the role of adolescents, parents and healthcare professionals in the decision-making process. They found a large inter-individual variation concerning preferences for information. However, importantly, none of the studies indicated preference for a high degree of independence in decision-making and in fact urging parents and adolescents towards independent decision-making may add to distress and confusion.

In a poignant article "Caring for the child with cancer at the close of life", Hurwitz et al(40) tell the story of a patient with terminal leukaemia (at second relapse) and describes the process of the child's involvement in end of life decision making. A few important comments and suggestions are made in this article to assist the clinician with this difficult situation. Asking the parents their preference for communicating prognostic information to their child will build trust between the parents and the medical team. The importance of being truthful when asked direct questions is emphasised. They also highlight the process of following prognostic disclosure with a discussion on goals of care.

Perhaps the most relevant comment for this literature review is that most parents and families desire to continue disease-directed treatment together with symptomatic care directed at improving QOL – "concurrent care"(40).

2.8 How does palliative chemotherapy differ in low-resource settings?

All the studies discussed up to this point in the literature review were set in high income countries where many of the patients present and are diagnosed early and have multiple treatment options available, which include standard chemotherapy, biological, and targeted therapy, clinical trials with the latest new chemotherapy and other drugs, as well as access to stem cell transplant. It is not unusual for most children to go through two or three chemotherapy regimens before being viewed as possibly not curable.(27) At this stage some clinicians continue to give more intense or experimental therapy without having the important discussions needed when the disease trajectory changes. This lack of prognostic disclosure may be as a result of reluctance of the clinician to engage with the family on such a deep level – thus it may be easier to just continue to a further (possibly desperate) treatment regimen.(10,26)

In an editorial piece in Acta Paediatrica 2016, Nicolas Andre(41) clarifies the connection between metronomic chemotherapy and palliative chemotherapy when he explains that the combination of disease control – even in metastatic or refractory tumours – with low levels of toxicity, makes metronomic chemotherapy ideal to use in a palliative setting. As an example the researcher reviewed the SIOP-PODC treatment guidelines for neuroblastoma in low- and middle-income (LMIC) settings.(42) It is recognised that many LMIC struggle with resources, cost of drugs, lack of access to monoclonal antibodies and biological treatments, and lack of access to bone marrow transplant. Knowing that advanced (high-risk) neuroblastoma needs very intense treatment with many of these modalities that are not accessible in LMIC, patients may be prescribed palliative care from the time of diagnosis.

A group of children from Mali, a LMIC in the North Western part of Africa, was treated with metronomic chemotherapy with palliative intent.(15) Half of the group (6/12) were treated with palliative intent using a metronomic regimen from the time of diagnosis, while the other half had

progressive disease on curative treatment. In other words, 50% of the patients included in this study did not previously receive any treatment with curative intent due to the advanced state of disease at diagnosis. Their diagnoses included stage IV neuroblastoma, bilateral retinoblastoma, trilateral retinoblastoma and bilateral nephroblastoma. The metronomic treatment was well tolerated and associated with disease stabilisation. Unfortunately, this study did not include QOL assessment.

2.9 Summary

The articles summarised in this literature review illustrate some of the more important issues around the use of palliative chemotherapy. For the purpose of the proposed survey, the opinions of health care professionals on the use of palliative chemotherapy were discussed in some detail with focus on the aims and perceived success thereof in treating children with incurable cancer. The paucity of data from LMIC was striking, with very few publications to be found.(15) By summarising the use of palliative chemotherapy in South Africa, and including some statistics from a single oncology unit, the hope is that a common ground will be established that can be used to move forward in the care for these patients in South Africa.

2.10 Rationale for the study

Despite advances in curing childhood cancer, some children will die from recurrent or incurable disease. When cure becomes unlikely, patients and health care professionals have to decide whether to offer further aggressive chemotherapy, to consider palliative chemotherapy or to offer supportive care only.

Palliative chemotherapy is given with the intent to improve quality of life in a patient with incurable cancer. Many factors may influence whether the use of palliative chemotherapy will be of benefit to the child. Within a family living in extreme poverty, the use of money to fund transport to hospital to get access to palliative chemotherapy may mean that there will be no money left for food or other basic needs.

Until now, no research has been published on the use of palliative or metronomic chemotherapy in Southern Africa. With many patients presenting late, with either incurable of very advanced cancer, the use of palliative chemotherapy may be important to improve quality of life and manage difficult symptoms in the end of life period. This study includes a birds-eye view of oncologists' opinions from all over South Africa, as well as zooming into the detail of what is happening in one unit with the overarching aim of giving a comprehensive and detailed snapshot of palliative chemotherapy in children with cancer in South Africa.

2.11 Aims and objectives

2.11.1 Part 1: Survey

Aim: To describe paediatric oncologists in South Africa's perspectives and practices regarding palliative chemotherapy

Objectives:

- To describe paediatric oncologists' treatment considerations regarding the general use of palliative chemotherapy.
- To assess treatment considerations that influenced paediatric oncologists' therapy recommendations for their most recent patient receiving palliative chemotherapy.

2.11.2 Part 2: File review

Aim: To investigate the use of chemotherapy at the end of life in patients treated at the paediatric oncology unit of Steve Biko Academic Hospital in Pretoria.

Objectives:

- To review the clinical course of patients who died during/after receiving treatment in the Steve Biko Academic Hospital paediatric oncology unit.
- To describe the use of palliative chemotherapy in this group of patients.

CHAPTER 3: Methodology

3.1 Methodology part 1: Survey

3.1.1 Study Design

Part one of the study was a cross-sectional quantitative survey.

3.1.2 Study Site

A link to the survey was sent out to all paediatric oncologists currently working with oncology patients in South Africa.

3.1.3 Study Population

All paediatric oncologists, fellows in paediatric oncology and medical officers working in paediatric oncology units on a permanent basis in all the provinces of South Africa were invited to take part.

3.1.4 Selection Criteria

- **Inclusion criteria:** All paediatric oncologists, fellows in paediatric oncology and medical officers working in paediatric oncology units on a permanent basis in all the provinces of South Africa were allowed to take part.
- **Exclusion criteria:** Fellows and medical officers who have just begun working in oncology (fewer than six months of time spent in the oncology service) were excluded, as well as paediatric registrars rotating in oncology service.

3.1.5 Sample size

There are 46 doctors working with paediatric oncology patients on a full time basis in South Africa. The aim was to get at least an 80% response rate (37 doctors).

3.1.6 Sampling method

An email link to the questionnaire was sent to all the doctors currently on the South African Children's Cancer Study Group (SACCSG) mailing list. The SACCSG is a group of all the paediatric oncologists in the country, and is the central body that co-ordinates all collaborative

research done on oncology patients in South Africa. All qualified oncologists, as well as haematologists working with paediatric oncology patients and fellows in paediatric oncology are members of this group. Members of the group were encouraged to forward the link to the questionnaire to any qualified doctors working with them full time in their units who may not yet be part of the SACCSG. The method used was convenience sampling; participants who were available and willing to take part were included. Although this sampling method is prone to significant volunteer bias, the very high response rate we managed to get makes our sample representative of the current group of paediatric oncologists in South Africa.

3.1.7 Data Collection Tool

Data collection tool: Web-based survey (see appendix 1). This survey was developed by a group of researchers at The Children's Hospital of Philadelphia in Pennsylvania, United States of America,(2) and their findings published in Pediatric Blood & Cancer journal in September 2012. We obtained written permission to use their survey and adapt it for our circumstances as necessary. Survey Monkey® (a commercially available tool for online surveys) was used to construct the online survey.

3.1.8 Data Collection Method

Emails were sent to all the SACCSG members and they had permission to forward it to any qualified doctors working full time in their units who were not on the mailing list. The email contained an introduction letter, explaining the purpose of the study as well as an explanation that the study will be anonymous and voluntarily and participation in the survey will be construed as providing consent.

Those interested had to follow a direct link taking them to the online questionnaire. All data were captured anonymously but doctors were asked demographic details such as gender, age category, years in practice and current workplace.

3.1.9 Data Storage and Confidentiality

E-mail addresses were stored on a password-protected private computer. Responses were captured anonymously and even though this is a small population, the results did not link the unit or province from where a reply came to any of the findings. Study data were password protected.

3.2 Methodology Part 2: File Review

3.2.1 Study Design

The second part of the study was a retrospective descriptive audit of patient files in a single centre.

3.2.2 Study Site

The audit was done on files of patients seen in the paediatric oncology unit at the Steve Biko Academic Hospital. The hospital is a tertiary academic hospital situated in Pretoria, South Africa. The oncology unit offers treatment to all patients from Northern Gauteng and Mpumalanga, as well as some patients from Limpopo province, and the neighbouring countries Zimbabwe and Mozambique (this depends on referral route). The unit sees an average of 110 new oncology and haematology patients per year. The unit comprises of a 10 bed day ward for administration of outpatient chemotherapy and blood products, as well as an inpatient ward with 30 beds. The 30 beds include five isolation rooms with two of these equipped for stem cell transplant.

3.2.3 Study Population:

This included patient files of all patients who died during or after treatment in the paediatric oncology unit, Steve Biko Academic Hospital. Folders of all the patients who died in the period from January 2012 to December 2018 were reviewed.

3.2.4 Selection Criteria

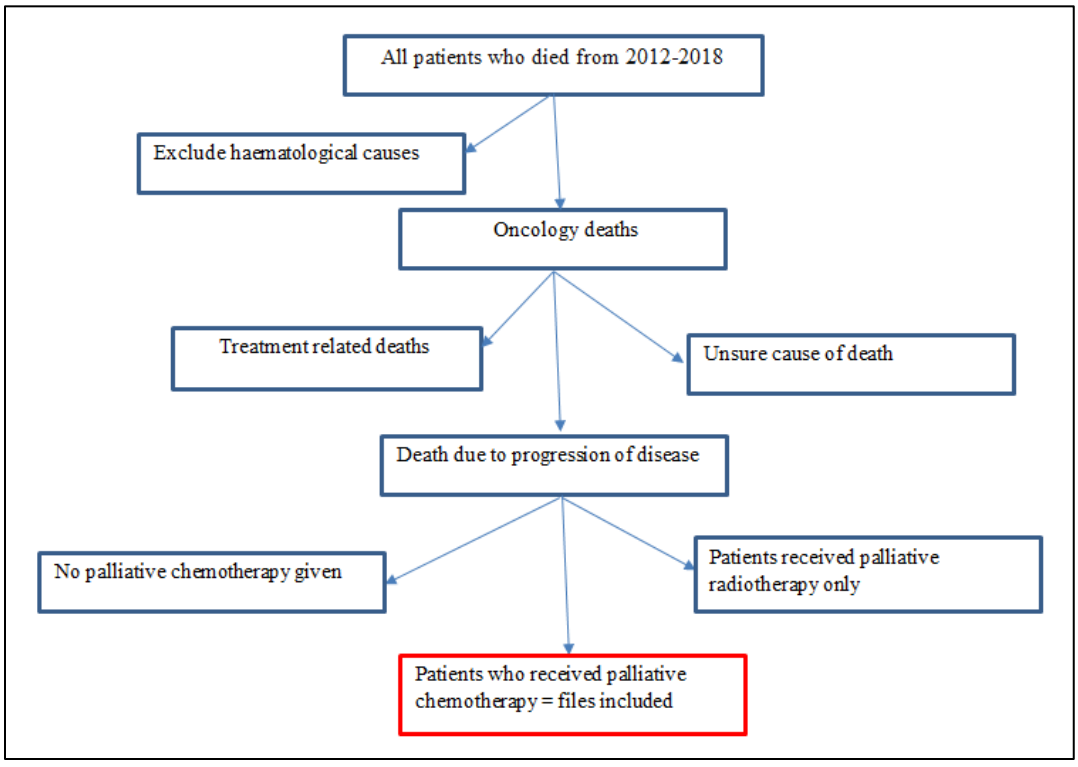
Folders of all the patients who died in the period from January 2012 to December 2018 were reviewed.

- **Inclusion criteria:** All paediatric oncology patients who died from incurable or relapsed disease and received palliative chemotherapy.
- **Exclusion criteria:** Patients who died during active treatment with curative intent, and patients diagnosed with benign haematological diseases (Fanconi anaemia, severe aplastic anaemia). All patients who died from incurable or relapsed disease and did not receive palliative chemotherapy.

3.2.5 Sampling method

Patient Files: The oncology unit has a list of all the patients managed by the unit who demised. This list was used to access the files for the patients on the list who died in the specified period (January 2012 to December 2018). Access to files was not a problem as all patient files are kept in a secure locked up file cabinet in the unit. This selection of files was scanned and all those who died while on active curative treatment were excluded. The remainder of the files were reviewed, and those patients who received palliative chemotherapy as part of their treatment were included in the final audit. Figure 1 explains the sampling process with the numbers of patient files in each category. A total of 74 patient files were included in the final sample.

Figure 1: Diagram of sampling process



3.2.6 Data Collection:

A data extraction tool was developed for the file audit (see appendix 3). This audit tool was developed based on the literature review taking into account factors that may play a role in the use of palliative chemotherapy. The data extraction tool includes the following topics:

a. Patient information including age, gender and diagnosis
b. Family structure
c. Stage of illness at diagnosis and stage when palliative chemotherapy was started
d. Documentation around palliative chemotherapy (decision and family discussion)
e. Aims of palliative chemotherapy
f. Regimen of palliative chemotherapy used (drugs, doses, route)
g. Cause and location of death

3.2.7 Data Storage and Confidentiality

Medical information was recorded from the files onto the data extraction spreadsheet and each file was allocated a study number. To maintain confidentiality, a separate log was kept for linking names and study numbers. All data was gathered from files directly onto an electronic spreadsheet to reduce the risk of data capture errors. All information is kept on a password protected laptop and backed up per institutional policy, which states all work is backed up weekly, to a secure server.

3.3 Data Analysis

3.3.1 Part 1: Questionnaire

Primary data analysis was done using Survey monkey's software. Descriptive statistics were calculated for physician and ''most recent patient'' characteristics. Differences in how individual respondents rank generic treatment considerations and how they rank the same considerations for their most recent patient were assessed.

3.3.2 Part 2: File Audit

The data from the data capture sheet was inserted into Excel, and descriptive statistics such as mean averages, median and proportions used to describe the data. Survival analysis was performed using the Kaplan-Meier method.

3.4 Ethical Considerations:

This study was researcher-funded and undertaken to fulfil requirements for the UCT Masters of Philosophy in Palliative Medicine. The research proposal was approved by the UCT HREC on 24/10/2017, reference 729/2017 (see appendix 4). On request the proposal was also then submitted to the UP HREC and approved on 07/11/2018, with reference number 571/2018 (appendix 5).

With regards to the survey, consent was explained in the document accompanying the questionnaire and then implied through completion of the survey. Medical doctors working in oncology are exposed to these difficult situations and decisions around palliative care on a continuous basis. The questionnaire required the respondents to answer questions relating to their patients treated with PC. The introduction to the survey included information to prepare respondents for these possibly emotionally taxing questions (appendix 2).

