

Master thesis in clinical nutrition

Parenteral nutrition in patients with incurable cancer:

A retrospective study of current practice at Haukeland

University Hospital

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Summary

Background: The use of PN therapy in patients living with incurable cancer is understudied, and there is a need for a stronger evidence base regarding this treatment in patients with incurable cancer.

Aims: This study aimed to describe the following aspects of PN treatment in patients with incurable cancer: indications for PN, dosage of PN given and dosage according to estimated energy requirements, administration of PN, duration of PN, reason for discontinuation of PN and survival on PN.

Methods: A retrospective medical chart review of patients with incurable cancer receiving PN at Haukeland University hospital from 2011 to 2018 was conducted. Data on patient characteristics related to the time before the start of and during PN treatment, administration of PN and dosages of PN, time of termination and reason for termination, were collected.

Results: Data from 133 medical charts were included. Mean (SD) age was 64 ($\pm 12,4$) years and 61 (45.9%) were male. The most common types of cancer were upper GI (n=48, 36.1%), and colorectal (n=31, 23.3%), and 111 (83.5%) of the patients had metastases. The most frequent indication for start of PN was insufficient oral and/or enteral intake. Most of the patients received PN daily. Mean (SD) estimated energy intake was 33 (6) kcal/kg/day. Median (Q1-Q3) start dose was 1000 (570-1100) kcal/day. Median highest dose received was 5 kcal/kg lower than estimated energy needs. Median (Q1-Q3) duration of treatment was 44 (18-99) days. Median (Q1-Q3) survival from start of PN was 81 (41-159) days. There was a positive correlation between duration of PN and survival from PN start, correlation coefficient $r_s=0.751$, $p<0.0005$.

Conclusion: The findings indicate that PN therapy in patients with incurable cancer was distributed across the population in terms of dosages, duration and survival. Most of the patients receive less than estimated energy needs from PN. Patients receiving PN for a longer period of time also survive longer. Discontinuation of PN was based on expected survival, complications related to treatment as well as tolerance to PN.

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List of abbreviations

BMI	Body mass index, kg/m ²
CRF	Case Response Form
CRP	C-reactive protein
CVC	Central venous catheter
ECOG	Eastern Cooperative Oncology Group
EN	Enteral nutrition
ESPEN	European Society for Clinical Nutrition and Metabolism
GLIM	Global Leadership Initiative on Malnutrition
GPS	Glasgow Prognostic Score
HPN	Home parenteral nutrition
IL	Interleukin
IVLE	Intravenous lipid emulsions
mGPS	modified Glasgow Prognostic Score
PATNIC	Parenteral Nutrition Therapy in Patients with Incurable Cancer
PN	Parenteral nutrition
PUFAs	Polyunsaturated fatty acids
QoL	Quality of life
TPN	Total parenteral nutrition
TNF	Tumour necrosis factor
WHO	World Health Organization

1 Introduction

1.1 Cancer

Cancer is a leading cause of mortality worldwide, responsible for 9.6 million deaths and 18.1 million new cases in 2018 [1]. The development of better tumour-directed treatments and multiple treatments as standards have resulted in more people living with metastatic disease and advanced cancer [2]. The 5-year prevalence of cancer worldwide was in 2018 estimated to be 43.5 million, and cancer is the second leading non-communicable disease in the world [2, 3]. In Norway, there were 34 190 new cases of cancer in 2018. More than 280 000 individuals are living with a cancer diagnosis or have previously had cancer. Due to an increasing life expectancy and a growing population, the number of cancer cases is expected to keep growing [4].

Staging of the cancer is used to decide treatment options, assessment of prognosis, and for comparing treatment outcomes. The tumour-node-metastasis classification system is a commonly used tool where the cancer is described based on the size of the primary tumour, number of nearby lymph nodes affected, and absence or presence of distant metastasis [5]. Advanced cancer can be locally or metastatic. Locally advanced cancer describes cancer that has grown outside the organ it started but has not yet spread to distant parts of the body. The cancer is termed metastatic advanced cancer if the cancer has spread from the primary site to other parts of the body [6]. Cancer at an advanced stage where the cancer can no longer be treated is often referred to as incurable or end-stage cancer [7]. Patients with incurable cancer might receive cancer treatment or disease-directed therapy to prolong life and alleviate symptoms. An increasing number of people living with an incurable cancer diagnosis leads to more patients in need of palliative care [8].

1.2 Palliative care

Palliative care aims to make life the best possible, both for the patient and relatives, in all stages of an incurable illness [7, 9]. The World Health Organization (WHO) defines palliative care as:

an approach that improves the quality of life (QoL) of patients and their families facing the problem 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 [10].

The main focus of palliative care is to prevent and alleviate symptoms and to help with spiritual/existential challenges and other difficulties the patient may have [11]. Anti-cancer treatment may be a part of the palliative care with an intention to prolong life and reduce symptoms [12]. Tailored palliative care aiming to reduce the number and severity of burdensome symptoms is considered as the best strategy to improve QoL in patients with incurable cancer [13]. It is recommended to introduce palliative care early in the disease trajectory, as it has shown to give better results in terms of survival, pain management, symptoms, and QoL [14-16].

Patients with incurable cancer often experience symptoms such as fatigue, pain, constipation, weakness, and anorexia, as a consequence of the disease and/or treatment. This may contribute to distress and diminish the patients' QoL [11, 13]. Other characteristics in patients with incurable cancer are weight loss, muscle wasting, and reduced physical function, making them prone to wasting conditions such as severe malnutrition, cachexia, and sarcopenia [17, 18].

1.2.1 Cancer cachexia

The wasting syndrome cancer cachexia is an adverse effect of cancer, associated with reduced physical function, reduced tolerance to anticancer treatment, and increased mortality [19]. The prevalence of cancer cachexia ranges from 50-80% in patients with incurable cancer [20, 21]. This leads to severe consequences both for the individual patient and for the health care system [22]. The international consensus from 2011 defines cancer cachexia as “a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment” [19]. Key characteristics of the cachexia syndrome are reduced nutritional intake, anorexia, systemic inflammation, and altered metabolism such as increased proteolysis and increased energy expenditure [19].

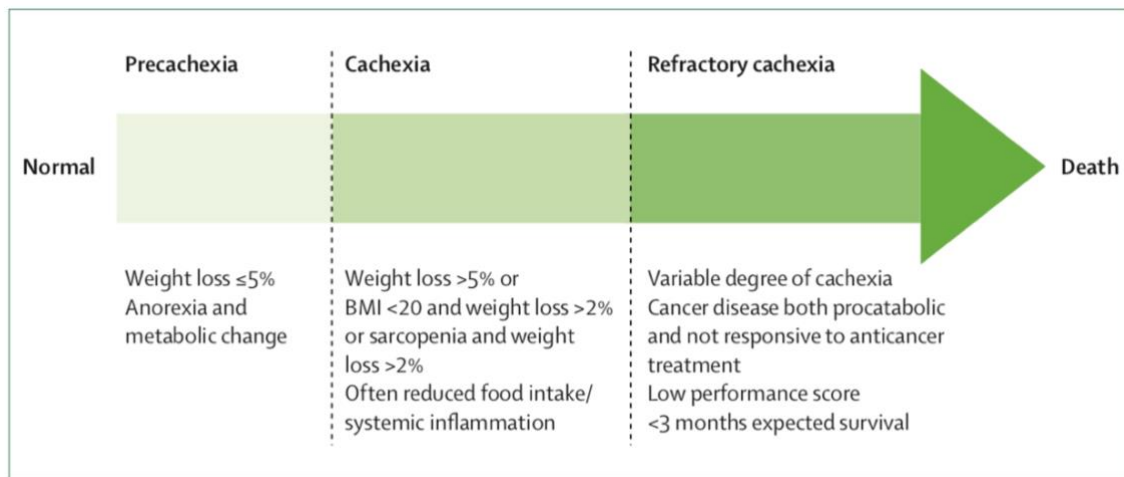


Figure 1. Three stages of cancer cachexia from Fearon et.al [19].

Cancer cachexia can develop progressively through three stages: pre-cachexia, cachexia, and refractory cachexia (figure 1) [19]. Pre-cachexia is recognized by involuntary weight loss below 5%, induced by metabolic change and anorexia. Factors such as cancer type and stage, the presence of systemic inflammation, reduced food intake, and lack of response to anticancer therapy impacts on the risk of progression to cancer cachexia [19]. Cancer cachexia is present when either weight loss exceeds 5% the last 6 months, or weight loss exceeds 2% along with either body mass index (BMI) < 20 kg/m² or sarcopenia [19]. Refractory cachexia is likely to develop in very advanced cancers or by rapidly progressive cancer unresponsive to cancer therapy. This condition is characterized by a low performance score, a life expectancy of less than 3 months, and no response to anti-cancer treatment [19].

1.2.1.1 Inflammation in cancer cachexia

The presence of a systemic inflammatory response is a major factor underlying nutritional and functional decline in cancer cachexia [23, 24]. The tumour releases inflammatory factors, including cytokines such as interleukin 1 (IL-1), IL-6, and tumour necrosis factor- α (TNF- α), which affect the brain, muscle, liver and fat function [25, 26]. These cytokines impact on the neuroendocrine control of appetite in the hypothalamus, resulting in anorexia and reduced food intake [25]. An imbalance between anabolism and catabolism, caused by the systemic inflammation, results in muscle wasting, with a decline in muscle mass and strength, and increased fatigue. The risk for cancer treatment toxicity is increased in cancer cachexia due to the stimulation of acute-phase protein production in the liver, which in turn leads to reduced drug clearance. Increased lipolysis and defective lipogenesis are caused by the cytokines, resulting in depleted energy stores in fat deposits [23, 27, 28].

The systemic inflammatory response alters the production of acute-phase protein in the liver, causing elevated C-reactive protein (CRP) levels and hypoalbuminemia [23]. These proteins can be used as specific biomarkers to assess the severity of the cancer-related systemic inflammation, alone or in combination, known as the Glasgow Prognostic Score (GPS) [23, 24]. The GPS provides a score based on the presence of hypoalbuminemia (≤ 35 g/L) and elevated CRP (>10 mg/L). Both hypoalbuminemia and elevated CRP provides a score of 2. If only one of the factors is abnormal, the score is 1. The score is 0 if neither of the factors are abnormal [24]. “The GPS was modified, termed mGPS, to reflect the observation that hypoalbuminemia without an elevated CRP concentration was rare and that hypoalbuminemia on its own was not associated with poor survival” [24]. A modified Glasgow Prognostic Score (mGPS) combines the indicators of decreased plasma albumin and elevated CRP (Table 1) [24]. An elevated mGPS has been associated with poor survival in patients with cancer [24].