Permission to conduct the file audit was granted by the Gauteng Department of Health and Steve Biko Academic Hospital (appendix 6). There was minimal risk to patients due to this being a retrospective audit of files with no direct involvement of patients.

CHAPTER 4: Results of survey

4.1 Introduction

Chapter 4 presents the results of the 41 participants' answers that were collected from 01/10/2018 until 13/11/2018. Initial emails were sent to the mailing list of the SACCSG, specifically targeting the forty-six paediatric oncologists, fellows, and medical officers working full-time in paediatric oncology. Forty-one of those responded, giving a response rate of 89%.

4.2 Demographic data

Table 1 summarises the demographic characteristics of the 41 paediatric oncologists who responded to the survey.

Table 1: Demographic characteristics of 41 paediatric oncologists

CHARACTERISTICS	n	%
Gender		
Male	9	22%
Female	32	78%
Age		
30 – 39 years	17	41.5%
40 – 46 years	12	29.3%
47 – 52 years	5	12.2%
53 – 58 years	3	7.3%
59+ years	4	9.8%
Current practice setting		
Academic hospital	21	51.2%
Private practice	6	14.6%
Combined private and academic	14	34.2%

Years since fellowship training in paediatric haematology/oncology		
<5 years	14	34.2%
6 – 10 years	6	14.6%
11 – 15 years	6	14.6%
16 – 20 years	4	9.8%
More than 20 years	4	9.8%
Full-time medical officer in paediatric haematology/oncology	1	2.4%
Busy with fellowship training in paediatric haematology/oncology	6	14.6%
Time spent on direct patient care		
<20%	0	0
20 – 50%	5	12.2%
51 – 75%	7	17.1%
>75%	29	70.7%
Time spent on oncology patients		
<20%	0	0
20 – 50%	5	12.2%
51 – 75%	7	17.1%
>75%	29	70.7%
Approximate number of new cancer diagnoses per year in practice		
0 – 50	14	34.2%
51 – 100	14	34.2%
101 – 150	11	26.8%
>150	2	4.9%
Number of patient deaths in a year		
0 – 1 deaths	2	4.9%
2 – 9 deaths	22	53.7%
10+ deaths	17	41.5%
Standard protocols for relapsed and refractory patients		
Yes for more than 75% of diagnoses	13	31.7%
Yes for 50 - 74% of diagnoses	20	48.8%
Yes for <50% of diagnoses	8	19.5%

Access to a paediatric palliative care program		
Yes	23	56.1%
No	9	21.9%
Occasionally	9	21.9%
Type of paediatric palliative care program		
Inpatient consult service	17	41.5%
Outpatient consult service	3	7.3%
Local hospice	10	24.4%
Other	11	26.8%

Survey respondents were mostly female (78%) and just over 70% were in the younger two age categories between 30 and 46 years. Almost half of the participants were either busy with training or newly qualified as paediatric haematologists/oncologists (48.7%). Most were working exclusively in the academic setting (51.2%) or combined academic/private (34.2%) with only 14.6% working solely in private practice. Most physicians (70.7%) spent more than 75% of their time on direct patient care of oncology patients.

New cancer diagnoses per year were more or less equally distributed between the three categories 0 – 50 (34.2%), 51 – 100 (34.2%) and 101 – 150 (26.8%) with only two respondents reporting seeing more than 150 new diagnoses per year. Most physicians (53.7%) had 2 – 9 paediatric oncology deaths per year, but 41.5% had more than 10 deaths per year. Just over half of the physicians (56%) reported access to a paediatric palliative care program, with an additional 22% reporting occasional access. The types of palliative programs included inpatient consult services (41.5%), local hospice access (24.4%), outpatient consult services (7.3%) and other, which were specified to be oncologist trained in palliative care, access to established palliative care services in the area, and all the above.

4.3 General experiences with palliative chemotherapy

The second part of the survey looked at the participants' general opinion on palliative chemotherapy. Participants were asked about their main goals when considering palliative

chemotherapy, and about the factors that influenced this decision. They were also asked how frequently their opinion differed from the opinions of their colleagues when considering palliative chemotherapy.

4.3.1 Recommending palliative chemotherapy

Most of the respondents reported that their individual preference regarding the use of palliative chemotherapy often (22.5%) or sometimes (67.5%) differed from that of their colleagues.

Question 12 asked when palliative chemotherapy should be recommended, mentioning two specific cases – a child who has relapsed disease, and a child for which no experimental therapies are available. Most physicians were either neutral or agreed that palliative chemotherapy should be recommended in both these situations (see figure 2). A total of 10 respondents (24.3%) would not recommend palliative chemotherapy for a child with a disease that has relapsed, and 9 respondents (22%) disagreed that palliative chemotherapy should be considered when there are no experimental therapies available.

Question 13 went on to assess the recommendation of palliative chemotherapy when considering the probability of death from the disease. Five percentage probabilities were given as options, and respondents had to say in which of these situations they would consider giving palliative chemotherapy. The answers to this specific question were very haphazard without any clear pattern (figure 3). However the weighted average of each option remained above 3, and there were more respondents who would recommend palliative chemotherapy in all the categories than those who would not. This is explained in figure 4 where the neutral responses were removed and those who agreed are compared to those who disagreed.

Figure 2: Recommending palliative chemotherapy in specific situations

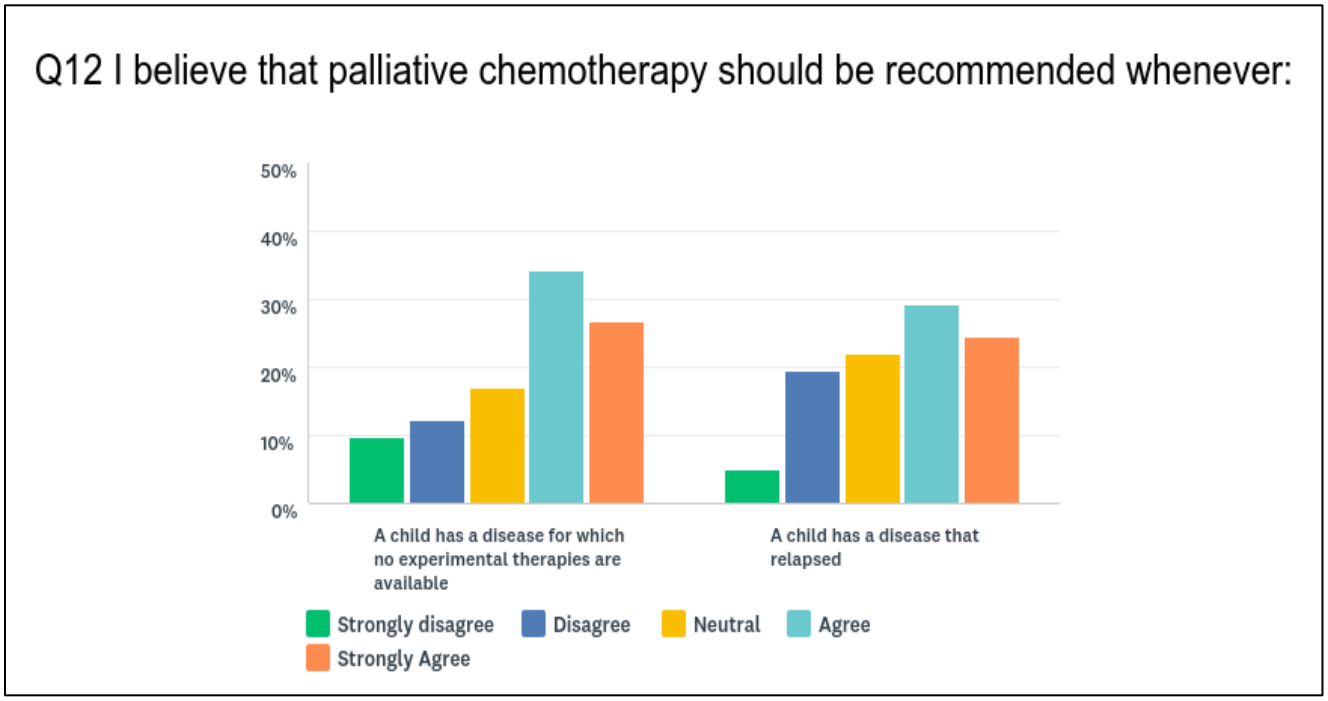


Figure 3: Recommending palliative chemotherapy depending on the probability of death from disease

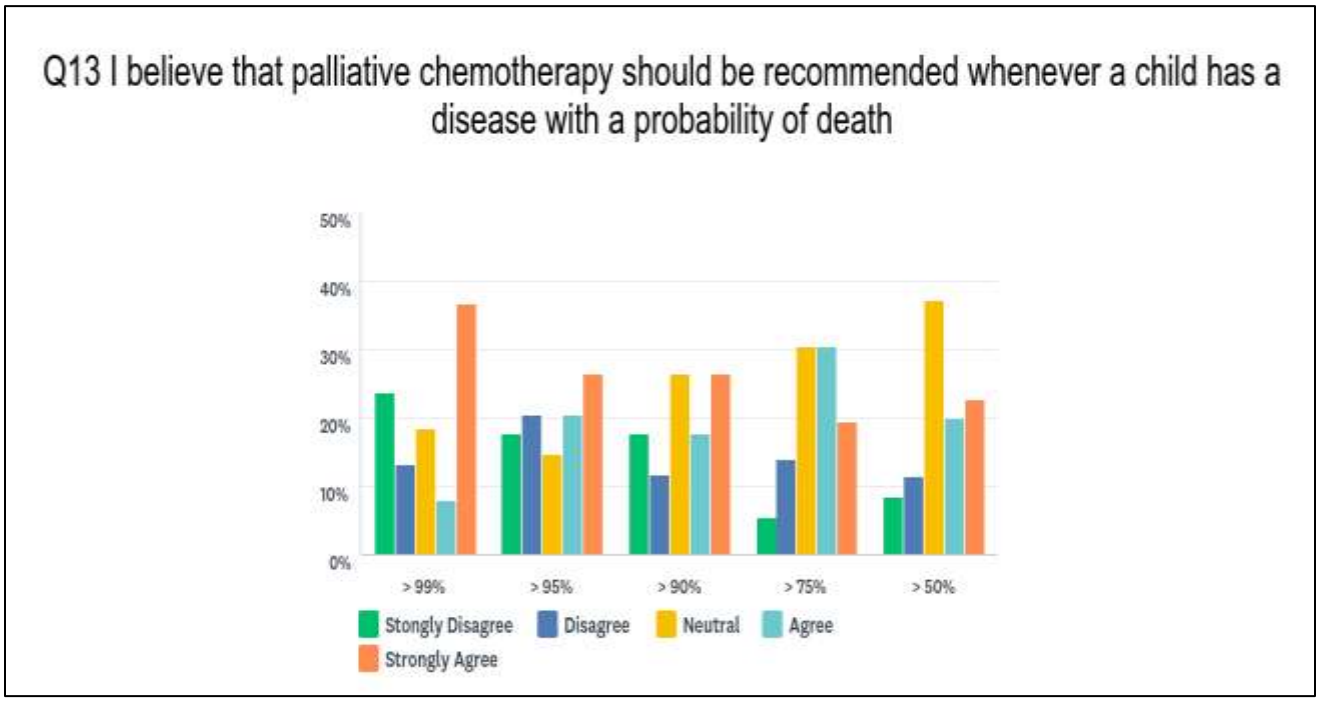
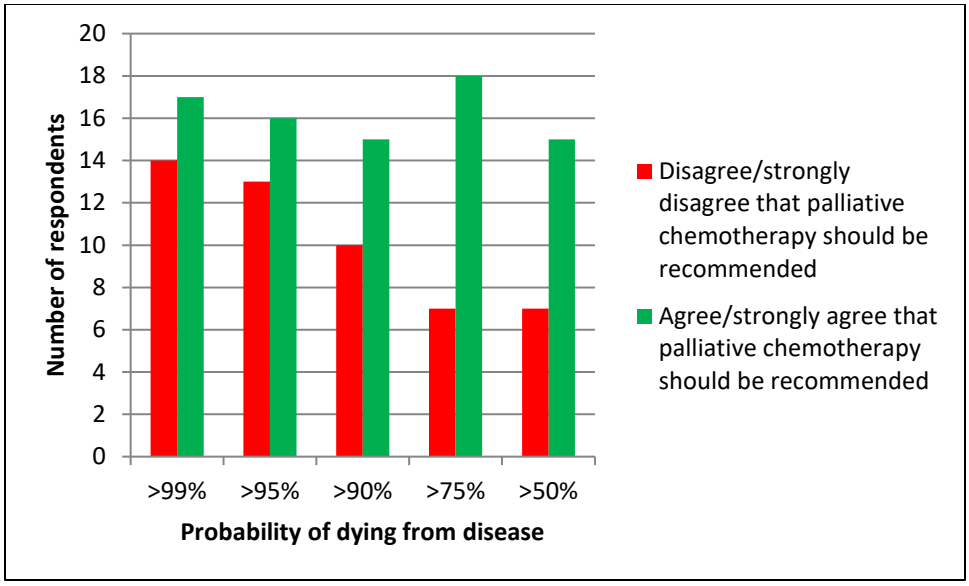


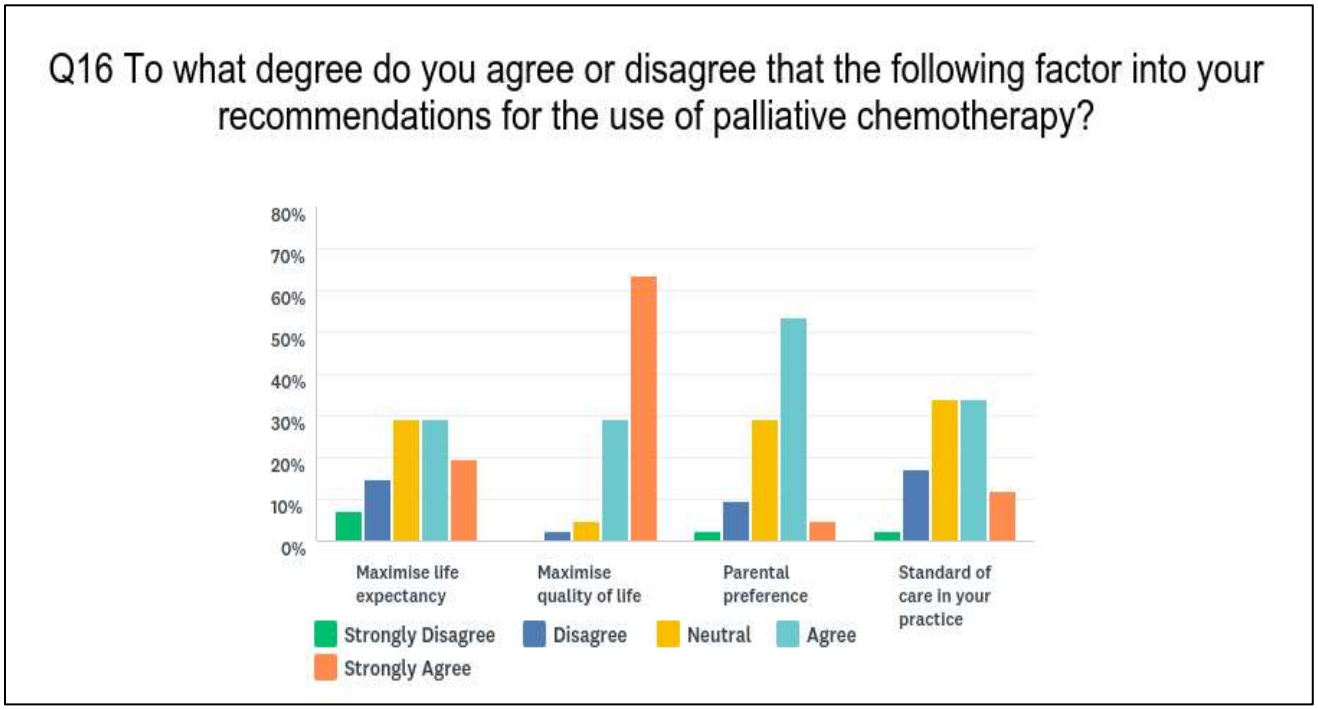
Figure 4: Comparing recommendation of palliative chemotherapy depending on probability of death, grouping positive and negative responses



4.3.2 Factors to consider when recommending palliative chemotherapy

Question 16 included four factors that physicians may consider when recommending palliative chemotherapy. Respondents were asked to rate how important each of these factors were in their personal decision-making around recommending palliative chemotherapy. The answers are summarised in figure 5. Most respondents (92.7%) agreed that palliative chemotherapy should be given to maximise quality of life. About half of the respondents (48.7%) either agreed or strongly agreed that maximising life expectancy is an important factor when considering palliative chemotherapy. Parental preference was also an important factor where 58.6% of respondents agreed that it should be an important consideration.

Figure 5: Importance of factors to consider when recommending palliative chemotherapy



Question 16 was followed by an open-ended question where respondents were asked to share other factors that they routinely prioritise when recommending palliative chemotherapy. A few themes emerged that can be summarised under the following headings:

(1) Symptom control
(2) Patient preference
(3) Family context
(4) Risk benefit ratio of proposed palliative chemotherapy
(5) Availability and cost of drugs
(6) Unrealistic expectations

<u>Theme 1: Symptom control</u>

Several respondents mentioned the importance of improving symptoms especially pain with the use of palliative chemotherapy.

Theme 2: Patient preference

The preference of the patient him/herself was a recurrent theme that emerged. The age of the patient, current quality of life, and the patient's own opinion on further chemotherapy seems to be an important consideration in many cases. The cultural beliefs of the patient were also mentioned.

Theme 3: Family context

The family as the patient's closest support system clearly plays an important role in these type of decisions around palliative chemotherapy. Specific issues that were mentioned include:

- Socio-economic demands on the family
- Improving the patient's condition to allow the family to come to terms with the diagnosis and prepare themselves
- Burden of treatment on the family
- Cultural and religious beliefs of family
- Travel distance from hospital, ability to get patient to hospital, place of residence
- Psychosocial support
- Parent request for chemotherapy

Theme 4: Risk benefit ratio of proposed palliative chemotherapy

Patients with relapsed disease and no known "curative" options should be considered for palliative chemotherapy. However, the following important considerations were mentioned with regards to risk benefit ratio of palliative chemotherapy:

- Type of cancer and sensitivity to simple oral therapy
- Toxicity of proposed treatment, minimal side-effects
- Ease of use, no need for IV access
- Cost of treatment relative to what is gained

Theme 5: Availability and cost of drugs

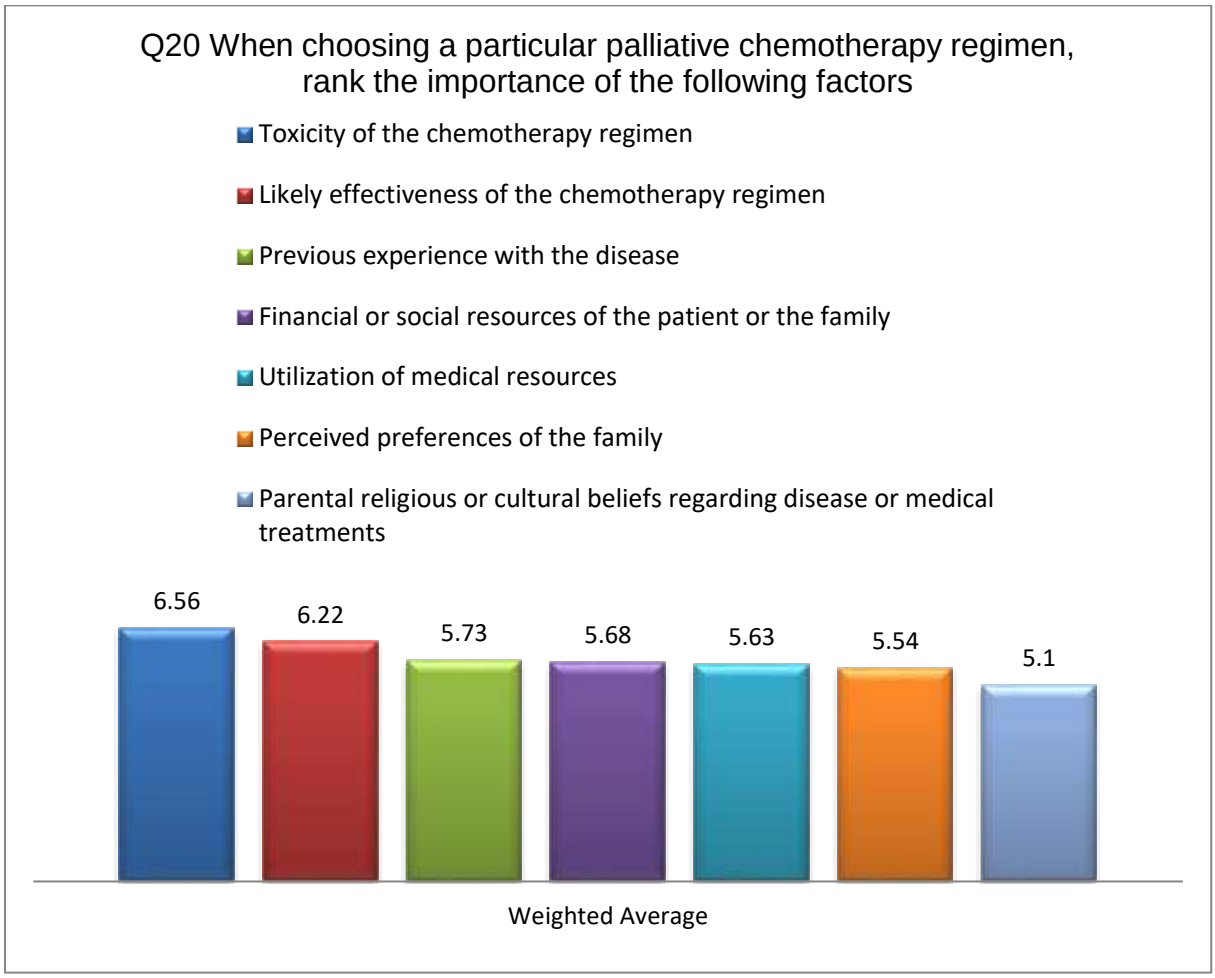
Availability of oral chemotherapy specifically, but also the cost of treatment were mentioned as important considerations. The availability of bone marrow donors and the issue of private medical aid support were also mentioned.

Theme 6: Unrealistic expectations

A last but important factor was mentioned – continuing with chemotherapy treatment may perpetuate unrealistic patient expectations and physicians may find it easier to continue disease-directed chemotherapy than to have the difficult discussions with patients and parents. In this situation, the fact that the chemotherapy is given for its palliative benefit (quality of life, symptom control) may not be made clear to the family and they may be under the false impression that the aim of the treatment is still curative.

4.3.3 Factors to consider when choosing a specific palliative chemotherapy regimen

Figure 6: Importance of factors when deciding on palliative chemotherapy regimen



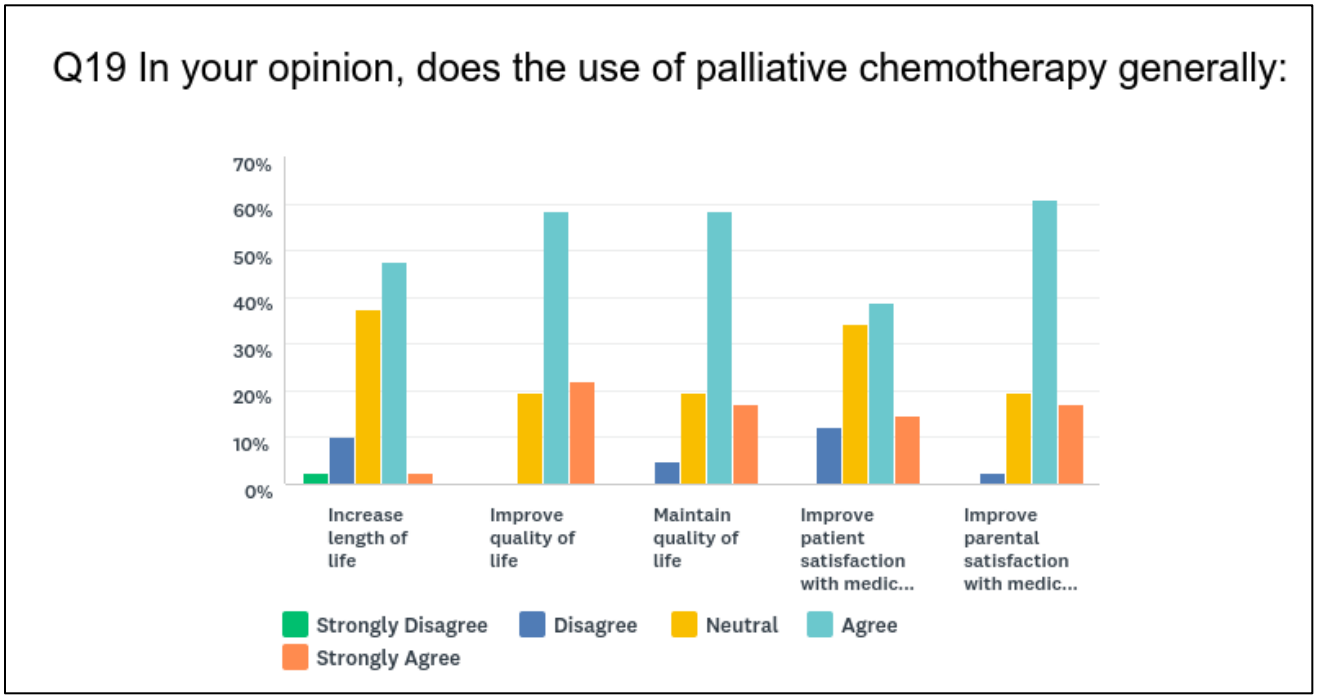
Question 20 assessed the factors that physicians may consider when choosing a specific palliative chemotherapy regimen. Respondents were again asked to rate how important each of these factors

were in their personal decision making around choosing a specific palliative chemotherapy regimen (these regimens may include oral or intravenous drugs, in-hospital or outpatient treatment, different type of drugs and frequency of treatment). In figure 6, these factors are depicted in order of most important to least important as viewed by respondents. A weighted scale was used to ask the question with 1 being not at all important, and 7 being extremely important. All seven factors had a weighted average of more than 5, showing that these were all important factors in the decision making process. However, the two most important factors were the toxicity of the regimen and the likely effectiveness (both scoring at more than 6 – very important). Of these seven factors, the one ranked least important was the parental religious of cultural beliefs around the disease and medical treatments.

4.3.4 Purpose of palliative chemotherapy

The last general question assessed the usefulness or purpose of palliative chemotherapy. Respondents were asked what their perceived effect was of palliative chemotherapy (in general) with regards to some specific aims. Figure 7 shows a summary of the five aims of palliative chemotherapy, and an overall positive opinion with most respondents agreeing that palliative chemotherapy improves all five these areas of patient care. Only 12.2% of respondents disagreed about palliative chemotherapy increasing lifespan, and improving patient satisfaction with medical care.

Figure 7: Perceived effects of palliative chemotherapy in general



4.4 Palliative chemotherapy experience with most recent patient

In the final part of the survey, participants were asked to consider their most recent patient for whom they prescribed palliative chemotherapy and answer the questions with that specific patient in mind. The patient may or may not have died. The patient's age and diagnosis were asked, as well as the type of chemotherapy regimen. Factors which influenced the decision to prescribe palliative chemotherapy were elicited, specifically whether it was given primarily for the purpose of parental wishes. In those cases where the patient had died, the number of chemotherapy regimens prior to death, as well as the timing of chemotherapy before death was recorded.

Table 2: Characteristics of most recent patients who received palliative chemotherapy

	n	%
Age		
<1 year	2	4.9%
1 – 5 years	11	23.8%
5 – 12 years	16	39.0%
>12 years	12	29.3%
Diagnosis		
Solid tumour, not CNS	29	70.7%
Leukaemia/Lymphoma	8	19.5%
CNS tumour	4	9.8%
How long have you been this patient's primary oncologist?		
0 – 6 months	10	24.4%
7 – 12 months	14	34.2%
13 – 24 months	7	17.1%
> 24 months	10	24.4%
How was the chemotherapy administered?		
Outpatient oral medication	28	68.3%
Outpatient intravenous medication	5	12.2%
Inpatient intravenous medication requiring 1-2 days hospitalisation	6	14.6%
Inpatient intravenous medication requiring >2 days hospitalisation	2	4.9%
Did the patient receive any palliative chemo primarily for the purpose of parental wishes?		
Yes	8	19.5%
No	33	80.5%
Has the patient died?		
Yes	26	63.4%
No	14	34.1%
Unsure	1	2.4%
CHARACTERISTICS OF THE 26 PATIENTS WHO DIED	**N=26**	
Time to death		

<1 week	0	0%
1-4 weeks	1	3.9%
1-3 months	7	26.9%
4-6 months	5	19.2%
6-12 months	8	30.8%
>12 months	5	19.2%
Number of palliative chemotherapy regimens received prior to death		
1 regimen	16	61.6%
2 regimens	4	15.4%
3 regimens	3	11.5%
4 regimens	3	11.5%
When did patient receive the last chemotherapy		
Last day of life	0	0%
Last week of life, but not on the last day	5	19.2%
Last month of life, but not in the last week	12	46.2%
Last three months, but not in the last month	9	34.6%
Location of death		
Home	14	53.9%
Hospital	12	46.1%

The 41 respondents all answered the questions about their most recent patient for whom they prescribed palliative chemotherapy (see table 2). Most of the patients had solid tumours (70.7%) with 19.5% with leukaemia and lymphoma, and only 9.8% brain or CNS tumours. Age categories from 1 to over 12 years were well represented but the largest group was the 5-12 year age group (39.0%). Most patients received outpatient oral palliative chemotherapy (68.3%) with only 8 patients (19.5%) requiring hospitalisation for inpatient intravenous chemotherapy. Chemotherapy was administered primarily for parental wishes in only 8 cases (19.5%). Timing of the start of palliative chemotherapy from the time of fist diagnosis differed widely, ranging from at the time of diagnosis to five years after diagnosis, with a mean of 8 months.