Table 1. The Glasgow Prognostic Score and modified Glasgow Prognostic Score, from McMillan [24].

The Glasgow Prognostic Score (GPS)	Points allocated
CRP ≤ 10 mg/L and albumin ≤ 35 g/L	0
CRP >10 mg/L	1
Albumin <35 g/L	1
CRP >10 mg/L and albumin <35 g/L	2
<i>The modified Glasgow Prognostic Score (mGPS)</i>	
CRP ≤ 10 mg/L and albumin ≥ 35 g/L	0
CRP > 10 mg/L	1
CRP >10 mg/L and albumin <35 g/L	2

CRP=C-reactive protein

1.2.2 Performance status

A decline in physical function is frequently seen in patients with incurable cancer as the cancer advances [29] and leads to reduced independence, affects the possibility to self-expression and increase the need for care [30]. One way of measuring physical function, often referred to as performance status (PS) is by objective methods assessed by health care providers’ perception of what a patient can do [31]. Performance status is related to survival, need for services and may help predict the ability to tolerate treatments [32]. The Eastern Cooperative Oncology Group (ECOG)/WHO Performance Scale is a tool often used to evaluate performance status in clinical practice and research [31, 33, 34]. In the ECOG performance scale, the score ranges from 0 to 5 where a score of 0 indicates normal activity. A score of 4 denotes completely disability and a score of 5 indicates death, as shown in Table 2 [34].

Table 2. ECOG performance status scale [34].

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

ECOG=Eastern Cooperative Oncology Group.

1.2.3 Malnutrition

Weight loss and malnutrition in advanced cancer are associated with increased morbidity and mortality, reduced QoL, physical function and tolerance to anticancer treatment [22, 23]. Malnutrition results from lack of intake and/or uptake and utilization of nutrients, leading to altered body composition and reduced physical and mental function [35]. Malnutrition is divided into three categories, based on the aetiology: disease-related malnutrition with inflammation, disease-related malnutrition without inflammation and non-disease related malnutrition [36]. Malnutrition without disease can be related to starvation, socioeconomic or psychological factors [36]. Disease-related malnutrition with inflammation is a condition that results from the activation of systemic inflammation by an underlying disease. “The inflammatory response causes anorexia and tissue breakdown, resulting in significant loss of body weight, alterations in body composition and decline in physical function” [36]. Disease-related malnutrition with inflammation is subdivided into chronic disease-related malnutrition and acute disease-related malnutrition [36].

The Global Leadership Initiative on Malnutrition (GLIM) describes a two-step approach for diagnosing malnutrition [37]. The first step is screening to identify every patient at risk of malnutrition by the use of a validated screening tool. The second step includes an assessment of clinical signs and causes for the patients identified at risk for malnutrition. A patient is assessed as malnourished with the presence of at least one phenotypic (non-volitional weight loss, low body mass index (BMI), reduced muscle mass) criterion and one aetiologic (reduced food intake or assimilation, malabsorption, disease burden/inflammatory condition) [37]. The severity of the malnutrition condition is determined based on the phenotypic criterion and divided into 2 categories: moderate or severe malnutrition [37].

1.3 Nutrition in patients with incurable cancer

Life expectancy in patients in a palliative care setting may vary from months to years, making them a heterogeneous group regarding anticancer treatment, symptom burden and nutritional challenges [22]. Weight loss is a frequent characteristic associated with impaired performance status, reduced tolerance to anticancer treatment, shortened survival and reduced QoL in these patients [22, 23]. The aetiology of cancer-related weight loss is complex, including anorexia and reduced food intake, reduced uptake of nutrients or cancer cachexia, alone or in combination [19, 22, 23]. Anti-cancer treatment can affect GI and induce nutritional related symptoms such as nausea, vomiting, abdominal cramps, mucositis, paralytic ileus and malabsorption [38]. All of which can affect a patient's appetite and food intake, resulting in weight loss and malnutrition. Nutritional care should be provided in a systematic sequence that involves distinct interrelated steps, called the nutrition care process (NCP) [36]. The NCP includes malnutrition risk screening, nutritional assessment, diagnostic procedure, nutritional care plan, nutritional therapy, monitoring and evaluating the effects of nutritional care and therapy, as well as documentation [36].

1.4 Medical nutrition therapy

Medical nutrition therapy includes oral nutritional supplements, enteral nutrition (EN) and parenteral nutrition (PN). It is called EN or tube feeding when the nutritional need is delivered to the gastrointestinal (GI) tract via a tube. Delivery of nutrients directly to the vein, intravenous feeding, is referred to as PN [36]. The term artificial nutrition has traditionally been used to describe EN and PN, but this term has been suggested replaced by medical nutrition therapy by the ESPEN guidelines recommendations on definitions and terminology of clinical nutrition [36].

In cancer patients, medical nutrition is indicated if patients are unable to eat adequately [22]. No food intake for more than one week, or an estimated intake of less than 60% of requirement for more than 1-2 weeks, is considered as an inadequate nutritional intake [22]. Nutritional therapy is recommended to be offered step by step, from nutritional counselling to parenteral nutrition (PN) [22]. Interventions focusing on oral nutrition intake, such as counselling and oral nutritional supplements, are first-line in nutritional treatment. An inadequate oral nutrition intake despite intervention indicates the need for EN. In patients with chronic insufficient dietary intake where EN is not sufficient or feasible and/or if patients have uncontrollable

malabsorption, PN is recommended [22]. In some cases, there might be appropriate to skip some steps or start at a higher level of intervention [39].

1.4.1 Parenteral Nutrition

Parenteral nutrition is intravenous administration of nutrients [36]. The term TPN is used if a patient receives nutrition exclusively from PN. Supplemental PN, partial PN or complementary PN refers to situations where PN is given in addition to EN or oral intake [36]. For patients with a functional GI tract, EN is preferable, but PN might be used as a supplement to EN or oral intake if it is not possible to cover a patient's nutritional need via the GI tract [36]. When PN is given outside of the hospital, it is referred to as home parenteral nutrition (HPN) [36].

1.4.1.1 Administration and composition of parenteral nutrition

Parenteral nutrition therapy can be administered through a peripheral or central vein, depending on vein access, the duration of treatment, and the osmolarity of the PN solution. A peripheral venous catheter (PVC) might be used if treatment is assumed to last for less than 7 days. If treatment is estimated to last for more than one week, a central venous catheter (CVC) should be considered [39]. Careful patient evaluation, monitoring and planning of the PN treatment is necessary in order to avoid complications and side effects of the treatment [40].

Parenteral nutrition solutions include macronutrients, water, electrolytes and micronutrients [36]. Carbohydrates, amino acids and lipids can either be administered separately, via a multi-bottle system or by using the all-in-one system [41]. The All-in-one system or multi-chamber bag system are mostly used in modern PN therapy and enables to infuse all daily needs for macronutrients, water, electrolytes and micronutrients from one bag [41]. Both standardized and individually compounded mixtures are available [39]. Standardized three-compartment bags, containing glucose, amino acids and lipids in separate chambers, are mostly used at hospitals in Norway. The solutions of nutrients in the different compartments are mixed immediately before administration and the addition of minerals, trace elements and vitamins is essential for the solution to be complete [39]. After mixing, the admixture should be administered within 24 hours.

The administration techniques of PN treatment have improved during the past decades, with considerable changes regarding the dosage, composition and distribution of the PN macronutrients [12, 42]. Energy is provided by the glucose, lipids and proteins [43]. Proteins are provided by solutions of crystalline amino acids [36], including the essential amino acids

[44]. An adequate energy substrate is needed in order to optimize protein utilization, and it is recommended that the provision of non-protein energy should be 100-150 kcal [43, 44]. Glucose is the only substrate of carbohydrates used in PN solutions today [44]. It is recommended that glucose should be administered at 3-6 g/kg per day in order to avoid acute and long-term complications, such as hyperglycaemia, hypoglycaemia and overfeeding [43, 45]. Hypercaloric PN practices in the early days of PN, aiming to reverse catabolism, particularly by the use of high glucose loads, have been replaced by more energy balanced PN solutions, after the integration of lipid emulsions [46, 47]. In long-term PN, the ratio of glucose to lipid is recommended to be between 70-85% from glucose and 15-30% from lipids [43].

Fat provides energy and essential fatty acids. In the PN solution, fats are provided in the form of intravenous lipid emulsions (IVLE). Lipid emulsions are composed of triglycerides with phospholipids as emulsifiers. Oil which provides triglycerides is suspended in an aqueous dispersion consisting of phospholipid, glycerol and water. Formation of globules of triglycerides and phospholipids, structurally similar to chylomicrons, occur during mixing of the components [48]. Lipid emulsions have traditionally been based on soybean oil, which is rich in pro-inflammatory polyunsaturated fatty acids (PUFAs). Modern IVLE have replaced some of the soybean oil with coconut oil providing medium-chain saturated fatty acids, olive oil and fish oil, rich in anti-inflammatory n-3 PUFAs [49, 50]. Some oils are also used in a mixed IVLE. SMOFlipid®, which is a lipid emulsion composed of soybean oil, medium-chain triglycerides from coconut oil, olive oil and fish oil [49], is currently in use at Haukeland University hospital.

In patients receiving PN as the only source of nutrition, multivitamins and trace elements should be added daily and monitored closely during treatment [51]. Multivitamin and mineral preparations added to the PN solution are designed to meet most of the patient's needs. These levels may be inadequate in some situations, i.e. if there is a risk for refeeding syndrome, and additional individual supplementation might be required [52].

1.4.2 Parenteral nutrition in patients with incurable cancer

The use of PN in patients with incurable cancer is a controversial subject due to conflicting evidence regarding its risks and benefits. There are large variations in its use worldwide, depending on ethical, medical and cultural considerations [53]. The ESPEN guidelines support PN in patients with incurable cancer who have failed oral and EN feeding and who have a life expectancy of longer than 2-3 months. However, the evidence supporting the beneficial effects

of PN is weak [12, 22, 54]. Before starting nutritional interventions in patients with incurable cancer, it is important to consider the cancer prognosis, expected benefits on QoL and potential survival, as well as potential burdens associated with the nutritional treatment [22]. “If expected survival is several months or years, nutrition therapy should be given with the aim to secure an adequate intake of energy and protein, to diminish metabolic disturbances, and to maintain an adequate performance status and subjective QoL” [23]. For patients with an expected survival from a few to several weeks, non-invasive interventions, primary aimed at psychosocial and existential support is recommended [23]. Medical hydration and nutrition are unlikely to provide any benefit for most patients in the terminal phase [22]. The ESPEN guidelines states that “there is little or no benefit from nutritional support in the last weeks of life, since it will not result in any functional or comfort benefit for the patient” [22]. The treatment is therefore recommended to be based on comfort and QoL and should be tailored to the patient’s symptomatic needs [23].

Early studies examining the effect of PN in patients with incurable cancer have failed to prove any positive benefits [12]. A meta-analysis from 1990, concluded that routine use of PN as well as research examining the effect of PN in patients receiving chemotherapy, should be strongly discouraged, due to potential harmful effects [55]. The conclusion from this meta-analysis [55], resulted in no randomised-controlled trials (RCTs) including patients with incurable cancer to be conducted for several decades [12]. The studies included in the meta-analysis were conducted in a period where PN therapy was given in hypercaloric amounts, with high glucose loads and infusion rates [12]. Composition of PN solutions, administration techniques and hygiene protocols has improved, making treatment safe [12]. Based on the evidence available, the use of current PN treatment in patients with incurable cancer is not known.

1.5 Objectives

The overall aim of this study is to describe the current practice of PN therapy in patients with incurable cancer, receiving PN at Haukeland University Hospital, Bergen from 2011-2018. More specifically, the following research questions will be investigated:

At start of PN:

- What is the indication for start of PN?
- What are the estimated energy needs and oral intake at start of PN?
- How is PN administered?

During PN:

- What are the dosages of PN used at start and what is the highest dose?
- How much of a patient's estimated energy needs are provided by PN?
- What is the duration of PN?

Termination of PN:

- What are the reasons for discontinuation of PN?

Survival on PN:

- How long do patients on PN treatment live?

2 Methods

2.1 Study design

This master project is part of a multicentre retrospective study which includes all patients with incurable cancer receiving intravenous nutrition between 2011 and 2018. The study is a collaboration between the Norwegian University of Science and Technology (NTNU) (project management), St. Olavs University Hospital (Trondheim), Vestfold Hospital (Tønsberg), Hospital in Telemark (Skien) and Haukeland University Hospital (Bergen). The study involves several health care levels as patients has discharged from the hospital with intravenous nutrition. This is exemplified by homecare services and institutions like long-care facilities or short-care facilities. This thesis is based on data collected at Haukeland University Hospital during October 2019 and February 2020.

Haukeland University Hospital and Helse Bergen treat almost 600.000 patients and contribute to the education of several thousand health care workers every year [56]. It is the second largest university hospital in Norway with regard to research production and employ about 800 persons engaged in research activities, which equals 300 full-time positions [57].

2.2 Patients

2.2.1 Patient recruitment

This study included patients with incurable cancer starting PN at the hospital and patients discharged from the hospital with PN, as well as patients starting PN at palliative care units and home, from 1st of January 2011 to 31st of December 2017. Subjects were identified through the delivery records of treatment aids, for delivering of infusion pump, provided by Home Care Equipment, Department of Clinical Engineering, Helse Bergen.

2.2.2 Inclusion criteria

Inclusion and exclusion criteria are presented in Table 3. Inclusion criteria were adult patients diagnosed with advanced/incurable cancer receiving PN treatment during the palliative phase of their disease, in the period from 1st of January 2011 to 31st of 2017. Patients had to be deceased within the data abstraction period to be included in the analysis. Exclusion criteria were patients still alive at the start of data abstraction.

Table 3. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Adult patients (aged >18 years) with advanced/incurable cancer • PN treatment during the palliative phase of the disease • Deceased at start of the data abstraction period 	<ul style="list-style-type: none"> • Still alive

PN=parenteral nutrition

The records of treatment aids for delivering of infusion pump did not provide any information regarding the patient's diagnosis, which type of infusion treatment that were given nor if the patients were still alive or deceased. Identification of subjects complying with the inclusion criteria were therefore done in a three-step manner, where step 1 included retrieve list of patients receiving infusion pump from records of treatment aids, step 2 included checking patients records for cancer diagnosis and death, and step 3 checked if the patient did receive PN in a palliative phase of his or her cancer diagnosis.

Step 1: List from records of treatment aids

Step 2: Checked journal for cancer diagnosis and death

Step 3: Check if the patient started PN when the disease was incurable

2.3 Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (REC) Mid Norway (Appendix 1) and conducted according to the criteria set by the Declaration of Helsinki [58]. The approval from REC gave exemption from gathering consent from relatives, due to the patients already being deceased and could not provide written consent. A Data Protection Impact Assessment (DPIA) was performed to comply with the requirements of General Data Protection Regulations (GDPR) [59]. The DPIA was approved by NTNU and the other collaborative institutions. A collaboration agreement between the NTNU and Haukeland University Hospital was signed (appendix 2). This study on patients died from cancer poses no risk to the patients. Each patient was given an identification (ID) number for de-identification in analysis and further use. The ID number were Centre specific and tied to the patient's name and medical record number. The link between ID number and patient name was stored using a patient enrolment log which function as a coding key. The coding key were stored in a dedicated location with a two-step locking procedure (locked in drawer and locked door in corridor).

2.4 Data collection

Data sources in this study were medical chart records of hospitals, palliative care units and primary health care services. Data were collected from the following sections from the patients' medical records; doctor journals, nurse journals, clinical dietitian journals, laboratory tests, image diagnostics, nutritional screening, and other registration tools scanned into the electronic medical journals. The master student acted as the data abstractor in this study. Data were also collected from the following hospitals: Voss Hospital, Haraldsplass Deaconess Hospital (HDS) and palliative care unit, Sunniva Centre for Palliative Care at HDS. Data on termination of PN were also retrieved from the following primary health care facilities: the home care services in the municipality of Bjørnafjorden, Meland nursing home in the municipality of Alver and Kleppestø nursing home in the municipality of Askøy. The master student performed requests via e-mail and telephone to the primary health care system in order to retrieve information regarding PN termination in cases where such data were not reported in the hospital journals.

2.4.1 Variables

Data collected is summarized in Table 4. From medical journal systems, data on demographics, comorbidities [60], cancer disease [5] and treatment, date of death, symptom registrations (Edmonton Symptom Assessment System, [61]), physical function (ECOG performance status scale [34]), biochemical data as well as registrations on nutritional status, food intake and PN treatment was retrieved. Data on estimated energy requirements were collected from the patient's journal. Method for estimating energy requirements was not registered. A pause in PN treatment was defined as a break of 1-14 days. A break lasting longer than 14 days was regarded as start of new PN treatment. If a patient had received PN treatment several times during his or her disease trajectory, data on the last PN treatment was registered. The duration of PN treatment was calculated from date of start of PN and date of PN termination. Survival from PN start was calculated from date of PN start and date of patient death. Survival from PN termination was calculated from date of PN termination and date of patient death. BMI (weight in kilograms/height in meters squared (kg/m²)) was calculated from height and weight registrations at PN start. Weight loss in kilograms (kg) at PN start were calculated from available body weight taken 4-6 months, 2-3 months and 2 weeks-1 months before PN start. Per cent weight loss at start of PN was calculated based on weight loss data. The mGPS was calculated from available CRP and albumin values, where CRP >10 mg/L and albumin <35 g/L provided a score of 2, a CRP level >10 mg/L provided a score of 1 and CRP ≤10 mg/L and

albumin ≥ 35 g/L provided a score of 0 [24]. Estimated energy needs in kcal/kg/day was calculated from data on estimated energy needs and weight registrations at start of PN. Start dose of PN in kcal/kg/day was calculated from PN start dose and weight registration at PN start. Maximum PN dose received in kcal/kg/day was calculated from maximum dose received and weight registration at PN start.

Table 4. Data collection

Assessment	At PN start	During PN
Demographics (year of birth, sex, main provision of care)	x	
Comorbidities	x	
Current medications	x	
Cancer type and stage (date of diagnosis and cancer stage at initiation of PN)	x	x
Oncology treatment (previous, ongoing and new treatment during PN)	x	x
Estimated energy requirements	x	
Food intake registrations	x	x
Parenteral nutrition (indication, infusion schedule, dose given, delivery rate, dose adjustments, pause in treatment, reason for termination)		x
Nutritional status (height, body weight, previous weight (4-6 months, 3-4 months and 14 days-1month before PN start, NRS2002)	x	x
Performance status (ECOG/WHO)	x	x
CT scan for body composition measures	x	x
ESAS symptom scale (fatigue, nausea, vomiting, shortness of breath, appetite, depression, anxiety, wellbeing)	x	x
Adverse events (oedema, ascites, dyspnoea, nausea, vomiting, diarrhoea, feeling cold, feeling warm, dizziness, headache, infections, thrombophlebitis, elevated levels of liver enzymes, sepsis, tachycardia, hypotension, hypertension)		x
Biological parameters (CRP, albumin, electrolytes)	x	x
Date of death		x
Calculated variables		
Duration of PN		
Survival from PN		
BMI, % weight loss		
mGPS		
Estimated energy needs in kcal/kg/day		
PN start dose in kcal/kg/day		
PN maximum dose in kcal/kg/day		

BMI=Body mass index; CRP=C-reactive protein; ECOG=Eastern European Cooperative Oncology group; ESAS=Edmonton Symptom Assessment System; kcal=kilocalories; kg=kilograms; mGPS=modified Glasgow Prognostic Score; NRS2002=nutrition risk screening [62]; WHO=World Health Organization

2.5 Data abstraction software

The data collection was performed by a web-based data collection system (WebCRF3) developed and administered by Unit of Applied Clinical Research, The Faculty of Medicine and Health Sciences, NTNU, Trondheim, Norway. A two-factor authentication was needed to access the Web-CRF as an extra level of security. This included a study user with password and a URC code sent to the user by SMS. The Web-CRF in this study is the 3.0 version. Data from the medical charts were directly entered to the Web-CRF electronically, by the data abstractor.

2.5.1 Research manual

A research manual for data abstraction has been developed to ensure standardizing and consistency of data collected from medical journals at several study sites by different abstractors (appendix 3). The research manual defined different variables related to the web-CRF and included information on the inclusion/-exclusion criteria, staging of cancer disease and comorbidity [60] as well as definition and response options on other parameters such as: performance status [34], nutritional status [62], symptoms [61], indication for PN start, PN infusion, and definition of pauses of PN treatment. The research manual was continuous subject to changes when challenging variables had to be described in further detail or clarified.