4.4.1 Factors which influenced the decision to prescribe palliative chemotherapy

In question 25 respondents were asked how important the same factors discussed in question 20 (figure 6) were when deciding on chemotherapy regimen were for this specific patient. The most important deciding factor remained toxicity of the chemotherapy regimen, but now the family preferences moved up in importance. The difference between physicians' treatment considerations in general compared to treatment considerations for their most recent patient was calculated. The mean and ranges of responses together with the standard deviations are shown in table 3.

Table 3: Differences in rating of palliative chemotherapy aims in general compared to aims achieved for most recent patient

	Importance of treatment factors in prescribing PC in general (1= not at all important to 5 = extremely important)		Importance of treatment factors in prescribing PC for most recent patient (1= not at all important to 5 = extremely important)	
Treatment considerations when prescribing palliative chemotherapy	Mean	Std. dev.	Mean	Std. dev.
Toxicity of chemotherapy	4.56	0.50	4.51	0.67
Effectiveness of chemotherapy	4.37	0.48	4.15	0.65
Previous experience with the disease	4.20	0.45	3.90	1.10
Family preferences	3.93	0.46	3.76	0.82
Financial resources of family	3.98	0.84	3.73	0.96
Use of medical resources	4.07	0.46	3.55	0.80
Religious beliefs of family	3.70	0.80	3.29	0.92

4.4.2 Effects of palliative chemotherapy for specific patient

Question 28 was designed to compare the aims and perceived effects of palliative chemotherapy in general (asked in question 19, see figure 7) with the effects of palliative chemotherapy on a specific patient. The difference between physicians' aims with palliative chemotherapy in general was compared to whether these aims were met for their most recent patient and calculated. The mean and ranges of responses together with the standard deviations are shown in table 4. Overall, there was only a small difference in the perceived effects of palliative chemotherapy in general compared to the effects experienced with the specific patient. Increase in lifespan was slightly higher than perceived, with improvement in quality of life reported in the specific patient to be as good as was expected in general.

Table 4: Differences in rating of palliative chemotherapy aims in general compared to aims achieved for most recent patient

	Importance of aim in prescribing PC in general (1= not at all important to 5 = extremely important)		Did PC accomplish aim for most recent patient (1= not at all important to 5 = extremely important)	
Aims of palliative chemotherapy	Mean	Std. dev.	Mean	Std. dev.
Increase length of life	3.38	0.79	3.61	1.10
Improve/enhance quality of life	4.02	0.64	3.98	0.92
Maintain quality of life	3.88	0.74	3.78	0.95

4.4.3 Toxicity related events as a result of palliative chemotherapy for specific patient

The last question looked at whether the patient suffered from any toxicity related events as a result of the palliative chemotherapy. Almost half of the patients (43.9%) had additional sick visits to the clinic, with 22% of patients needing hospital admission for toxicity related side effects. None of the patients needed ICU level care. Eleven patients (26.8%) needed invasive procedures due to toxicity. Only two patients (5%) died due to chemotherapy related toxicity.

4.4.4 Experience with palliative chemotherapy in patients who had died at time of survey

The second part on the survey asked the respondents to answer questions specifically about the most recent patient for whom they had prescribed palliative chemotherapy (see table 2). Twenty-six (63.4%) of these patients had died at the time of the survey. Among these 26 patients, 38.4% had received more than one palliative chemotherapy regimen prior to their death. Furthermore, 19.2% of this group of patients had received chemotherapy in the last week of life, and 65.4% were receiving chemotherapy in the last month of life. About half the patients (53.9%) died at home, and the other half 46.1% died in hospital.

CHAPTER 5: Results of file review

5.1 Introduction

Chapter 5 presents the results of the file review that was done to assess the use of palliative chemotherapy in the Steve Biko Academic Hospital paediatric oncology unit over the period January 2012 to December 2018 (7 years).

5.2 File selection

Figure 8: Process of file selection for review

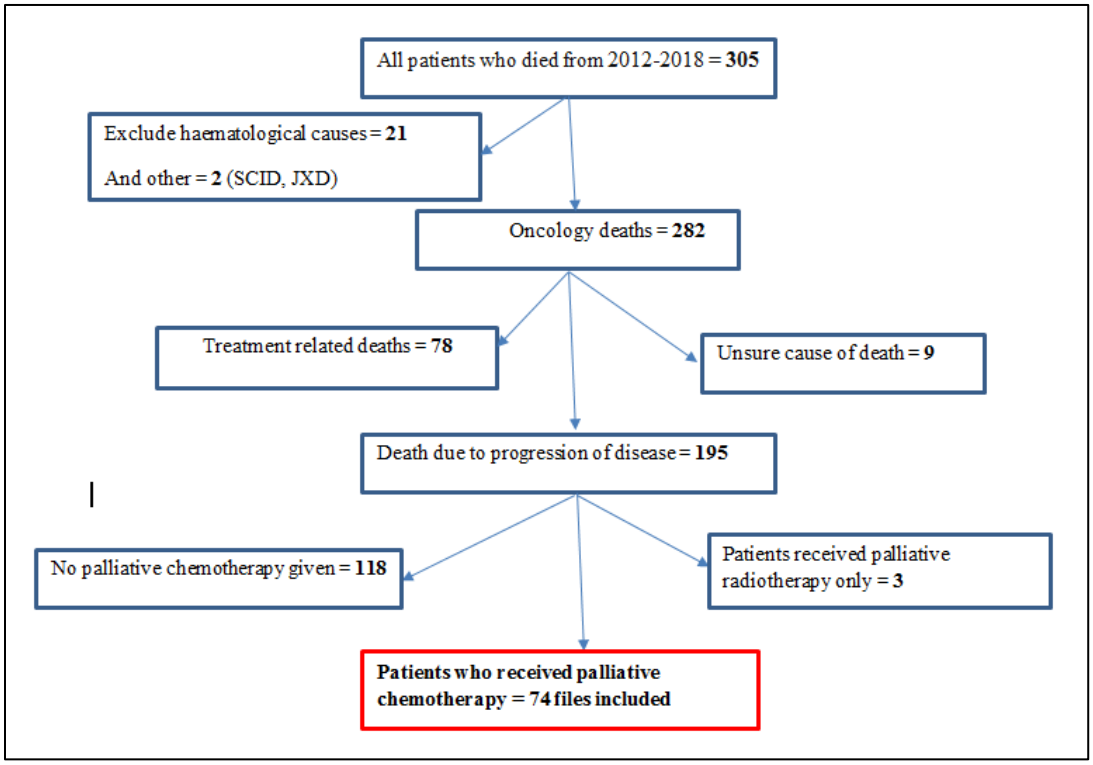


Figure 8 explains how the files of patients who received palliative chemotherapy were selected to be included in the file review. Of the 305 patients who died in this 7 year period, 282 (92.5%) were oncology patients. Of the oncology patients, 195 (69.1%) died of progression of disease, 78 patients (27.7%) died of treatment related complications, and the remaining nine patients died of causes unrelated to their primary cancer diagnosis. The group who died of progression of disease (195 patients) included patients who died while on active treatment with curative intent, as well as

patients who died within the first three days of admission. Out of this group of 195 we selected the files of the patients who received palliative chemotherapy, this came to a total of 74 files (37.9% of the 195 patients who died of progression of disease, and 26.2% of the total group of 282 oncology patients who died during this 7 year period). There were 3 patients in total who were treated with palliative radiotherapy, and did not receive any chemotherapy.

5.3 Demographic data

5.3.1. General characteristics

Table 5 shows the general characteristics of the 74 patients who received palliative chemotherapy. The median age at diagnosis was 6.0 years with a range of 0.3 to 17.6 years. There were more males (60.8%) than females and most of the patients (56.8%) were residing in Mpumalanga province. Only eight of the patients (10.8%) had no parents, and almost half of the patients (48.6%) were cared for by both parents.

The location of death was at home for just more than half of the patients (52.7%). About a third (35.1%) of the patients died in the oncology unit and 10.8% in the local hospital (closer to home). Only one patient, a 16 year old adolescent with osteosarcoma, died in the local hospice.

Table 5: General characteristics of patients included in file review (n=74)

CHARACTERISTICS	n		%
Gender			
Male	45		60.8%
Female	29		39.2%
Age at diagnosis (years)			
Median		6.0	
Range		0.3-17.6	
Age at death (years)			
Median		7.1	
Range		1.7-18.8	

Province of residence			
Gauteng	28		37.8%
Mpumalanga	42		56.8%
Limpopo	2		2.7%
North West	2		2.7%
Family structure			
Both parents alive and well	56		75.7%
Mother only	6		8.1%
Father only	3		4.1%
No parents	8		10.8%
Not documented	1		1.4%
Primary caregiver			
Both parents	36		48.6%
Mother	23		31.1%
Father	2		2.7%
Grandparent(s)	6		8.1%
Sibling	4		5.4%
Other	3		4.1%
Place of death			
Home	39		52.7%
Oncology ward in treating hospital	26		35.1%
Hospital closest to home	8		10.8%
Hospice	1		1.4%

5.3.2 Location with reference to oncology unit and local hospital

Figure 9 and 10 illustrate the addresses of the patients included in this review (each star represents a patient's home address). Their average distance to the local hospital was 16.4 km, with the

furthest being 94 km. The average distance to the oncology unit was 164.2 km, with 24 patients (32.4%) travelling more than 200km to receive specialised oncology care as well as palliative chemotherapy.

Figure 9: Physical addresses of all patients included in the file review (n=74)

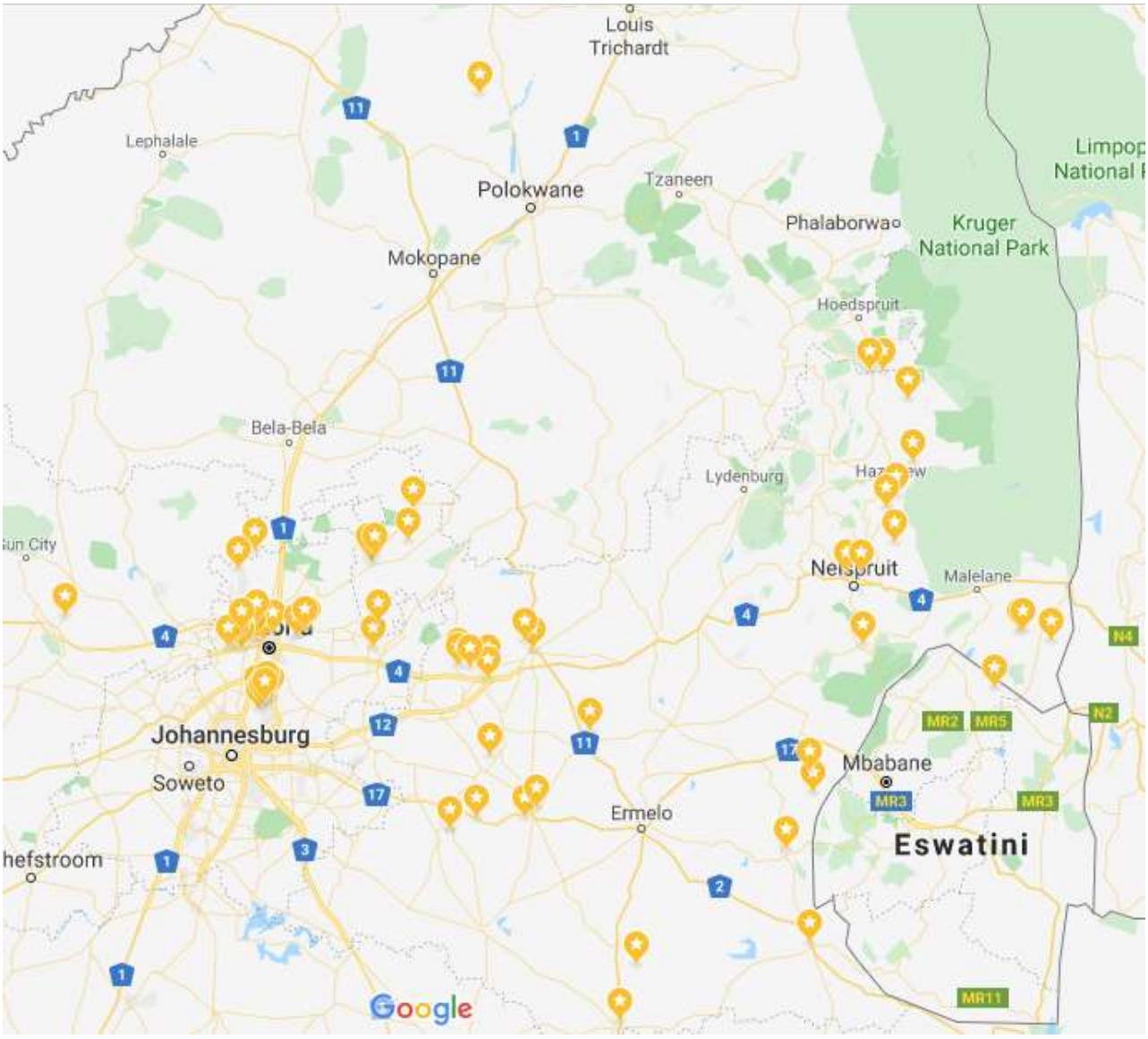
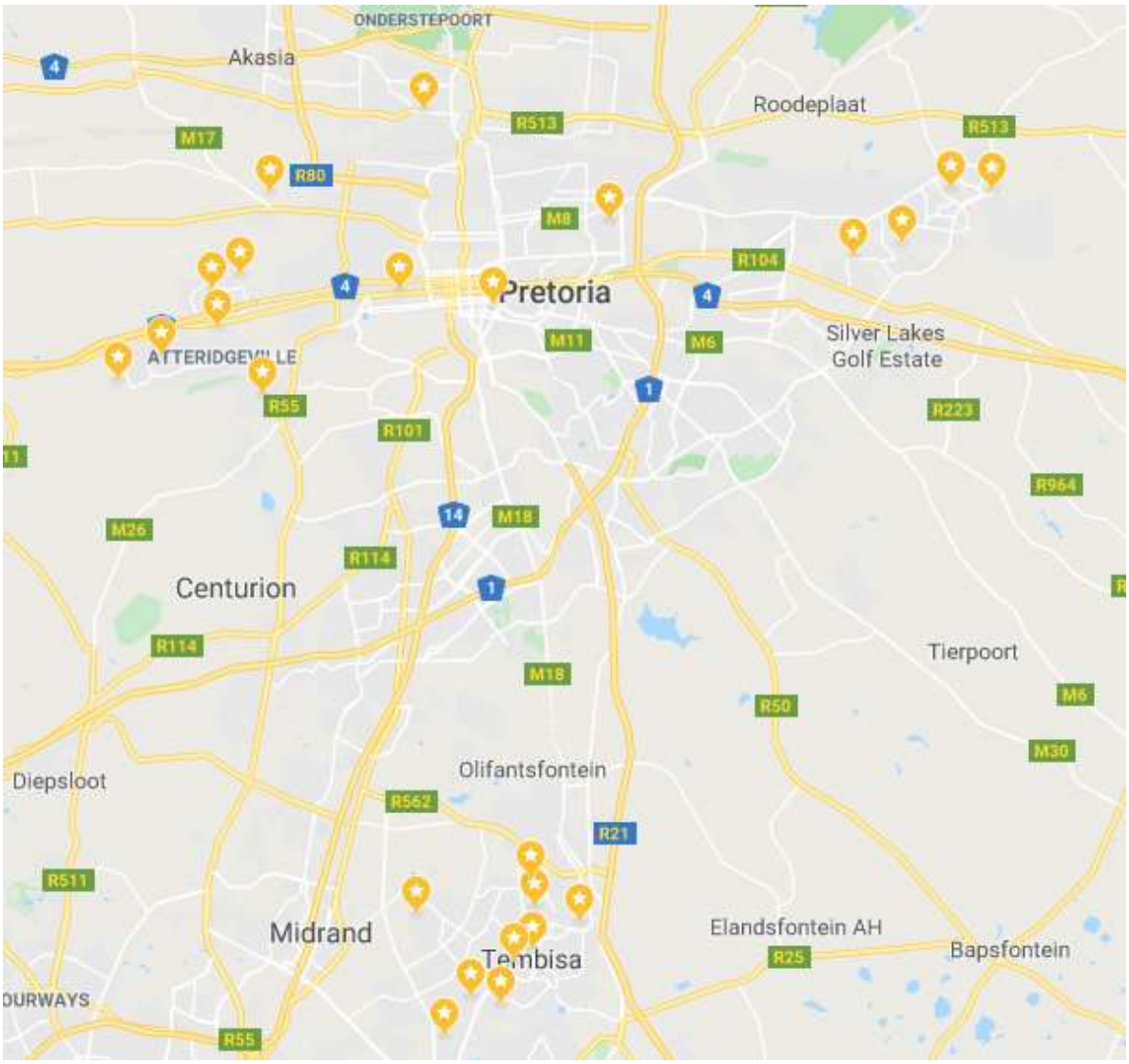