2.5.2 Data monitoring

An overview of variables monitored is presented in Table 5. The data abstractor was introduced to the Web-CRF by the research team at NTNU prior to data collection. Data abstractor and the research team were frequently in contact with each other during the data abstraction period. When uncertainty regarding documentation arose, this was solved by discussion. Monitoring of data was performed by the research team in Trondheim post data abstraction. Starting dose in all patients registered with a start dose of ≥ 1600 kcal/day was controlled by the monitor. Monitoring of the rest of the variables was done by randomly checking 10% of the included CRFs towards the original medical records. Randomization of the 133 included CRFs was performed in Microsoft® Excel (version 16.35), by using the formula: =RANDBETWEEN(A1;A133), which generated 13 numbers from the sample. When error was detected, this was consecutively corrected by abstractor with monitor present. Sources of data verification by monitoring included variables on eligibility criteria, PN treatment and cancer stage (Table 5).

Table 5. Overview of variables monitored

Sample monitored	Source of data verification
The entire population	PN start dose \geq 1600kcal/day Were PN start dose of 1600 kcal/ day or more correctly registered?
10 % of the population	Eligibility criteria Was patient dead by end of data abstraction? Did patient receive PN between 1 st of January 2011 and 31 st December 2017? Was patient diagnosed with advanced/ incurable cancer? PN treatment Was date of PN start correctly registered? Was date of PN termination correctly registered? Was Indication for PN start correctly registered? Cancer disease Was list of medication correctly registered? Was disease stage at PN start correctly registered? Was disease stage during PN treatment correctly registered?

PN=parenteral nutrition, kcal=kilocalories

2.6 Data processing and analyses

The data abstraction and processing are presented in figure 2. The datafiles extracted from the Web-CRF were stored using a dedicated solution for secure processing of sensitive personal data in research, SAFE, provided by UiB. Access to the SAFE-desktop for this project demanded a two-factor authentication. In addition to a username and password, the user needed to supply a one-time code received as a text message. All processing of data and analyses were conducted using this safe desktop.

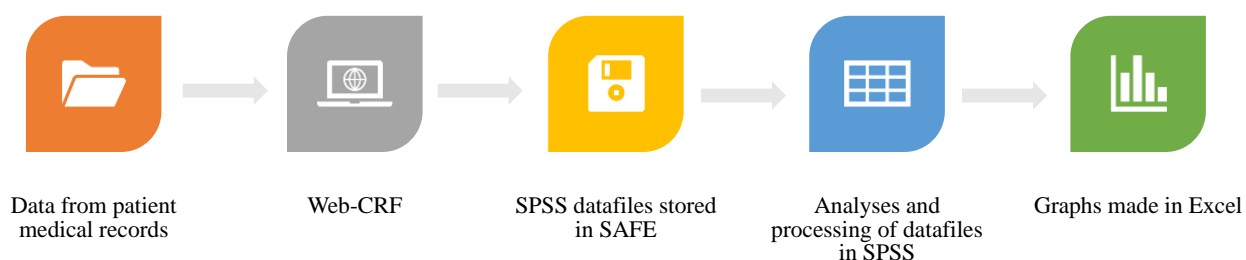


Figure 2. Process of data abstraction and processing.

Statistical analyses were performed by using the statistical program IBM SPSS (version 25.0.0.2). Graphs were made in Microsoft® Excel (version 16.35). Demographics such as age, weight, gender, height, BMI and weight loss were reported as means with standard deviation (SD). Normality was assessed by normality tests, histograms, normal and detrended Q-Q plots. Continuous variables were reported as mean with (SD) values or median with minimum and maximum (min-max) or inter quartile range (IQR) with upper and lower quartiles (Q1-Q3)

based on normality. A Wilcoxon signed-rank test was conducted to determine any difference in median values of PN max dose and estimated energy needs in kcal/kg/day. A Spearman's rank-order correlation with scatterplot was run to assess the relationship between survival from PN start and duration of PN. Kruskal Wallis Test for independent selections was used to compare multiple non-parametric variables. Post Hoc Test with pairwise comparisons by Dunn's Procedure with a Bonferroni correction for multiple comparisons was used to locate any difference between groups in multiple group analysis. Missing data were handled by excluding cases in SPSS. Statistical significance level was set at $p < 0.05$ (2-sided) level.

2.7 Contribution by the master student

The master student was responsible for all data abstraction at Haukeland University hospital. In patients discharged from the hospital to a palliative care unit, long-term facility or home with PN treatment, the student was responsible to contact these to request information regarding data not reported in the hospital journals. This included communication with the primary health care system at different levels.

3 Results

3.1 Population

3.1.1 Patient identification

The three-step sample selection process is illustrated in figure 3. From the delivery records of infusion pumps provided by Home Care Equipment, Department of Clinical Engineering, Helse Bergen, 263 patients receiving infusion pump in the period 2011-2018 were identified. Five of these patients were not found in the journal record system of the hospital. Out of 258 patients examined for eligibility, 125 (48.4 %) were excluded due to still being alive (n=79), being a child (n=1), no received PN treatment (n=14), no cancer diagnosis (n=16), having a curable cancer disease (n=10), patients starting PN before 2011 or after 2017 (n=3) and uncertainties regarding last PN treatment, meaning that we could not for sure say if the PN treatment was the patient's last, due to patient moving to another region and might receive PN at another health region (n=2). In total 133 (51.6%) out of the 258 eligible patients were included in the master thesis.

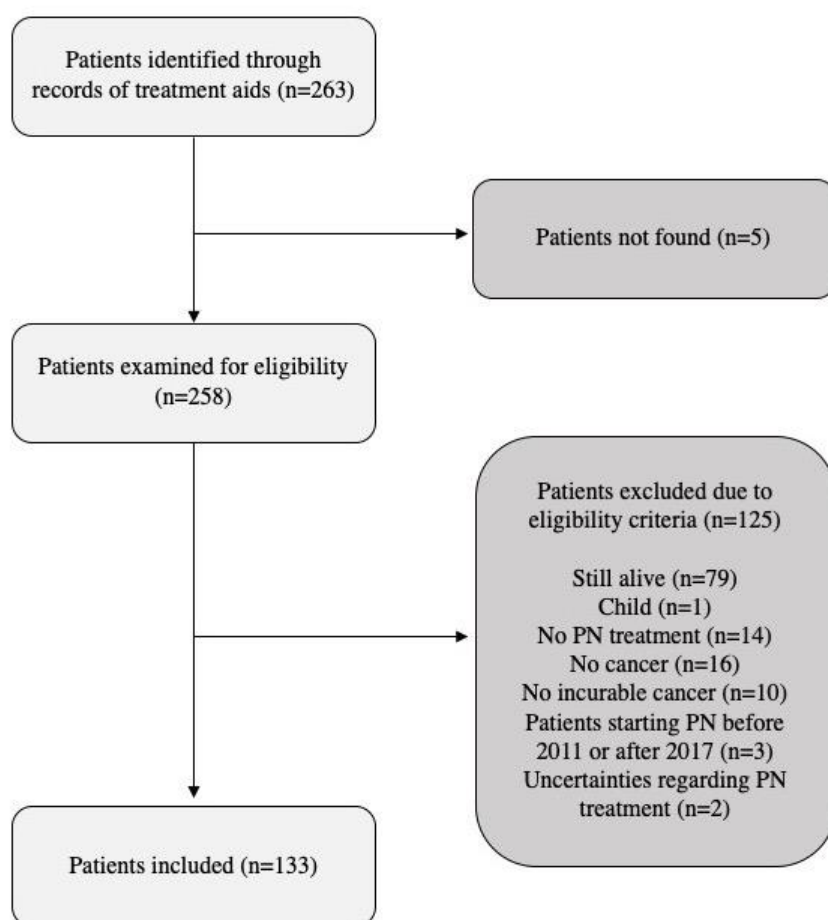


Figure 3. Sample selection flow chart. PN=parenteral nutrition, n indicates number of cases.

3.1.2 Patient characteristics

Patient characteristics are summarized in Table 6. Mean (SD) age of the population was 64 ($\pm 12,4$) years and 61 (45.9%) were male. Hospital/palliative care unit was the main provision of care for most of the patients included in this study (n=98, 73.7%). The most common types of cancer were upper GI (n=48, 36.1%) and colorectal (n=31, 23.3%). Cancers listed under “other” were cancers of unknown primary site, peritoneum, prostate, bone, head and neck, lymphoma and connective tissue of pelvis, appeared in 16 (12.0%). At start of PN, 111 (83.5%) of the patients were diagnosed with metastatic cancer. Metastases in peritoneum-mesentery was the most common sites of metastasis and reported in 46 (34.6%) of the cases. Metastasis in the liver were present in 41 (30.8%), in lymph nodes 39 (29.3%) and peritoneal carcinomatosis in 38 (28.6%). Performance status assessed by ECOG/WHO performance status scale was only documented in 61 (45.9%) of the patients at start of PN. Performance status ≤ 2 was most frequent (n=40, 30.1%). Twenty-one (15.5%) of the patients were registered with a performance status 3 at start of PN.

Table 6. Patient characteristics

Characteristics	Patients, n (%) (n=133)	Mean (SD)
Age in years		64 (\pm 12,4)
Gender		
Female	72 (54.1%)	
Male	61 (45.9%)	
Main provision of care		
Hospital/ Palliative care unit	98 (73.7%)	
Home	34 (25.6%)	
Long-term care facilities	1 (0.8)	
Cancer diagnosis		
Upper GI tract	48 (36.1%)	
Colorectal	31 (23.3%)	
Gynaecological	16 (12.0%)	
Small intestine	9 (6.8%)	
Bladder	6 (4.5%)	
Lung	4 (3.0%)	
Breast	3 (2.3%)	
Other	16 (12.0%)	
Stage of cancer disease		
Local	10 (7.5%)	
Locally advanced	12 (9.0%)	
Metastatic	111 (83.5%)	
Location of metastasis		
Peritoneum-mesentery	46 (34.6%)	
Liver	41 (30.8%)	
Lymph nodes	39 (29.3%)	
Peritoneal carcinomatosis	38 (28.6%)	
Lung	19 (14.3%)	
Bone	13 (9.8%)	
Other	28 (21.1%)	
Performance status		
ECOG 1	10 (7.5%)	
ECOG 2	30 (22.6%)	
ECOG 3	21 (15.5%)	
ECOG 4	0	
No ECOG registered	72 (54.1%)	

ECOG=Eastern European Cooperative Oncology group; mGPS=modified Glasgow Prognostic score; SD=standard deviation, n indicates number of cases.

An overview of ongoing anti-cancer treatment and use of medications and at PN start is presented in Table 7. Most of the patients (n=115, 86.5%) had at some point received different anti-cancer treatments for their cancer disease (data not shown). Fifty-two (39.1%) out of 133 patients received anti-cancer treatment at start of PN, whereof ongoing chemotherapy was the most frequent (n=36, 27.1%). Current medications included medication of regular use as well as medication prescribed and used when necessary at start of PN. The medications were registered in selected drug groups (Table 7). The most frequent medications in this population were antiemetics (n=102, 76.7%), non-opioid analgesics (n=98, 73.7%) and opioids (n=92, 69.2%). Other medications included among other things thyroid hormones, oestrogens, mucolytics and lipid-lowering drugs.

Table 7. Current medications, ongoing and previous anti-cancer treatment

Anti-cancer treatment and medication	n (%)
Ongoing anti-cancer treatment	
None	81 (60.9%)
Chemotherapy	36 (27.1%)
Targeted therapy	5 (3.8%)
Radiotherapy	5 (3.8%)
Chemo-radiotherapy	3 (2.3%)
Immunotherapy	3 (2.3%)
Current medication	
Antiemetics	102 (76.7%)
Opioids	98 (73.7%)
Non-opioid analgesics	92 (69.2%)
Drug(s) for acid related disorders	81 (60.9%)
Laxatives	71 (53.4%)
Sedatives/anxiolytics	65 (48.9%)
Heart medication/antihypertensives	48 (36.1%)
Anticoagulants	45 (33.8%)
Antibiotics	35 (26.3%)
Corticosteroids	28 (21.1%)
Neuroleptics	25 (18.8%)
Anticholinergics	18 (13.5%)
Antidepressants	17 (12.8%)
Diuretics	17 (12.8%)
Antimycotics	17 (12.8%)
Antidiarrheals	15 (11.3%)
NSAIDS	10 (7.5%)
Co-analgesics	7 (5.3%)
None	1 (0.8%)
Other	67 (50.4%)

NSAIDS=Nonsteroidal anti-inflammatory drugs, n indicates number of cases.

Data on anthropometric measures and biological parameters on inflammation are presented in Table 8. Bodyweight at start of PN was available in 126 (91.0%) patients. Mean (SD) BMI was 21,2 (\pm 4,0) kg/m². Weight loss within the past four to six months before PN start was available for 88 (66.2%) patient. Mean (SD) weight loss within the past four to six months before PN start was 11.6 (\pm 8,2) %. Nutritional risk screening was performed in 63 (47.4%) patients at PN start. Malnutrition diagnosis was registered in 77 (57.9%) of the patients. Most of the patients were registered with severe protein-energy malnutrition (n=36, 27.1%). Serum CRP was available for 124 (93.2%) patients at PN start. Most of the patients had an elevated CRP level at PN start (n=97, 72.9%). Serum albumin was available for 107 (80.5%) patients. Hypoalbuminemia was detected in 53 (39.8%) of the patients at start of PN. The mGPS was available for 101 (75.9%) patients. A mGPS of 2 was reported in 44 (33.1%) patients.

Table 8. Data on anthropometric measures and inflammatory markers.

Variables	Mean (SD)	n (%), (n=133)
Height, cm		
Female	165 (±5,5)	71 (53.4%)
Male	178,4 (±6,4)	61 (45.9%)
Missing, n		1 (0.7%)
Bodyweight, kg	61,9 (±12,5)	
Female	58,1 (±12,2)	65 (48.9%)
Male	66,4 (±11,4)	56 (42.1%)
Missing, n		12 (9.0%)
BMI, kg/m ²	21,2 (±4,0)	
<18,5		29 (21.8 %)
18,5-24,9		73 54.9%)
25-29,9		14 (10.5%)
>30		5 (3.8%)
Missing, n		12 (9.0%)
Weight loss before PN start, %		
4-6 months before PN start	11,6 (±8,2)	88 (66.2%)
Missing, n		45 (33.8%)
2-3 months before PN start	8,1 (±8,2)	91 (68.4%)
Missing, n		42 (31.4%)
2 weeks-1 months before PN start	2,5 (±6,6)	95 (71.4%)
Missing, n		38 (28.6%)
NRS2002		63 (47.4%)
Not at nutritional risk (score< 3)		9 (6.8%)
At nutritional risk (score≥ 3)		50 (37.6%)
Missing, n		4 (3.0%)
Malnutrition diagnosis (ICD-10)		77 (57.9%)
Severe protein-energy malnutrition (E43.00)		36 (27.1%)
Moderate protein-energy malnutrition (E44.00)		15 (11.3%)
Unspecified protein-energy malnutrition (E46.00)		26 (19.5%)
CRP, mg/L		
CRP≤10		27 (20.3%)
CRP>10		97 (72.9%)
Missing, n		9 (6.8%)
Albumin, g/L		
<35 mg/L		53 (39.8%)
≥35 mg/L		54 (40.6%)
Missing, n		26 (19.5%)
mGPS		
0		25 (18.8%)
1		32 (24.1%)
2		44 (33.1%)
Missing, n		32 (24.1%)

BMI=body mass index, cm=centimetre, kg=kilograms, mGPS=modified Glasgow Prognostic Score, NRS2002=nutrition risk screening; ICD-10: International classification of diseases version 10, n indicates number of cases.

3.2 Parenteral nutrition

3.2.1 Indication for start of parenteral nutrition treatment

Indication for start of PN was available in 132 patients. Indication and number of indications for start of PN are presented in Table 9. The most frequent indication for start of PN was “insufficient oral and/or enteral intake” reported in 82 (61.7%) of the cases followed by GI malfunctions in 52 (39.1%) patients. Several indications were possible, and GI malfunctions were often listed together with insufficient oral intake and weight loss and malnutrition were often listed together with insufficient oral and/or enteral intake.

Table 9. Indications for start of PN.

Indication(s) for start of PN	n (%), (n=133)
Insufficient oral and/or enteral intake	82 (61.7%)
Gastrointestinal malfunctions	52 (39.1%)
Weight loss	31 (23.3%)
Subileus	21 (15.8%)
Patient wish	12 (9.0%)
Short bowel syndrome	9 (6.8%)
Promote tolerance for cancer treatment	8 (6.2%)
Other	41 (30.8%)
Numbers of indications	
1	48 (36.1%)
2	53 (39.9%)
3	24 (10.1%)
≥4	7 (5.3%)

PN=parenteral nutrition, n indicates number of incidents.

3.2.2 Energy requirements and food intake

Data on estimated energy needs and food intake at PN start is presented in Table 10. Energy requirements were estimated in 80 (60.1%) out of 133 patients at PN start. Mean (SD) estimated energy requirement was 1781 (± 228) kcal in women and 2176 (± 354) kcal in men, equivalent to mean (SD) 33 (6) kcal/kg/day. Food registrations were available for 15 (11.3%) patients at PN start, ranging from 1-5 days of registration showing a mean intake of 655 kcal/day in women and 952 kcal/day in men. Seventy-one (53.4%) of the patients were referred to clinical dietitian in relation to start-up and/or follow up of PN treatment. Number of consultations with clinical dietitian at start-up/during PN treatment ranged from 1-36, with a median of 2 consultations per patient (data not shown).

Table 10. Estimated energy needs and registered intake of food and energy at PN start

Variables		n (%), (n=133)
Estimated energy needs, kcal	Mean (SD)	
Female	1781 (228)	42 (31.6%)
Male	2176 (354)	38 (28.6%)
Total	1969 (354)	80 (60.1%)
Missing, n		53 (39.9%)
Estimated energy needs, kcal/kg	Mean (SD)	
Total	33 (6)	76 (57.1%)
Missing, n		57 (42.9%)
Registered food intake at PN start, days	Median (min-max)	
Female	1 (1-5)	5 (3.8%)
Male	2.5 (1-5)	10 (7.5%)
Total	2 (1-5)	15 (11.3%)
Registered energy intake at PN start, kcal	Mean (SD)	
Female	655 (338)	5 (3.8%)
Male	952 (321)	10 (7.5%)
Total	853 (346)	15 (11.3%)

PN=parenteral nutrition; SD=standard deviation; kcal=kilocalories, n indicates number of cases.

3.2.3 Administration of parenteral nutrition

An overview of administration of PN are presented in Table 11. Main route for infusion was transthoracic venous port (n=79, 59.4%). Many patients received PN treatment both via peripheral vein and central vein at different times of PN treatment. Several options regarding route of administration were therefore possible. Nine (6.8%) patients received PN through a short-term CVC, while 44 (33.1%) patients received PN through a CVC not further specified. Volumat Agilia was the most commonly used infusion pump (n=112, 84.2%). Ambix Active was also registered in some patients (n=9, 6.8%), and some patients switched from Volumat Agilia to Ambix Active during treatment. Several options were therefore possible. The use of no pump was registered in 2 patients. SmofKabiven was the most common PN solution (n=107, 80.5%) followed by Olimel (n=33, 24.8%). Other PN solutions listed were Kabiven and Oliclinomel. Several options were possible since the hospital may change their main distributor of solutions each third year. Delivery rate of PN was registered in 79 (59.4%) of the patients and starting delivery rate was available for 32 (24.1%) of these patients. Median starting delivery rate was 75 ml/hour. The median delivery rate during treatment was 100 (80-120) ml/h (data not shown). Most of the patients received infusion at varies time during day or night and were therefore listed with “cyclical infusion – other” (n=86, 64.7%). Infusion during night-time was registered in 38 (28.6%) of the patients. Most of the patients (n=122, 91.7%) received PN 7 days a week, although some received PN every other day or less (n=9, 6.8%).