Figure 10: Physical addresses of patients from Gauteng province

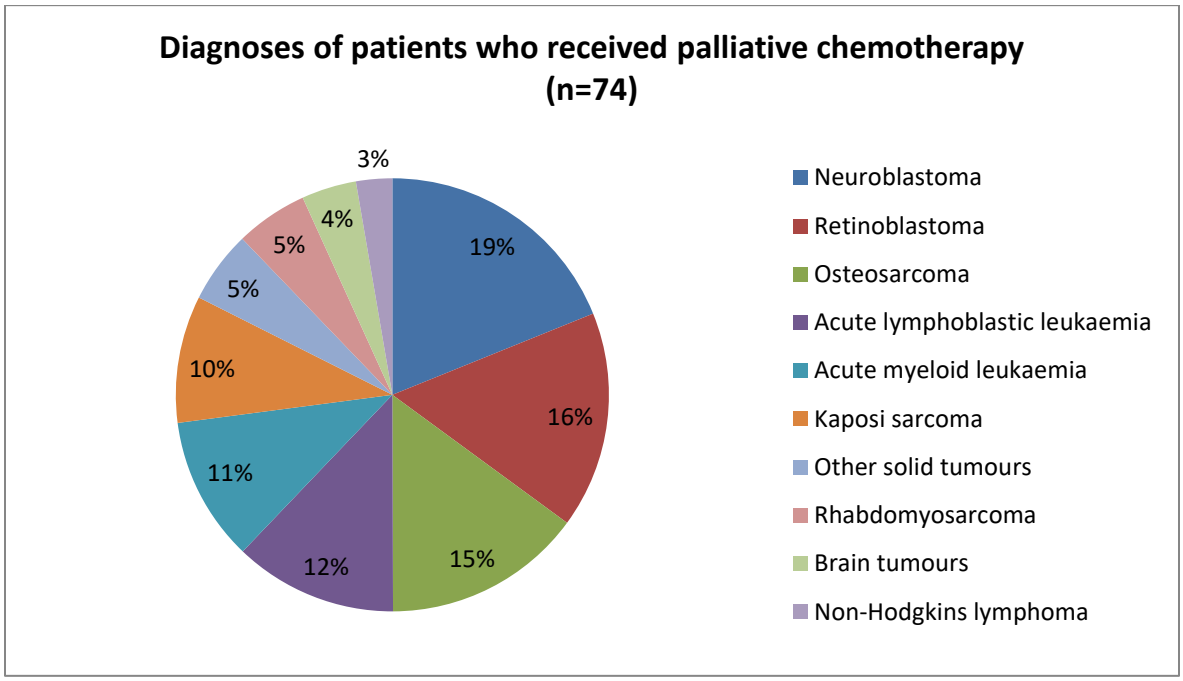


5.3.3 Cancer diagnoses of patients

Figure 10 illustrates the cancer diagnoses of the 74 patients, with the three most common diagnoses being neuroblastoma (18.2%), retinoblastoma (15.6%) and osteosarcoma (14.3%). Comorbidities that were recorded in the files included human immunodeficiency virus (HIV) infection in 11 patients (14.3%), and one patient each with diabetes mellitus, haemophilia A (severe) and Fanconi anaemia. Of the eleven patients with HIV infection, eight patients had HIV-related malignancies (seven with Kaposi sarcoma and one patient with non-Hodgkins lymphoma). The other three patients with HIV disease had malignancies most likely not related to the HIV, which were

retinoblastoma, osteosarcoma and acute lymphoblastic leukaemia. The patient with Fanconi anaemia developed acute myeloblastic leukaemia.

Figure 11: Diagnoses of the 74 patients who received palliative chemotherapy



5.4 Initiation of palliative chemotherapy

Table 6: Initiation of palliative chemotherapy in the oncology unit at SBAH

	n	%
Stage of disease at initiation of palliative chemotherapy		
As first line treatment	47	64.9%
At time of first relapse	19	24.7%
At time of second relapse	7	9.1%
At time of third relapse	1	1.3%
Diagnosis of patients who received palliative chemotherapy as first line treatment (n=47)		
Neuroblastoma stage IV	13	27.7%
Retinoblastoma stage IV and V	11	23.4%
Metastatic osteosarcoma	10	21.3%
Kaposi sarcoma – widespread multi-system disease	6	12.8%
Brain tumours	2	4.3%
Metastatic rhabdomyosarcoma	2	4.3%
Metastatic Ewing sarcoma	1	1.3%
Desmoplastic small round cell tumour (DSRCT)	1	1.3%
Metastatic nasopharyngeal carcinoma	1	1.3%

5.4.1 Stage of disease when palliative chemotherapy was initiated

Table 6 summarises the different aspects of the initiation of palliative chemotherapy in the unit over the past 7 years. The first aspect looks at the stage in the disease trajectory when the decision was made to initiate palliative chemotherapy. In 47 patients (63.5%) the disease was deemed incurable at diagnosis, and chemotherapy given for the purpose of palliation. A total of 27 patients were given palliative chemotherapy at relapse of disease; of these 19 (25.7%) patients were at first relapse, 7 (9.5%) at second relapse and only one at third relapse.

5.4.2 Time from diagnosis to initiation of palliative chemotherapy

Table 7: Time from diagnosis to start of palliative chemotherapy

	Number of patients	Median (years)	Range (years)
All patients included	**74**	**0.1**	**0-7.2**
As first line treatment	47	0.1	0-1.5
At time of first relapse	19	1.1	0.3-6.4
At time of second relapse	7	2.8	1.0-7.2
At time of third relapse	1	3.4	

A summary of the time from diagnosis to initiation of palliative chemotherapy is shown in table 7. Because more than half of the patients received palliative chemotherapy as a first line treatment, the median time to start of palliative chemotherapy in the whole group together is 0.1 years (1.2 months, or 36 days). However when divided into groups the median time to start palliative chemotherapy becomes longer with the subsequent relapses. The longest time from diagnosis to start of palliative chemotherapy was 7 years and 3 months in a patient with acute promyelocytic leukaemia who relapsed for the second time.

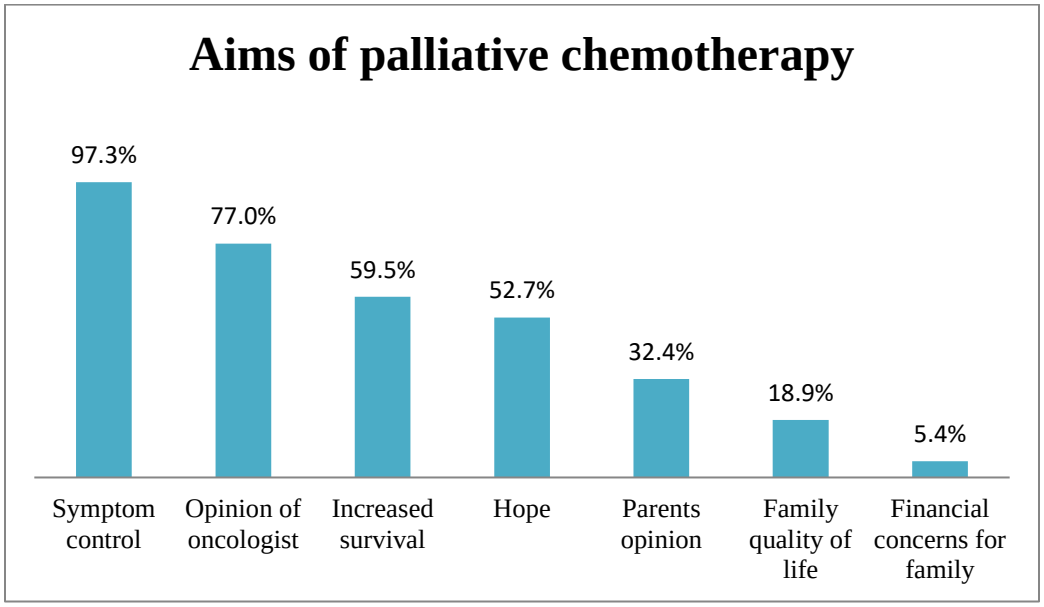
5.4.3 Decision, documentation and aims of palliative chemotherapy

The decision to change the treatment aim to palliative was documented in all the files reviewed. The files were scrutinised to see whether there was documentation of any family discussion around this decision, and only just more than half of the files (40 files, 54.1%) had clear documentation of a discussion with parents, caregiver or family.

Six possible aims of palliative chemotherapy were included in the datasheet used to capture data from the files. These aims were documented in the patient files as part of the documentation of the decision for palliative chemotherapy. Figure 11 illustrates the findings around the main aims of using palliative chemotherapy in these 74 patients. The most important reason for using palliative chemotherapy in this group of patients was to improve symptom control, this was a documented aim in 97.3% of patients. The opinion of the parents played an important role in 32.9% of the cases. There were three documented cases where the parents insisted on chemotherapy (this was

intravenous in-patient chemotherapy) against the advice of the treating oncologist, and it was administered as palliative chemotherapy.

Figure 12: Aims of using palliative chemotherapy



5.5 Palliative chemotherapy regimens

5.5.1 Palliative chemotherapy regimens according to diagnosis

Table 8 summarises the palliative chemotherapy regimens used in the 74 patients whose files were reviewed. It includes the need for admission (in or outpatient treatment) as well as the number of cycles of chemotherapy administered. Of the total group of 74 patients, 55 (74.3%) received intravenous and/or intrathecal treatment (with of without oral chemotherapy), while the remaining 19 (25.7%) received only oral palliative chemotherapy. Inpatient chemotherapy needing prolonged admission to hospital with the risk of neutropaenic sepsis were administered to 27 of the 74 patients (36.5%), mostly the patients with osteosarcoma (10 patients) and neuroblastoma (10 patients).

Table 8: Palliative chemotherapy regimens by disease

	Number of patients	Route	Inpatient or outpatient
ALL	**9**		
Combinations of oral chemotherapy including: Prednisone, 6-thioguanine, 6-mercaptopurine, methotrexate	6	PO	Outpatient
Prednisone, 6-thioguanine and vincristine	1	PO/IV	Outpatient
Prednisone and intrathecal chemo	2	PO/IT	Outpatient
AML	**8**		
Combinations of oral chemotherapy including: Prednisone, 6-thioguanine, 6-mercaptopurine	6	PO	Outpatient
6-thioguanine and cytarabine	1	PO/IV	Outpatient
6-thioguanine and intrathecal chemo	1	PO/IT	Outpatient
Non-Hodgkins lymphoma	**2**		
Combinations of oral chemotherapy including: Prednisone, 6-mercaptopurine	2	PO	Outpatient
Neuroblastoma	**14**		

Rapid COJEC (time intense)	3	IV	Inpatient
Rapid COJEC with surgery and radiotherapy/MIBG	4	IV	Inpatient
Rapid COJEC followed by second line chemo (VEC or oral cyclophosphamide)	2	PO/IT	Inpatient
COJEC or OPEC/OJEC every 3 weeks	2	IV	Inpatient
VEC chemotherapy	1	IV	Outpatient
Oral cyclophosphamide	2	PO	Outpatient
Osteosarcoma	**11**		
EURAMOS MAPIE (five drug combination)	3	IV	Inpatient
EURAMOS MAP (three drug combination)	7	IV	Outpatient
Oral cyclophosphamide	1	PO	Outpatient
Retinoblastoma	**12**		
VEC chemotherapy	7	IV	Outpatient
VEC chemotherapy + IT	4	IV	Outpatient
VEC chemotherapy + radiotherapy	1	PO	Inpatient
Kaposi sarcoma	**7**		
Prednisone/Vincristine/Bleomycin/Daunorubicin	7	IV	Outpatient
Brain tumours	**3**		
VEC chemotherapy	3	IV	Outpatient
Rhabdomyosarcoma	**4**		
IVADo (Ifosfamide/Vincristine/Adriamycin/Doxorubicin)	2	IV	Inpatient
VAC	1	IV	Outpatient
Cyclophosphamide	1	PO	Outpatient
Nasopharyngeal carcinoma	**1**		
5-FU, Cisplatin, Radiotherapy	1	IV	Inpatient

Desmoplastic small round cell tumour	**1**		
VEC chemotherapy	1	IV	Outpatient
Ewing sarcoma	**1**		
VEC chemotherapy and radiotherapy	1	IV	Inpatient
Nephroblastoma			
ICE chemotherapy	1	IV	Inpatient

5.5.2 Effect of palliative chemotherapy on survival time

Figure 13: Survival curve starting with the date of the initiation of palliative chemotherapy

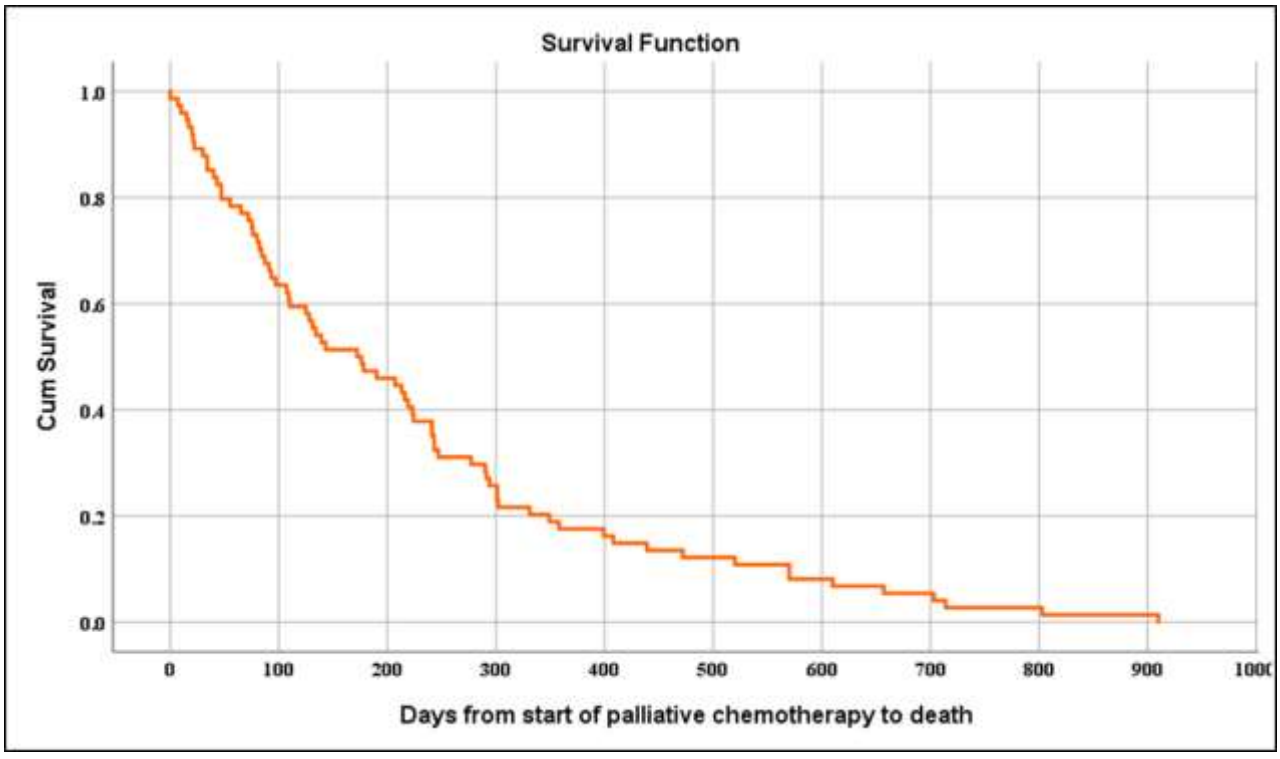


Figure 12 shows the survival curve for the period between the initiation of palliative chemotherapy and death. The median duration of this interval between the initiation of palliative chemotherapy

and death was calculated to be 174 days (range 0-910 days). Survival curves according to diagnosis, from initiation of palliative chemotherapy, is illustrated in figure 13.

Table 9 summarises the median duration and range of the interval between the initiation of palliative chemotherapy and death for the three most common solid tumours (neuroblastoma, retinoblastoma and osteosarcoma) - the median time from initiation of palliative chemotherapy until the time of death was around 225 days (7 months) while the median for the haematological malignancies were much shorter around 90 days (3 months).

Figure 14: Survival curve for patients on palliative chemotherapy

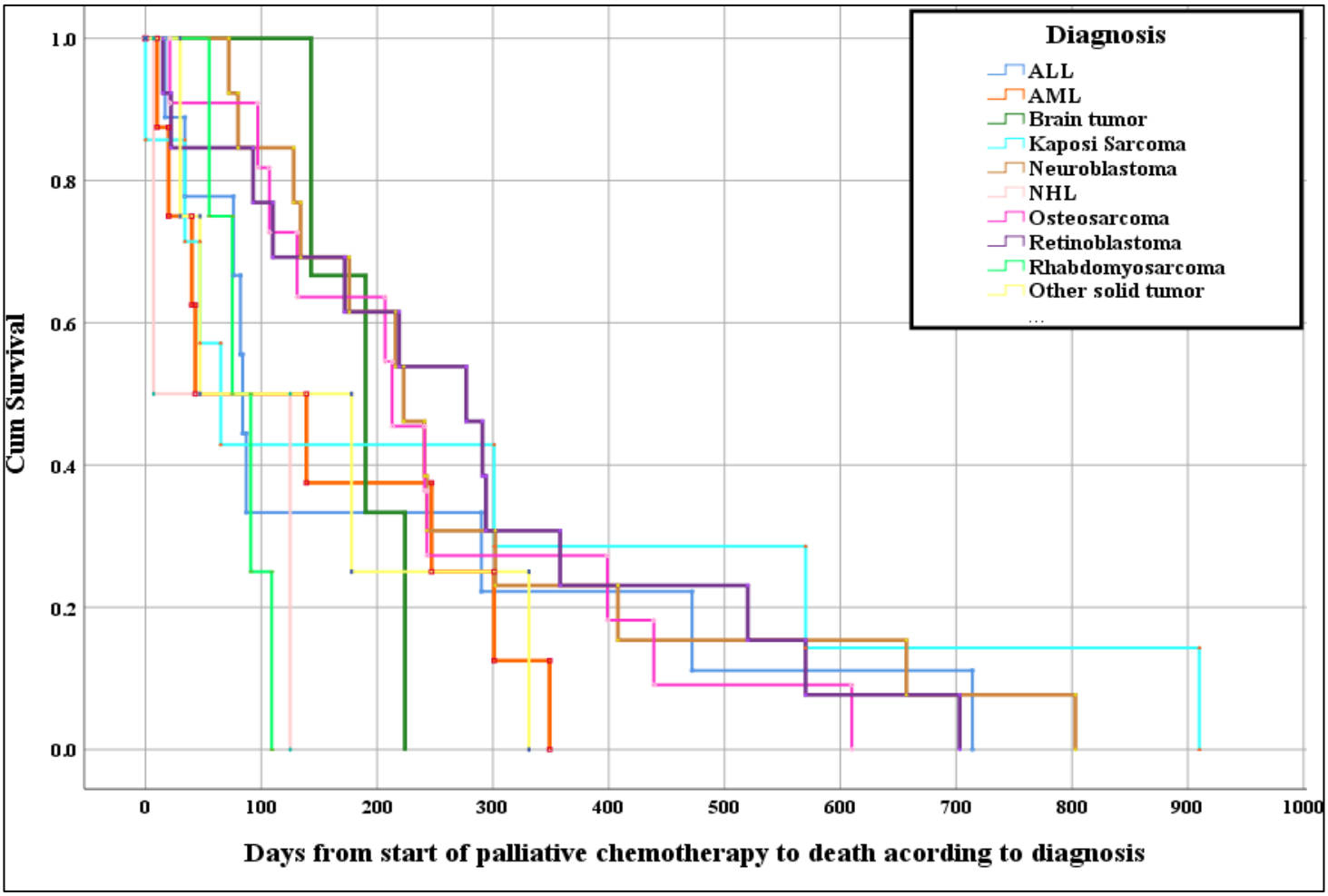


Table 9: Time from the start of chemotherapy until death for the five most common diagnoses

Diagnosis	Number of patients	Median (days)	Range (days)
Neuroblastoma	14	232	72-803
Retinoblastoma	12	248	15-703
Osteosarcoma	11	213	21-610
ALL	9	84	17-714
AML	8	91	10-349

5.6 Cessation of palliative chemotherapy

5.6.1 Decision, documentation and reason for stopping palliative chemotherapy

The decision to stop palliative chemotherapy was documented clearly in 28 of the 74 files (37.8%), and 25 of the 74 files (33.8%) had documentation of an end of life discussion with the family. These were not all the same files as the ones who had a documented decision to stop palliative chemotherapy.

Reasons recorded for stopping chemotherapy are represented in table 10. The ten patients who completed the planned number of cycles had the following diagnoses: retinoblastoma (4 patients completed 6 cycles of VEC chemotherapy), neuroblastoma (2 patients completed the rapid COJEC protocol), osteosarcoma (2 patients completed the 5-drug MAPIE protocol), Kaposi sarcoma (one patient completed 6 cycles of treatment), and nasopharyngeal carcinoma (one patient received the full treatment of 5FU with cisplatin for 3 cycles and radiotherapy).

Table 10: Reasons recorded for stopping palliative chemotherapy

Reasons for stopping palliative chemotherapy	n=28	%
Progression of disease while on PC	15	53.6%
Completed the planned protocol of PC	10	35.7%
Too much financial stress on the family	1	3.6%
Side-effects from PC	1	3.6%
Absconded	1	3.6%

5.6.2 Time from end of palliative chemotherapy to death

The median time from the last palliative chemotherapy to the time of death was 30 days (range 0-742 days) for the whole group of patients. When separated into groups of patients with solid tumours (55 of 74, 74.3%) and those with leukaemia/lymphoma (19 of 74, 25.7%), the median time from last palliative chemotherapy for solid tumour patients was 40 days (range 0-742 days). Of the 19 patients with leukaemia/lymphoma, 17 (89.5%) were on oral palliative chemotherapy at the time of death, while only 6 of the 55 patients with solid tumours (10.9%) died while on palliative chemotherapy.

Of the total group of 74 patients, 38 (51.4%) received palliative chemotherapy in the last 30 days of life. However, when separated again into the two groups (solid tumours and those with leukaemia/lymphoma), only 21 of the 55 patients with solid tumours (38.2%) received palliative chemotherapy in the last 30 days of life.

5.6.3 Outcome of palliative chemotherapy with regards to quality of life

Although no formal assessment of quality of life was done in these patients, improvement in symptoms and activity level was recorded as improvement in QOL in this file review. Just more than half of the patients (41 of 74, 55.4%) had documentation of symptomatic improvement in their files when reviewed.

The next chapter links the findings of this study with the published literature reviewed previously.

CHAPTER 6: Discussion

6.1 Introduction

The study's main aims were to describe paediatric oncologists in South Africa's perspectives and practices regarding palliative chemotherapy, and to investigate the use of chemotherapy at the end of life in patients treated at the SBAH paediatric oncology unit. The researcher demonstrated that paediatric oncologists in South Africa are using palliative chemotherapy mostly with the aim of improving quality of life. From the single centre experience, patients may benefit from palliative chemotherapy with regards to prolonging life as well as quality of life, but they need to be selected carefully and the intention of treatment made clear from the onset. A discussion follows on the findings of the survey as well as that of the file review.

6.2 Recommending palliative chemotherapy

A few questions in the survey looked at different issues around whether or not to recommend chemotherapy. In all these questions, a majority of the paediatric oncologists were either neutral or agreed that palliative chemotherapy should be recommended. Those with a truly negative attitude towards the use of palliative chemotherapy were in the minority.

Concerning factors that physicians may consider when recommending palliative chemotherapy, the most important treatment considerations and aims were to minimise toxicity of the chemotherapy regimen and to improve quality of life. Parental preference was in general not reported to be one of the most important factors when deciding on palliative chemotherapy. This is in contrast to the original study by Kang et al(2) done in the USA using this same survey, where adherence to parent preferences ranked as the second most important consideration after toxicity, when prescribing palliative chemotherapy. Compared to the findings by Kang et al, where 40.8% of patients received palliative chemotherapy primarily for parental wishes, in our study only 19.5% of patients received treatment primarily because the parents requested it. There may be different reasons why parental preference was less important than in the USA survey. South African parents, especially the majority of patients treated in government hospitals, may not have the same level of knowledge and empowerment, and the access to information is likely to be less than that in the

USA. The question also arises whether South African oncologists are still managing patients in a more paternalistic manner than their USA counterparts.

In our study, the most important treatment considerations were largely achieved as expected in the most recent patient treated with palliative chemotherapy. There was no great difference between the aims and treatment considerations in general, and the achievement of these aims and treatment considerations as reported for the most recent patient. Again, this differs from the Kang study where the treatment considerations and aims were not achieved to the degree expected in the experience with the most recent patient. In the much larger group of oncologists in the USA (a total of 422 participants), they found that a decrease in symptoms and maintaining or improving quality of life was not achieved as expected.

Individual opinions and preferences differ greatly with regards to recommending palliative chemotherapy - this had been examined in various studies examining health care professionals' opinions on palliative chemotherapy.(2,18,33,43,44) Results from Wusthoff et al(19) specifically demonstrated a large variability in treatment goals, perceived chances for cure as well as the degree to which further curative intervention would be considered desirable for each patient. Our study also showed that for most respondents (36/40, 90%), their individual preferences regarding the use of palliative chemotherapy sometimes or often differs from that of their colleagues. The lack of evidence-based guidelines in the field of palliative chemotherapy, especially in children, causes physicians to rely on their previous experience, perceptions of toxicity, and parents' opinion to make these very difficult recommendations.

Parents have reported in some studies (32,45) that the most significant factor in their decision making around palliative chemotherapy was the opinion and recommendation of the treating oncologist. This emphasises the importance for the oncologist of examining beliefs about benefits and burdens of palliative chemotherapy, and the aims and goals of prescribing it to patients in situations where disease-directed treatment may be questioned. By involving the paediatric oncology community in completing this survey, it would be an unexpected benefit if this study could be the start of discussions around these sometimes controversial decisions.

6.3 Palliative chemotherapy patients: Comparing SA to the USA

When comparing the USA group of patients reported on in the survey Kang et al, some of the important differences included: significantly more patients with CNS tumours treated with palliative chemotherapy in the USA compared to South Africa, and more patients in the USA had received second, third and fourth line chemotherapy regimens before being started on palliative chemotherapy. Administration routes and admission for palliative chemotherapy were comparable between the two surveys. The number of osteosarcoma and neuroblastoma patients receiving intense intravenous chemotherapy in the SBAH group caused a much higher number of these patients to need admission for intravenous chemotherapy (although the aim was still palliative).