Table 11. Administration of PN

Administration of PN	n (%)
Route for infusion	
Transthoracic venous port	79 (59.4%)
Peripheral venous catheter	68 (51.1%)
Central venous catheter	44 (33.1%)
Hickman catheter	20 (15.0%)
Short term central venous catheter	9 (6.8%)
Type of infusion pump	
Volumat Agilia	112 (84.2%)
Unknown	13 (9.8%)
Ambix Active	9 (6.8%)
No pump	2 (1.5%)
PN solution	
SMOFkabiven	107 (80.5%)
Olimel	33 (24.8%)
Other	4 (3.0%)
Infusion type	
Cyclical infusion – other	86 (64.7%)
Cyclical infusion – nightly infusion	38 (28.6%)
Missing	9 (6.8%)
PN treatment days a week	
7 days	122 (91.7%)
4 days	6 (4.5%)
3 days	3 (2.3%)
1, 2, 5 or 6 days	0
Missing	2 (1.5%)

PN=parenteral nutrition, n indicates number of cases

3.2.4 Dosage of parenteral nutrition

Details on PN treatment and dosages are presented in Table 12. Starting dose of PN was available in 132 patients (99.3%). Median start dose (Q1-Q3) was 1000 (570-1100) kcal. The population was divided into 4 subgroups based on the amount of energy provided by the PN start dose: ≤ 500 kcal, >500 kcal- ≤ 1000 kcal, >1000 kcal- ≤ 1500 kcal and >1500 kcal. Most of the patients was allocated to the group with a PN start dose >500 kcal- ≤ 1000 kcal (n=70, 52.6%).

Table 12. PN start dose

Variables	Kcal/day, median (Q1-Q3)	n (%), (n=133)
PN start dose	1000 (570-1100)	132 (99.3%)
Subgroups based on PN start dose		
≤500 kcal	446 (245-500)	11 (8.3%)
>500 kcal-≤1000 kcal	1000 (550-1000)	70 (52.6%)
>1000 kcal-≤1500 kcal	1100 (1050-1100)	40 (30.1%)
>1500 kcal	1600 (1600-1710)	11 (8.3%)
Missing		1 (0.7%)

PN=parenteral nutrition; kcal=kilocalories. N indicates number of cases.

A comparison of median PN start dose, maximum dose received, and minimum dose received during PN treatment in subgroups defined by PN start dose is presented in figure 4. Twenty-seven (20.3%) of the patients did not have any dose adjustment from PN start dose. Median (Q1-Q3) start dose for these patients was 1100 (1000-1600) kcal (data not shown).

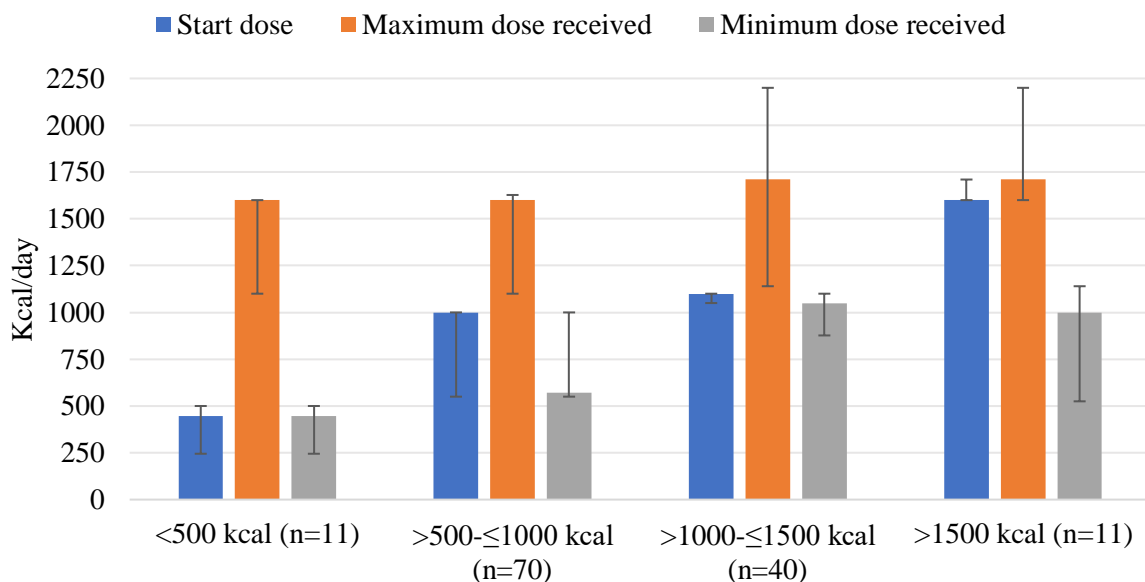


Figure 4. Histogram of median PN start, maximum and minimum dose in subgroups defined by PN start dose. Error bars indicates IQR expressed as range (Q1-Q3). Kcal=kilocalories, n indicates number of cases.

A histogram comparing PN start dose, maximum PN dose received and estimated energy needs in kcal/kg/day are presented in figure 5. Median (Q1-Q3) estimated energy needs was 33 (28-36) kcal/kg/day. Median (Q1-Q3) highest dose PN received was 28 (23-31) kcal/kg/day, which is 5 kcal/kg/day lower than median estimated energy needs, $p < 0.001$ assessed by Wilcoxon Signed Rank Test. Median (Q1-Q3) per cent of the energy needs this dose covered was 88 (71-100) % (data not shown). Median (Q1-Q3) start dose was 15 (12-19) kcal/kg/day.

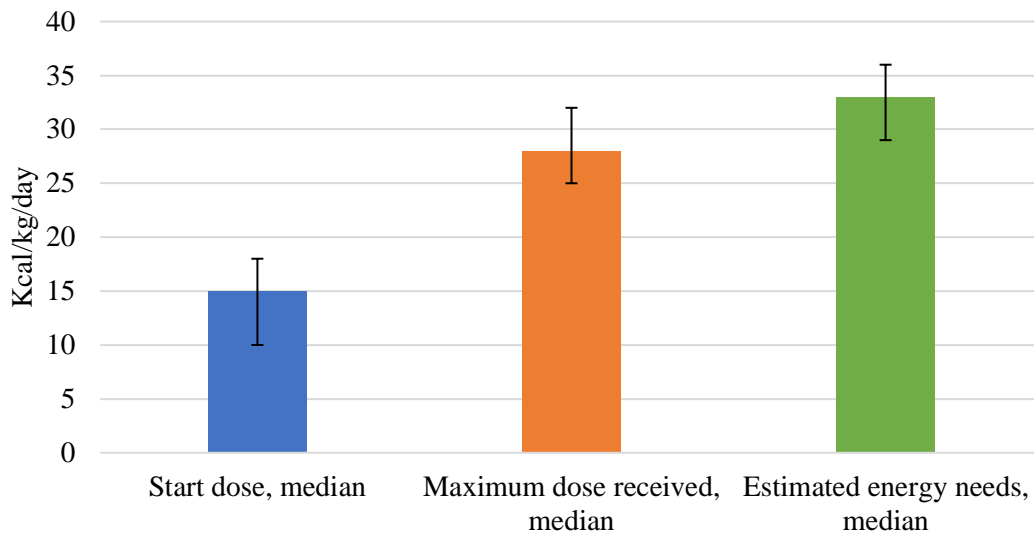


Figure 5. Histogram of median PN start dose and maximum dose of PN received compared to estimated energy needs. Error bars in indicates IQR expressed as range (Q1-Q3). Kcal=kilocalories; kg=kilograms; PN=parenteral nutrition, n=76.

3.2.5 Duration of parenteral nutrition

Date of PN termination was available in 111 (83.5%) out of 133 patients. Duration of PN treatment in all patients and subgroups based on the duration of PN are presented in table 13. Median (Q1-Q3) duration of PN was 44 (18-99) days. About 50% of the patients received PN ≤ 2 months.

Table 13. Duration of PN in days

	Days, median (Q1-Q3)	n (%) (n=133)
Duration of PN	44 (18-99)	111 (83.5%)
Missing		22 (16.5%)
Subgroups based on PN duration		
≤ 2 weeks	6 (2-12)	24 (18.1%)
>2 weeks- ≤ 1 month	21 (19-22)	22 (16.5%)
>1 month- ≤ 2 months	43 (29-47)	17 (12.8%)
>2 months- ≤ 3 months	67 (64-75)	18 (13.5%)
>3 months	139 (107-290)	30 (22.6%)
Missing, n		22 (16.5%)

PN=parenteral nutrition;Q=quartile. N indicates number of cases.

Table 14 shows a comparison of mGPS at start of PN, pauses during PN treatment and survival from PN start and PN termination in subgroups defined by PN duration. There was a difference in mGPS at start of PN ($p=0.04$) assessed by Kruskal Wallis Test for independent selections. The mGPS at PN start was higher in the group receiving PN >2 weeks- ≤ 1 month compared to patients receiving PN ≤ 2 weeks when pairwise compared with Dunn's Post Hoc Test with a Bonferroni correction for multiple comparisons. ($p=0.04$). A Spearman's rank-order correlation was run to assess the relationship between survival from PN start and duration of

PN. There was a positive correlation between duration of PN and survival from PN start, correlation coefficient $r_s=0.751$, $p<0.0005$ (scatterplot not shown). Survival from PN start was higher in patients receiving PN >3 months compared to patients receiving PN ≤ 14 days ($p<0.001$), >1month- ≤ 2 months ($p<0.001$) and >2 months- ≤ 3 months ($p=0.005$) when pairwise compared with Dunn’s Post Hoc Test with a Bonferroni correction for multiple comparisons.

Table 14. The mGPS at PN start, pauses during PN and survival from PN start and termination in subgroups defined by PN duration.

Variables	≤ 2 weeks (n=24)	>2weeks- ≤ 1 month (n=22)	>1month- ≤ 2 months (n=17)	>2months- ≤ 3 months (n=18)	>3months (n=30)
PN start					
mGPS, n (%)					
0	6 (25.0%)	2 (9.1%)	2 (11.8%)	2 (11.1%)	6 (20.0%)
1	7 (29.2%)	2 (9.1%)	3 (17.6%)	6 (33.3%)	9 (30.0%)
2	3 (12.5%)	11 (50.0%)	7 (41.2%)	8 (44.4%)	8 (26.7%)
Missing, n (%)	8 (33.3 %)	7 (31.8%)	5 (29.4%)	2 (11.1%)	7 (23.3%)
During PN					
Pauses					
Yes, n (%)	12 (50%)	2 (9.1%)	9 (52.9%)	11 (61.1%)	21 (70%)
Unknown, n (%)	1 (4.2%)	3 (13.6%)	5 (29.4%)	3 (16.7%)	5 (16.7)
Number of pauses, median (Q1-Q3)	1 (1-2)	2 (1-2)	2 (1-3)	1 (1-2)	2 (1-3)
Survival					
Survival from PN start, days, median (Q1-Q3)	37 (17-137) *	47 (26-164) *	58 (43-95) *	77 (68-96) **	167 (131-322) *,**
Survival from PN termination, days, median (Q1-Q3)	33 (6-129)	26 (3-144)	8 (5-52)	6 (2-24)	9 (5-43)

PN=PN; mGPS=modified Glasgow Prognostic Score; SD=standard deviation; Q=Quartile. Kruskal Wallis Test for independent selections, Post Hoc Test, Pairwise comparisons by Dunn’s Procedure with a Bonferroni correction for multiple comparisons; * $p<0,001$, ** $p=0,005$. N indicates number of cases.

3.2.6 Reasons for discontinuation of parenteral nutrition

Reason for discontinuation of PN was registered for 112 (84.2%) patients and are presented in Table 15. Several options were possible. Most of the patients had a singular reason for PN termination (n=78, 58.6%). The most common reason for PN termination was “patient is terminal/has short/very short expected survival” (n=50, 37.6%). Reasons listed under “other” included: “patient does not wish to receive life-prolonging treatment”, “patient does no longer benefit from PN”, “rapidly progressive disease/disease progression”, “patient wish”, “patient wish due to no perceived benefits”. Reason for PN termination was listed as unknown in 7 (5.3%) patients.

Table 15. Reason(s) for discontinuation of PN treatment

Reason for discontinuation of PN treatment	n (%)
Patient is terminal/short/very short expected survival	50 (37.6%)
Complications related to PN treatment	16 (12.0%)
Transition to oral food intake	10 (7.5%)
Recovery of GI tract functions	9 (6.8%)
Transition to enteral nutrition treatment	8 (6.0%)
Unknown	7 (5.3%)
Patient wish due to burden of PN treatment	6 (4.5%)
Patient wish to resume oral food intake	4 (3%)
Other	27 (20.3%)
Number of reasons	
1	78 (58.6%)
2	33 (24.6%)
3	1 (0.8%)

GI=gastrointestinal, PN=parenteral nutrition, n indicates number of cases.

3.2.7 Survival

Data on survival were available for all of the patients. Details are presented in Table 16. Median (Q1-Q3) survival for the population was 81 (41-159 days). Half of the patients survived ≤ 3 months (n=71, 53.4%).

Table 16 Survival from PN start.

	Survival in days, median (Q1-Q3)	n (%), (n=133)
Survival from PN start	81 (41-159)	133 (100%)
Subgroups based on survival from PN start		
≤ 1 month	19 (14-22)	19 (14.3%)
>1 month- ≤ 2 months	41 (33-47)	28 (21.1%)
>2 months- ≤ 3 months	69 (66-80)	24 (18.0%)
>3 months- ≤ 6 months	119 (104-152)	34 (25.6%)
>6 months	303 (226-428)	28 (21.1%)

PN=parenteral nutrition, n indicates number of cases.

The mGPS at PN start and indications for PN start in subgroups defined by survival from PN start is presented in Table 17. There was no difference in the distribution of mGPS at PN start between the subgroups (p=0.7), assessed by Kruskal Wallis test for independent selections. Insufficient oral and/or enteral intake followed by GI malfunctions/subileus was the most frequent indications for start of PN across the subgroups (table 17).

Table 17. The mGPS at PN start and indication(s) for start of PN in subgroups defined by survival.

Variable	≤1 month (n=19)	>1 month- ≤2 months (n=28)	>2 months- ≤ 3 months (n=24)	>3 months- ≤ 6 months (n=34)	>6 months (n=28)
mGPS, n (%)					
0	3 (15.8%)	5 (17.9%)	5 (20.8%)	6 (17.6%)	6 (21.4%)
1	3 (15.8%)	3 (10.7%)	9 (37.5%)	10 (29.4%)	7 (25.0%)
2	5 (26.3%)	13 (46.4%)	7 (29.22%)	11 (32.4%)	8 (28.6%)
Missing	8 (42.1%)	7 (25%)	3 (12.5%)	7 (20.6%)	7 (25.0%)
Indication for start of PN, n (%)					
Insufficient oral and/or enteral intake	13 (68.4%)	17 (60.7%)	16 (66.7%)	20 (58.8%)	16 (57.1%)
GI malfunctions/subileus	9 (47.3%)	14 (50.0%)	16 (66.7%)	20 (58.8%)	14 (50.0%)
Weight loss	3 (15.8%)	5 (17.9%)	7 (29.2%)	9 (26.5%)	7 (25.0%)
Patient wish	3 (15.8%)	5 (17.9%)	2 (8.3%)	2 (5.9%)	0
Short bowel syndrome	0	2 (7.1%)	0	0	7 (25.0%)
Promote tolerance for anti-cancer treatment	0	0	1 (4.2%)	4 (11.8%)	3 (10.7%)
Other	8 (42.1%)	7 (25.0%)	10 (41.7%)	12 (35.3%)	10 (35.7%)

GI=gastrointestinal; mGPS=modified Glasgow Prognostic Score; PN=parenteral nutrition, n indicates number of cases.

4 Discussion

The PATNIC-study is to our knowledge the first study examining current practice of PN therapy in patients with incurable cancer in Norway. The study is a multi-centre study and includes two university hospitals and two local hospitals. PN therapy in patients with incurable cancer is subject to debate due to conflicting evidence regarding its risks and benefits. We know little about how PN is administered in this patient group in terms of dosages, duration and survival. This study aimed to describe the current practice of PN therapy in patients with incurable cancer at Haukeland University Hospital in the period 1st of January 2011 to 31st of December 2017. First, the main findings of the study will be presented, followed by discussion of method and results.

4.1.1 Main findings

In total, 133 patients were included. Cancers in the upper GI tract and colorectal cancer were the most common types of cancer and the majority of the population had metastases at PN start. The majority of the patients had suffered from weight loss demonstrating severe malnutrition at PN start. The most common reported indication for PN start was insufficient oral and/or enteral intake followed by GI malfunctions/subileus. Food registrations were conducted in 15 (11.3%) patients at PN start and showed a low intake in all patients, supporting indication of nutritional treatment according to guidelines. Mean (SD) estimated energy requirements was 33 (6) kcal/kg/day. Data on dosages of PN indicates that most of the patients starts on a low dose and that the maximum dose ever received is lower than estimated energy requirements. Some does also have one or more pauses during treatment, resulting in a lower overall dose of PN received. About one-half of the patients receive PN \leq 2 months and 53.4 % of the population survives \leq 3 months. Most of the patients receive PN therapy a few weeks or days from death. Discontinuation of PN was based on expected survival, complications related to treatment and patient wishes related to treatment.

4.2 Discussion of methods

This study is a retrospective medical chart review, where pre-recorded data from patient journals at Haukeland University hospital were collected. Some limitations regarding the study design and methods as well as advantages will be discussed in further detail.

4.2.1 Limitations

4.2.1.1 Incomplete/missing data

The data used in this study were not originally recorded in order to answer the research questions set prior to the study. This implies that the level of documentation and quality of the data is uncertain when using retrospective study design. Some records may be incomplete or lost with time, which may result in missing data in some variables [63, 64]. Initially, we wanted to investigate treatment plans, goals and evaluation of PN among other things, but due to lack of documentation practice and systematic reporting, this was not possible. We also experienced that some variables had more missing data than other variables, e.g., data on food intake at start of PN, ESAS symptom scale, performance status and infusion rates of PN. Lacking data on some of the variables in a patient journal can lead to nonresponse bias, which implies that subjects with missing data may differ systematically from the others [63]. Cases with missing variables were handled by excluding them from the analysis, resulting in a reduced sample size. In our experience, documentation practices on PN treatment vary among health care professionals. Data on PN treatment were available in various amounts in almost all patients in this study, making it possible to describe PN treatment in terms of dosages and duration for this population. However, reporting of PN in terms of doses were not done systematically, and doses were registered both in volume of the prescribed PN dose in millilitres and kcal/day. Nevertheless, in cases where patients were in and out of the hospital and experienced dose adjustments, reduced amounts of PN given due to complications or pauses in treatment, increase the chance of lacking data on PN treatment for some patients. Also, data on PN termination were in some cases non-retrievable in the journal system of the primary health care municipalities due to an updated journal system. The most ideally for data collection of this study would have been a system where information at different health care levels and from different health care providers were available in one platform, making it possible to look at PN treatment at all levels in the health care system.

4.2.1.2 Quality and sources of information

Difficulty in interpreting or verifying documented information and variability in the quality of documentation practices among health care personnel may pose a challenge in retrospective chart reviews [63, 65]. There may also exist a spectrum of data quality in patients' medical journal, depending on different documentation practices [63]. Variables in this study were collected from journals based on free-text format as well as scanned documents into the patient

journals (e.g., patient curve which included data on weight registrations, PN treatment and medications, food registrations). In some cases, we experienced difficulty in interpreting documented information (e.g. interpret handwriting) in the patient journals. The hospital has also been through a transition from medical curves in paper-format to electronic curves. We experienced that it was a lot more efficient to collect information from the patient journals on variables such as medication, PN treatment, actually dose given and type of solution as well as weight registrations, in patients where the use of electronic curves had been implemented. The electronic curves may also give more reliable information, due to the prescriptions are being directly entered to the data programme, which reduces the risk for abstraction bias (e.g., when interpreting handwriting or converting ml of doses to kcal). The chance of different quality of information gathered in this study is present due to the use of different systems of reporting in the medical records.

4.2.1.3 Training of data abstractor

Interpreting data in patient's medical journal and how to enter and code data is challenging and requires training [66]. Training of the data abstractor in terms of how to use and enter data in the Web-CRF was performed prior to data collection. Briefing in the electronic chart system was not done, due to different chart systems at the different study centres. However, the research manual included detailed information on which documents in the patient's journal different variables could be found. The data abstractor was also frequently in contact with the research team when challenges in reporting different variables arose, which is in line with recommendations for conducting a retrospective medical chart review [64].

4.2.1.4 Data abstraction

In this study, we used a web-based case report form and collected data were directly entered the Web-CRF. Direct registration of data into the database reduces "the number of omitted, illegible or mistranscribed entries", which can occur when using paper-based response forms [63]. It is recommended that data abstractors of medical record studies are blinded to the research questions of the study to "decrease subjectivity in classification in relation to personal theories about the study's aims" [63]. Data abstraction was performed by the master candidate, which means that the data abstractor was not blind to the research questions of the study. This may increase the potential for abstraction bias when assigning and interpreting values of certain study variables collected from the medical records [63, 66], and constitutes a limitation. The abstractor's accuracy may increase when the abstractors know that their reliability is being

monitored [66]. Monitoring of the data abstractor is therefore recommended [66]. This study included contact between the research team and data abstractor during the data abstraction period. Monitoring was also performed post data abstraction, which may reduce the risk of systematic errors and thereby ensure good data control [66].