Surprisingly, there were many similarities between the patients discussed by respondents as the "most recent patient" in the two surveys. These similarities included period from last chemotherapy to time of death, administration routes and admission for palliative chemotherapy, as well as place of death. It is the hope of the researcher that these similarities across continents and settings are a reflection of the paediatric oncologists' inherent value systems that should be guiding all medical decision-making, to do what is best for the patient and family.

6.4 Demographic details of patients who received palliative chemotherapy at the SBAH oncology unit

The demographics of this group of patients are a good representation of the demographics of all patients treated in the oncology unit in SBAH. Childhood cancer is more common in males with a ratio of boys to girls of 1.2 reported in a large epidemiological study published in 2010,(46) so the male predominance of 60.8% is expected. The median age of 6.0 years in our group is also close to the 5 years 10 months reported in the epidemiological study. As expected when looking at the demographics of patients treated in the unit, more than half of the patients were from Mpumalanga province and a third of the patients included in this review travelled more than 200km to receive oncology care and palliative chemotherapy. The role that this distance from the oncology unit plays in the provision of palliative care and decisions around palliative chemotherapy has not been explored and the researcher could not find any literature that specifically asked questions around

distance from oncology units and its effects on quality palliative care. It is our impression and concern that the time and financial implications of travel may have a direct impact on the quality of life of the family, and should be a consideration in decision making about palliative chemotherapy and end of life care plans.

6.5 The role of HIV in patients receiving palliative chemotherapy

South Africa is still one of the countries with the largest HIV epidemics in the world. In 2017, 19% of adults in South Africa were living with HIV. The prevalence reported for the 0-14 year age group in the 2017 statistics was 2.7%.(47) In our group of patients who received palliative chemotherapy, 11 of 74 (14.9%) were HIV infected, with eight of the infected patients having HIV-related malignancies (Kaposi sarcoma, Non-Hodgkins lymphoma). This is a high prevalence when compared to the national prevalence figures, however, these patients have HIV-related malignancies so it is expected that the rate of HIV infection in this group of patients who died due to childhood cancer will be higher. It has been well documented that HIV infection predisposes children to the development of malignancies, and that without effective antiretroviral treatment the prognosis of HIV-related malignancies is dismal.(48) However, with the use of ART the outcomes of these children are much improved.

6.6 Palliative chemotherapy as first line disease-directed treatment

Palliative chemotherapy as first-line treatment is commonly used and labelled as palliative in adult oncology settings with incurable tumours with metastases including metastatic breast cancer, upper gastrointestinal cancer, pancreatic cancer and colorectal cancer.(25) However, the researcher struggled to find paediatric literature willing to label first-line chemotherapy as palliative in the setting of childhood cancer. There may be many reasons for this but most importantly, childhood tumours tend to be more chemo-sensitive than those seen in adults. It is also a possibility that paediatric oncologists may struggle to call treatment “palliative” from the onset of treatment. One article on the management of soft tissue sarcomas did mention clearly that although metastatic soft tissue sarcoma may respond to chemotherapy, there is limited evidence that chemotherapy improves overall survival, and it is, therefore, considered to be palliative therapy in this setting.(49)

6.6.1 Palliative chemotherapy as first line treatment for metastatic osteosarcoma

For the purpose of selecting patient files to include in the review, we included all the patients who had what we deemed to be incurable disease at the time of presentation. This included patients with osteosarcoma (with extensive metastatic disease or inoperable primary tumours e.g. extensive iliac bone involvement) who received the same intense chemotherapy regimen as would be used for patients with localised disease. However, it was made clear from the time of diagnosis, and documented in the patient file, that the aim of the intense chemotherapy was palliation. Only two of the eleven patients with osteosarcoma manage to complete the full protocol, all the other had progression of disease while on chemotherapy and improvement in QOL was documented in less than half the patients treated with chemotherapy. This type of intense intravenous in-hospital chemotherapy could lead to prolonged admissions, which may have a profoundly negative impact on the QOL of the patient in the last months of life. It may be advisable to give a limited number of cycles and assess the response rather than committing to treat extensive metastatic osteosarcoma with a full course of chemotherapy. There is not enough evidence yet to suggest that oral metronomic chemotherapy can be used with positive effect, but Zapletalova et al did report some palliative effect in osteosarcoma patients treated with the COMBAT regimen.(13)

6.6.2 Palliative chemotherapy as first line treatment for stage IV neuroblastoma

The group of stage IV neuroblastoma patients differed from the osteosarcoma group in that only about a third of them (5/14, 35.7%) received only intense chemotherapy. A further six of the patients also received intense chemotherapy, which was followed by one or more of the following treatment modalities: surgery, MIBG treatment, external beam radiotherapy and/or oral chemotherapy. This was all given with palliative intent and patients had a good response with regards to improvement in QOL (12/14, 85.7%). It is well described in the literature that cure rates for stage IV neuroblastoma are low, but that patients may initially respond well to chemotherapy before eventually relapsing.(42) At the time of relapse there are more options for palliative management including MIBG treatment, external beam radiation and further chemotherapy (e.g. oral cyclophosphamide together with topotecan or irinotecan, as well as temozolamide). Relapsed disease has a 5-year overall survival of <10%.

Our experience with the mixed regimens we used as palliative chemotherapy in this group of patients with stage IV neuroblastoma showed good improvement in quality of life in most patients, allowing them good QOL and time at home with families before the inevitable relapse and eventual death. No patient has survived a diagnosis of stage IV neuroblastoma in our unit in the past seven years.

6.6.3 Palliative chemotherapy as first line treatment for stage IV retinoblastoma

Treatment of overt extraocular or intracranial retinoblastoma with palliative chemotherapy from the time of diagnosis is a less controversial topic. The SIOP-PODC guidelines(50) clearly state that even though the chances of cure are very poor, that the tumour is very chemo-sensitive, so palliative chemotherapy usually has a significant role in improving quality of life (shrinking the fungating exophytic tumours and improving pain significantly). These guidelines state that standard-dose chemotherapy with an intention of prolonging life should be offered to children with stage IV disease. The combination of vincristine, etoposide and carboplatin (VEC) does not often cause significant toxicity and can be administered as outpatient intravenous chemotherapy. The 12 patients included in our study all received this VEC chemotherapy (between one and nine cycles), and four patients also received intrathecal chemotherapy. One patient received external beam radiation as well.

Our experience with treating these patients concur with what is stated in the SIOP-PODC guidelines, improved quality of life was documented in 8 of the 11 patients (72.7%). We have subsequently extended our use of VEC chemotherapy in the palliative setting to some other diagnoses (brain tumours, hepatoblastoma) because of the low toxicity, ease of administration and positive experience in the patients with advanced retinoblastoma.

6.7 Goals of palliative chemotherapy

In all 74 patient files, the decision to give chemotherapy with the aim of palliating was documented. Only 54.1% of the files had a documented family discussion to prove that this change in the disease and treatment trajectory was explained and discussed with them. Our datasheet included seven possible options as considerations when making the decision to start palliative

chemotherapy, and it can be compared to the findings of Tomlinson et al who reported on the same seven factors as indicated by 128 health care professionals working in Toronto, Canada, in interviews. In comparison, the different factors were ranked in the same order of importance, with only the opinion of health care professionals rated more important in the SBAH group. This was due to semantic differences in how the question was viewed – the Toronto study asked the importance of the opinion of other health care professionals, while the SBAH study considered the health care professional's own opinion of the proposed palliative chemotherapy. Excluding the health care professional's opinion, the three most important considerations for both these settings were the child's quality of life, increase in survival time and hope.

6.8 When should palliative chemotherapy be stopped?

Palliative chemotherapy was stopped for different reasons in the SBAH group. Progression of disease while on chemotherapy is a clear indication that the chemotherapy is not having the desired effect, and then it should be strongly considered rather not to offer further treatment with possible toxicity.

Almost all the patients with leukaemia/lymphoma died while on oral chemotherapy. It can become a difficult decision when to stop the oral "leukaemia maintenance"-type chemotherapy for these patients as toxicity is minimal and the disease can progress slowly for a long time before suddenly decompensating.

In adult palliative chemotherapy literature there is a continuous debate around the inappropriate use of chemotherapy in the last 30 days of life.(22–25) It is the opinion of the researcher that this argument may not have the same validity in the treatment of incurable childhood cancer, especially when the chemotherapy used with palliative intent does not have significant toxicity. In our group of solid tumour patients, the median time from stopping chemotherapy to the time of death was 40 days, and 21 of the 55 patients (38.2%) received chemotherapy within the last 30 days of life. Of these 21 patients, 12 had improvement in symptoms because of the palliative chemotherapy.

In ten of our patients, we elected to stop palliative chemotherapy because they had completed the protocols we were using (e.g. rapid COJEC). We have since learnt from experience that in patients

who responded well and who have good QOL the use of oral chemotherapy as maintenance after completion of intense chemotherapy may extend the time to relapse and may manage symptoms better for a longer period.

6.9 Place of death

More than half of the patients included in this study died at home, and only about a third died as inpatients in the oncology unit. There may be different reasons for the higher than usual amount of patients dying at home – it is our impression that these patients likely had more counselling and preparation for the likely outcome because of repeated palliative chemotherapy visits, and that the parents were better prepared for the patients dying at home. The study unfortunately did not include any detail on the end of life experiences of the patients and families, as detailed information on this was not available in their files. Future research into palliative chemotherapy will aim to include a discussion with parents on the end of life journey of each child and family.

6.10 Limitations of the study

Although the rate of response to our survey was excellent (41/46, 89.1%) the number of paediatric oncologists in the country is small and therefore the findings of this survey may not be significant. The fact that the survey was quantitative limited the amount of information that was gathered from the oncologists who responded. The accuracy of the answers about the most recent patient may not reflect their usual practice, since it specifically focuses on one patient. Furthermore, the self-reporting format of the questionnaire can lead to both social desirability bias and recall bias. Social desirability bias happens when participants answer questions in a way that they feel might be viewed favourable by others. However, the responses were anonymous, which should have minimised social desirability bias. Recall bias remains a problem since oncologists might report what they would want to do instead of a reliable recollection of actual events in their practice.

When reflecting on the wording of the questionnaire, there may be some concern about the clarity of the specific question related to patients needing ICU level care. The question did not take into account that patients may not be considered as candidates for ICU care due to their poor prognosis

– this has implications for the conclusion that none of the patients needed ICU level care. This question would have had more value if it was worded in such a way that respondents could answer whether or not the patient may have been offered ICU level care if there were no limitations on access to care or services.

With regards to the file review, it was done retrospectively and there was no objective quality of life questionnaire or interview done to establish the QOL improvements. We looked at documented symptoms, clinic visits and admissions to hospital recorded in files to decide on the effect on QOL. Documentation of symptoms was done at each visit but not always with the same amount of detail. This remains a limitation and would be much more accurate if done as part of a prospective study.

The file review was purely descriptive, and patients' QOL and symptoms were recorded but not compared to a group of patients who did not receive chemotherapy as part of their palliative care. Due to the limited information available from the file review, we could not assess end of life events and the quality of deaths as this is not part of standard information recorded in the files. Reporting on symptom control and QOL will be much better if done as part of a prospective qualitative interview-based study. As discussed in the literature review, the perspective of parents and patients are extremely important when discussing palliative chemotherapy and making decisions about palliative treatment. Repeated qualitative measurements of the child and family's QOL and its associations with palliative chemotherapy should be a research priority in future

CHAPTER 7: Conclusion and recommendations

7.1 Implications of the findings

The study met its aim in exploring how South African paediatric oncologists use palliative chemotherapy, and reporting on a single unit's experience with palliative chemotherapy. Results of the study suggest that palliative chemotherapy plays a very important role in the management of children with incurable cancer, and that the aim of improving quality of life is reached in many patients by using palliative chemotherapy. However, the use of chemotherapy for the purpose of palliation is haphazard and protocols are greatly lacking, and oncologists are mostly relying on their own previous experience to make these very important decisions. Our findings should challenge paediatric oncologists in South Africa to carefully examine their expectations of the use of palliative chemotherapy in children with incurable cancer.

7.2 Recommendations and further studies

There is a lack of end-of-life research in paediatric oncology. This study provided a birds-eye view on the use of palliative chemotherapy in children, but also showed clearly that many decisions around end of life care and decision making are better researched using a qualitative, prospective, interview-based approach. Repeated measurements of the child and family's QOL and its associations with palliative chemotherapy should be a research priority in future, especially in our setting where many of the patients are from indigent communities and travel very far to reach oncology care. These measurements should also include transport costs, time in hospital, and use of scarce resources. The selection of patients more likely to benefit from palliative chemotherapy also needs to be researched, with the aim of identifying better predictive biomarkers.

The role of introducing standardised protocols and guidelines for the use of palliative chemotherapy countrywide may be a worthwhile discussion to introduce to the community of paediatric oncologists in South Africa. A great advantage of the use of standardised protocols will be the collection of data in a larger group of patients that can eventually provide more information about efficacy of palliative chemotherapy. The fact remains, however, that the aims are not easily measurable and that there may be different goals of treatment for different families.

7.3 Plan for dissemination of findings

Feedback concerning the file review will be given to the oncology unit staff and the paediatric department of SBAH, the plan is to do this at a departmental meeting.
The researcher also plans to discuss the results at the biannual meeting of the SACCSG and plans to submit an abstract for presentation at the South African Clinical Oncology (SACO) meeting as well as submit an article for review and publication in a peer-reviewed journal such as Pediatric Blood and Cancer or the South African Medical Journal. An abstract will also be submitted to the international Paediatric Palliative Care conference happening in Rome in 2020.

This research is relevant especially for LMIC faced with many patients presenting very late to health care facilities. The comparison of our survey to the same survey done in the USA will be of interest to the paediatric oncology community worldwide. It will also be important to discuss the results with palliative care specialists, not just the oncology community.

7.4 Conclusion

This study brings valuable new insight into the South African oncologist's perspective on the use of palliative chemotherapy. Although the overall attitude towards the use of palliative chemotherapy is positive, there is great inter-individual variation in opinions and experience. Even the definition of palliative chemotherapy is still unclear and debatable. The lack of empirical data to justify recommendations concerning palliative chemotherapy remains a problem, and the researcher hopes that this study will spark productive discussion and planning towards more structured use of palliative chemotherapy in children with cancer in South Africa.

CHAPTER 8: References

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APPENDICES

APPENDIX 1: Online survey

Title: Use of palliative chemotherapy in South Africa: National survey of paediatric oncologists and experience in a single unit.

PALLIATIVE CHEMOTHERAPY SURVEY

(Based on survey created by Tammy Kang and Chris Feudtner, The Children's Hospital of Philadelphia, Pennsylvania)

What is your gender?		Male
		Female

What is your age group?		30 – 39 years
		40 – 46 years
		47 – 52 years
		53 – 68 years
		69+ years

Which of these categories best characterises your practice type?		Private practice
		Academic
		Combined private and academic
		Other

Approximately how much of your time is spent on direct patient care?		< 20%
		20 – 50%
		51 – 75%
		> 75%

Approximately how much of your time is spent on direct patient care of <u>oncology patients?</u>		< 20%
		20 – 50%
		51 – 75%
		> 75%

How many years have passed since you completed your fellowship training in paediatric haematology/oncology		0 – 5 years
		6 – 10 years
		11 – 15 years
		16 – 20 years
		> 20 years

		Working as medical officer
		Busy with fellowship training

Of the oncology patients you have cared for, how many have died in the past year?		0 – 1
		2 – 9
		10+

Approximately how many new cancer diagnoses per year are there among patients in your practice?		0 – 50
		51 – 100
		101 – 150
		> 150

Do you have standard protocols in place for the management of relapsed and refractory patients?		Yes for more than 75% of diagnoses
		Yes for 50-74% of diagnoses
		Yes for <50% of diagnoses

Do you have access to a paediatric palliative care programme?		Yes
		No
		Occasionally

What type of paediatric palliative care programme do you have access to?		Inpatient consult service
		Outpatient consult service
		Local hospice
		Other

General experiences in the use of palliative chemotherapy:
Physicians often differ in their opinions of when to recommend a palliative approach. There are clearly many factors that go into a decision to pursue palliative versus curative therapies. Please answer the following questions using your general experiences with the use of palliative chemotherapy.

I believe that palliative chemotherapy should be recommended whenever:	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
A child has a disease that relapsed					
A child has a disease for which no experimental therapies are available					

I believe that palliative chemotherapy should be recommended whenever a child has a disease with a probability of death:	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
>99%					
>95%					
>90%					
>75%					
>50%					

In your experience what percentage of children whose disease is <u>likely</u> fatal receive palliative chemotherapy?		

In your experience, what percentage of children whose disease is <u>uniformly</u> fatal receive palliative chemotherapy?		

To what degree do you agree or disagree that the following factor into your recommendations for the use of palliative chemotherapy?	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Maximise life expectancy					
Maximise quality of life					
Parental preference					
Standard of care in your practice					

How often does your individual preference regarding the use of palliative care differ from that of your colleagues		Never
		Sometimes
		Often
		Always

If there are other factors that you routinely prioritise when recommending palliative	

chemotherapy, can you share them with us?	

In your opinion, does the use of palliative chemotherapy generally:	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Increase length of life					
Improve quality of life					
Maintain quality of life					
Improve patient satisfaction with medical care					
Improve parental satisfaction with medical care					

When choosing a particular palliative chemotherapy regimen, rank the importance of the following factors	Not at all	Moderately unimportant	Somewhat unimportant	Neutral	Somewhat important	Very important	Extremely important
Previous experience with the disease							
Toxicity of the chemotherapy regimen							
Likely effectiveness of the chemotherapy regimen							
Parental religious or cultural beliefs regarding disease or medical treatments							
Perceived preferences of the family							
Utilisation of medical resources							
Financial or social resources of the patient or family							

Please answer the following questions with regarding to <u>your most recent</u> primary patient for whom you prescribed palliative chemotherapy. This patient may or may not have died.

Diagnosis	Solid tumour, not CNS
	Leukaemia/Lymphoma
	CNS tumour
	Other

Age of the patient		<1 year
		1 – 5 years
		5 – 12 years
		> 12 years

When you first prescribed palliative chemotherapy for this patient, how much time had elapsed since the patient was first diagnosed?		

How long have you been the patient's primary oncologist?		0 – 6 months
		7 – 12 months
		13 – 24 months
		> 24 months

In this particular case, to what degree do you agree or disagree that the following factored into your decision of which palliative chemotherapy regimen to prescribe?	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Previous experience with the disease					
Toxicity of the chemotherapy regimen					
Likely efficacy of the chemotherapy regimen					
Parental religious or cultural beliefs					
Perceived preferences of the family					
Utilisation of medical resources					

Financial or social resources of the patient or family					

Did the patient receive any palliative chemotherapy primarily for the purpose of parental wishes?		Yes
		No

How was the chemotherapy regimen you prescribed administered?		Outpatient oral medication
		Outpatient intravenous medication
		Inpatient intravenous medication requiring 1-2 day hospitalisation
		Inpatient intravenous medication requiring 1-2 day hospitalisation
		Inpatient intravenous medication requiring 1-2 day hospitalisation

Did the palliative chemotherapy your patient received	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Increase length of life					
Improve or enhance quality of life					
Maintain quality of life					
Cause any chemotherapy related toxicity that required additional sick clinic visits					
Cause any chemotherapy related toxicity that required additional hospitalisations					

Did this patient experience any of the following toxicity related events as a result of the palliative chemotherapy?	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Sick visits (clinic)					
Hospitalisations					
ICU level care					
Invasive procedures					
Patient death					

Has this patient died?		Yes
		No
		Unsure

In cases where the patient has died, please complete the following questions:

Time to death from start of palliative chemotherapy?		< 1 week
		1 – 4 weeks
		1 – 3 months
		4 – 6 months
		6 – 12 months
		> 12 months

Number of palliative chemotherapy regimens received prior to death?		1 regimen
		2 regimens
		3 regimens
		4 or more regimens

When did the patient receive the last chemotherapy?		Last day of life
		Last week of life but not on the last day
		Last month of life but not in the last week
		Last three months, but not in the last month

Location of death?		Home
		Hospital
		Other

APPENDIX 2: Information sheet for questionnaire

Study title: Use of palliative chemotherapy in South Africa: National survey of paediatric oncologists and experience in a single unit.

You are invited to take part in a research study on the use of palliative chemotherapy in South Africa. Before you decide to take part it is important that you understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Ask questions if anything you read is not clear or if you would like more information. Take time to decide whether or not to take part.

STUDY TEAM AND RESEARCH GOALS

The study team consists of Ané Büchner, currently a Masters in Palliative Care Student at the University of Cape Town, under the supervision of Dr Michelle Meiring (paediatric palliative care specialist) and Professor Alan Davidson (head of the Red Cross Children's hospital paediatric oncology/haematology unit). The aim of this questionnaire is to collect data from all the oncology units in South Africa about the current use of palliative chemotherapy. In contrast to many first world countries, children with a diagnosis of cancer often present to a treating center at a late stage, making curative treatment difficult. Palliative chemotherapy can be used to improve quality of life and manage symptoms. The use of palliative chemotherapy in South Africa has never been studied. This study will be part of Ané's MPhil thesis and will improve our understanding of the use of palliative chemotherapy in South Africa, with the ultimate aim of improving the quality of life of our patients.

WHAT WILL PARTICIPATING INVOLVE?

You are invited to complete a web-based survey that will take 20-30 minutes to complete. If you are disconnected or unable to complete the questionnaire in one sitting, the link will remember where you left off and you will be able to continue answering questions when reconnected. In the survey you will be asked general questions about your oncology treatment center, access to palliative care, and your general experience in the use of palliative chemotherapy. You will also be asked a series of questions on <u>your most recent patient</u> for whom you prescribed palliative

chemotherapy. To answer these questions you may need the folder for this patient when you complete the questionnaire. All the questions are tick-boxes and you will not be required to type in any answers.

WHY HAVE YOU BEEN INVITED TO TAKE PART?

We are inviting you to take part because you are on the South African Children's Cancer Study Group (SACCSG) mailing list and you are either a qualified oncologists, haematologist working with paediatric oncology patients, or a fellows in paediatric oncology.

Members of the SACCSG are encouraged to forward the link to this questionnaire to any qualified doctors working with them full time in their units who may not yet be part of the SACCSG.

DO YOU HAVE TO TAKE PART?

Participation in this survey is voluntary. Your work or relationship within the community and SACCSG will not be affected by whether you take part in this study. You have the right to refuse participation, refuse to answer specific questions, or withdraw at any time without any consequences whatsoever.

ARE THERE RISKS OR BENEFITS TO TAKING PART?

We aim to respect your privacy. Your answers to the questionnaire will not have your name attached to them in any publication. We do not anticipate any potential risks to your patients. The benefits to the study will be to get a more complete picture of the current use of palliative chemotherapy in South Africa, with the aim of increasing knowledge in the field, and in doing so improve the quality of life for patients with incurable cancer diagnoses.

WILL TAKING PART BE CONFIDENTIAL?

Names will not be used in the data collection or analysis process. The patient information gathered in the second part of the questionnaire will not be presented in publication in a format that could be used to trace the patient.

HOW WILL INFORMATION BE RECORDED, STORED AND PROTECTED?

Survey results will be retained on a password-protected external hard drive of the principal investigator with hard copies at the University of Cape Town. Survey results will be stored for two years from the end of the study.

WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?

The results will be published in the principal investigator's Master's thesis. The aim will also be to publish in peer-reviewed journals as well as present it at relevant conferences.

WHO SHOULD YOU CONTACT WITH ANY QUESTIONS?

If you should have any questions concerning the survey please contact Ané Büchner (ane.buchner@up.ac.za) who is the principal investigator of the study.

Thank you

Ané Büchner (Paediatric oncologist, University of Pretoria; MPhil Palliative Medicine candidate, University of Cape Town)

APPENDIX 3: Data extraction tool for file review

Title: Use of palliative chemotherapy in South Africa: National survey of paediatric oncologists and experience in a single unit.

DATA COLLECTION SHEET

Demographic information

Study number	

Hospital number	

Name and surname		

Date of birth	dd	mm	yyyy

Age	y	m

Gender		Male		Female

Address	

Province	

Closest hospital to home	

Travel to oncology unit	Hours	
	Km	

Family structure		Parents both alive and well
		Single mother
		Single father
		No parents

Guardian	

Number of siblings	**Age of sibling**	**Gender of sibling**
0		
1		
2		
3		
4		

5		
6		
7		
8		

Ethnicity	

Source of income		Parents both working
		Father working
		Mother working
		Other family member salary
		Child support grant
		Care dependency grant
		Foster care grant
		Grant for older persons

Housing		Formal housing
		Informal settlement

Access to electricity		Yes
		No

Amenities		Water inside house
		Water outside the house
		Flushing toilet inside the house
		Flushing toilet outside the house
		Pit latrine outside the house

Clinical information

Diagnosis	

Stage at diagnosis	

Stage when palliative treatment started		No curative treatment offered
		1st relapse
		2nd relapse
		3rd relapse
		other

Time from diagnosis to start of palliative chemotherapy	

Was decision to start palliative chemotherapy clearly documented?		Yes
		No

Was family discussion on palliative chemotherapy done and documented?		Yes
		No

Aim(s) of palliative chemotherapy		Increased survival time
		Child's quality of life
		Hope
		Family's quality of life
		Opinion of health care professionals
		Financial considerations
		Opinion of parents
		Other:
		Other:
		Not documented

Palliative regimen	**Drug**	**Dose**	**Route**

Reason(s) why palliative chemotherapy stopped		Side-effects
		Progression of disease
		Other:
		Other:
		Not documented

Was decision to stop palliative chemotherapy clearly documented?		Yes
		No

Was end of life discussion with family and/or patient done and documented?		Yes
		No

Cause of death		Progression of disease
		Treatment related
		Other:

Place of death		Home
		Local hospital
		Oncology unit
		Other

How long before death was last palliative chemotherapy received		< 1 week
		1 week to 1 month
		1 to 3 months
		> 3 months

APPENDIX 3: UCT HREC approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone (021) 406 6492
Email: sumayah.arieff@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

24 October 2017

HREC REF: 729/2017

Dr M Meiring
Department of Paediatrics & Child Health
C/o Naomi Fray
Entrance 5, Falmouth Building
FHS

Dear Dr Meiring

PROJECT TITLE: USE OF PALLIATIVE CHEMOTHERAPY IN SOUTH AFRICA: NATIONAL SURVEY OF PAEDIATRIC ONCOLOGISTS AND EXPERIENCE IN A SINGLE UNIT- (MPhil-candidate-Dr A Buchner)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC)for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study, subject to the following; -

1. Please add the UCT FHS HREC contact details to the informed consent document.
2. Please also confirm that local REC approval at Steve Biko is not required in addition to the CEO's approval?

Approval is granted for one year until the 30 October 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr A Buchner will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

HREC 729/2017

APPENDIX 4: UP HREC approval

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 03/14/2020.

7 November 201

Approval Certificate
New Application

Ethics Reference No.: 571/2018
Title: Use of palliative chemotherapy in South Africa: National survey of paediatric oncologists and experience in a single unit.

Dear Dr A Buchner

The **New Application** as supported by documents received between 2018-11-06 and 2018-11-07 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 2018-11-07.

Please note the following about your ethics approval:

- Ethics Approval is valid for 1 year and needs to be renewed annually by 2019-11-07.
- Please remember to use your protocol number (571/2018) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers
MBChB MMed (Int) MPharmMed PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health)

Research Ethics Committee
Room 4-60, Level 4, Tswelopele Building
University of Pretoria, Private Bag X323
Arcadia 0007, South Africa
Tel +27 (0)12 356 3084
Email deepeka.behari@up.ac.za
www.up.ac.za

Fakulteit Gesondheidswetenskappe
Lefapha la Disaense tša Maphelo

APPENDIX 5: Permission to access data from files at SBAH

Permission to access Records / Files / Data base at the Steve Biko Academic Hospital

To: Chief Executive Officer/Information Officer Steve Biko Academic Hospital

From: The Investigator
Dr Ané Büchner

Re: Permission to do research at Steve Biko Academic Hospital

I am a clinician and researcher working at the Paediatric Haematology and Oncology Unit, Department of Paediatrics at Steve Biko Academic Hospital. I am requesting permission to conduct a study on the Steve Biko Academic Hospital grounds that involves access to patient records. The study is being conducted as part of a Masters in Palliative Medicine degree at the University of Cape Town, under supervision of Dr Michelle Meiring and professor Alan Davidson.

The request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No. 2 of 2000.

The title of the study is: Use of palliative chemotherapy in South Africa: National survey of paediatric oncologists and experience in a single unit.

The researchers request access to the following information:

Access to the clinical files, record book and the data base.

We intend to publish the findings of the study in a professional journal and/ or at professional meeting like symposia, congresses, or other meetings of such a nature.

We intend to protect the personal identity of the patients by assigning each patient a random code number.

We undertake not to proceed with the study until we have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Cape Town.

Yours sincerely

A. Büchner

Permission to do the research study at this hospital and to access the information as requested, is hereby approved.

Chief Executive Officer

Steve Biko Hospital
Dr
DR AP VAN DER WALT
DIRECTOR CLINICAL SERVICES

Signature of the CEO

STEVE BIKO
PRIVATE BAG X169
2017 -05- 19
PRETORIA 0001
ACADEMIC HOSPITAL

Hospital Official Stamp