4.2.1.5 Plotting errors and data quality control

The study included many registrations of different variables for each patient and the chance of mistakes in plotting values into the Web-CRF, are present. The chance of plotting error may be increased in cases where the value had to be manually registered, i.e. plotting of values on biological parameters, weight, height, kcal of PN received. We performed a data control in SPSS by testing for outliers in the sample on variables such as blood samples and data on PN duration. Outliers in the data files from the Web-CRF were double-checked towards the journal system and corrected when errors were detected. By doing this, one provides one extra data control and enables to correct for possible punching-errors that may occur during data entering, thereby reducing the risk of systematic bias. Even though we performed one extra data control in SPSS, we cannot exclude the occurrence of other possible punching errors. The chance of plotting errors is present using this study design.

4.2.1.6 Population

It is recommended to use multiple systems to identify patients, as it may help capture all eligible patients for inclusion for the given period, thereby reduce selection bias [66]. However, we did in this study only use one system to identify patients receiving PN therapy: by records of treatment aids for delivering of infusion pump. There might be a chance that patients receiving PN exclusively at the hospital and who were not discharged from the hospital with an infusion pump, were missed during the patient enrolment. However, we still believe that we identified most of the patients by this method. Other methods (e.g., search for diagnosis/codes for diagnoses) probably wouldn't result in better identification of eligible patients, as one is dependent on an infusion pump for PN to be given.

4.2.1.7 Control group

Since there is no obvious way to match a heterogenic palliative population or even to identify them, historical controls were not used. It would have been difficult, or even impossible, to find matching controls with the e.g. same age, gender, diagnosis, anti-cancer treatment, prognosis, degree of malnutrition, performance status to properly match the PN group and we did not have

any list over potential controls. The design used in this study is descriptive and even if we had a control group, we would not be able to conclude on e.g., whether patients survive longer or live better with PN or not.

4.2.2 Advantages

An advantage of using this study design is that it is less resource-intensive, in terms of time consumption as well as it requires less effort compared to prospective studies [64]. It also enables assessment of a large sample at limited cost as well as an easy collection of routinely recorded information [64]. If we were to collect all this data prospectively, it would have taken the same amount of years, as the timeframe we have collected data from (7 years). The study also enables assessment of a large sample at limited cost as well as an easy collection of routinely recorded information [64]. Recall bias for events in the past is and the need for intrusion into patient's time for assessment as a part of the study is minimized, and the design is not prone to losses to follow-up [64]. In the case of this study, we have the opportunity to retrospectively gather information on a treatment in a patient population which is highly debated and which we know little about (e.g., how PN is administered and used in this patient's group). Identification of which patients with incurable cancer receiving PN treatment, what type of cancer diagnosis they have, indication for start of PN treatment as well as dosages and duration of treatment, is valuable information scientists can use when designing studies in future research. The results may also contribute to generating hypotheses to be studied further in more expensive prospective studies.

4.3 Discussion of results

4.3.1 Indication for start of PN

The most frequent indication for start of PN was insufficient oral and/or enteral intake reported in 82 (61.7%). This differs from findings in the systematic review by Tobberud et al. summarizing the effects on PN therapy in patients with advanced cancer, where GI function was reported as the main indication for PN in 79% of the patients [12]. Many of the patients in our study had lost weight the past 4-6 month before PN start, which indicates that they were not able to cover their nutritional needs. The weight loss data may also indicate that nutritional deficits were present at PN start in many of the patients, which is also supported by reported malnutrition diagnosis in 57% of the patients. In general, the ESPEN guidelines recommend EN in patients with insufficient oral intake and intact GI tract [54]. We did not

record if patients had gone through other nutritional interventions during their disease trajectory prior to PN. However, insufficient oral and/or enteral intake may indicate that either oral intake, enteral intake via EN or both are insufficient or not possible. Also, several indications were possible and insufficient oral/enteral intake was often listed together with GI malfunctions. GI malfunctions, subileus and short bowel syndrome were, in total, listed as indications for PN start in 82 (61.7%) of the patients. Patients with GI malfunctions may not be able to cover their energy needs by oral intake or even at all. PN therapy is indicated in patients with incurable cancer with intestinal obstruction if they are expected to die sooner from starvation than from tumour progression [54], and the use of PN seems to be supported by the guidelines in this population. One Swedish observational study of the prevalence and use of EN, PN and intravenous glucose in cancer patients enrolled in specialized palliative care did report eating difficulties and weight loss as the most common indications for PN [67]. Compared to our results, this suggests that insufficient oral intake as an indication for PN is commonly used in clinical practice.

Summarizing the indications for start of PN, the findings suggest that the use of PN in patients with incurable cancer were in line with the guidelines for PN in patients with cancer. However, survival may have an impact on start of PN treatment in these patients and will be further discussed under the section on survival on PN.

4.3.2 Energy requirement and food intake registrations

4.3.2.1 Estimated energy requirements

Energy requirement was estimated at start of PN in 60% of the study population. Method of estimation was not recorded, and both rule of thumb (eg., kcal/kg/day) and equations might have been used. The mean (SD) estimated energy requirement was 33 (6) kcal/kg/day. This is a bit higher compared to the guidelines on nutrition in cancer patient which recommends that total energy expenditure should be assumed to be similar to healthy individuals, ranging from 25-30 kcal/kg/day [22, 54]. Several factors may impact on a patient's resting energy need (REE), including level of systemic inflammation (cachexia), energetic demand of the tumour, presence of metastases and alterations in body composition [68]. For cancer patients undergoing chemotherapy, the variations in REE may be described as a U-shaped curve, independent of cancer type and stage [69]. When estimating energy requirements (e.g., by using Harris-Benedict equation) the risk of over - or underestimating a patient's energy need (by up to 25%)

throughout the treatment period, is present [69]. This constitutes a risk of both under- and overfeeding, which in turn may have undesired metabolic effects [22].

To sum up, the estimation of energy requirements may be difficult due to individual difference and may under- or overestimate the energy requirements of a patient. Based on the data, it seems estimated energy needs in patients with incurable cancer receiving PN are higher than the recommendations [22, 54], which poses a risk for overfeeding, followed by complications, in these patients. Future studies should integrate the use of indirect calorimetry, which is the gold standard of measurement of basal metabolic rate, to accurately tailor the nutritional treatment according to the measured needs of these vulnerable patients with a life-limiting disease [68].

4.3.2.2 Oral food intake

Oral food intake registrations at PN start suggests that patients had an oral intake <60% of their estimated energy needs at start of PN (data not shown), which support the use of insufficient oral/enteral intake as an indication for PN start. Oral food intake was only documented in 15 (11.3%) of the patients at PN start, making a generalization about food intake in this study difficult. However, reduced food intake is common in patients with cancer [23, 70] and patients diagnosed with GI cancers with metastases, may have a reduced oral food intake due to GI-related symptoms affecting the patient's ability to eat [71]. GI malfunction was listed as an indication for start of PN in many of the patients in this study, which may strengthen the assumption of low food intake in the whole population. A patient's food intake may impact what dosages of PN is provided. For future studies on PN therapy, data on food intake prior to treatment as well as during treatment should be integrated, to be able to adjust the dosages of PN according to oral intake as well as have the opportunity to report on the total energy intake in these patients. Several days of food intake registrations might not be appropriate prior to PN in patients with weight loss and who have had an insufficient intake over time, and other retrospective dietary assessment methods may be used. During treatment, food intake registrations may be appropriate.

4.3.3 Administration of parenteral nutrition

4.3.3.1 Administration route and delivery rate

Most of the patients received PN through the central vein, which is the preferred route for infusion of long-term PN. Delivery rates of PN were not routinely recorded in the patient's journal. The median infusion rate during treatment was 100 (80-120) ml/h recorded in 79

(59.4%) patients. The median infusion rate equals 1.6 ml/kg/h when divided on the median weight of the population, and is in line with the recommendations from Fresenius Kabi, saying that the infusion rate should not exceed 2.0 ml/kg/hour for SmofKabiven for central vein, [72]. However, a lack of systematic reporting makes it difficult to conclude on these data.

4.3.3.2 Type of infusion

Cyclical infusions at varies time during the day or night were most frequent. Normally, one may think that PN treatment during night-time is preferred so that the patients do not need to be attached to an infusion pump during daytime. PN infusion during daytime may be more practical at the hospital but may impact on the patient´s freedom to move and do daily activities, due to the physical attachment to the infusion pump during infusion of PN. Patients may also experience it as a burden to be dependent on an infusion pump several hours a day. Nightly infusion may, therefore, be an option. The disadvantages of PN during night-time may be disturbances in sleep due to alarming infusion pump, as well as the need for toilet visits during night due to the fluid PN provides. Most of the patients received PN on a daily basis, but some patients did receive PN every other day or less. PN every other day or less may be convenient for supplemental PN, as it may reduce the total burden of PN treatment due to fewer infusions a week with fewer disturbances during night or day. Since the patient is not bound to an infusion pump daily, this gives him/her the ability to move more freely. This may, in turn, contribute to the maintenance of self-care by reducing these limitations patient´s may experience during PN.

4.3.4 Dosages of PN

4.3.4.1 Start dose

Median start dose of PN treatment in this population was 1000 kcal/day. Based on the subgroups defined by PN start dose, it seems that although some of the patients starts on a lower dose, they have a dose adjustment during treatment and the maximum dose received provides about the same amount of energy compared to patients starting on a higher dose. For the patients with a PN start dose >1500 kcal, we see that they do not increase much from start dose. The median lowest dose received in this group was 1000 kcal (figure 4), indicating that this group have a reduction in the initial dose. Twenty-seven (20.1%) of the patients did not have any dose adjustment from PN start dose. Median start dose for these patients was 1100 kcal. Dose adjustments may say something about a patient´s tolerance to PN treatment. Higher doses might indicate better tolerance to PN, compared to lower doses. There are no standards for dose and volume administration of either PN or simple hydration treatment in palliative care, and such

invasive treatments can cause significant complications such as hepatic dysfunction, electrolyte abnormalities and volume overload [73, 74]. Current guidelines are based on descriptive studies and expert consensus resulting in vague recommendations such as “applications of PN always requires careful weighting of expected individual benefits and risks” [22]. Enhanced evidence of PN tolerance is needed to reduce symptom burden and improve personalized nutritional care for patients with incurable cancer.

Patients who have had an insufficient intake over time may be at risk for refeeding syndrome. “Refeeding syndrome is defined as the potentially fatal shifts in fluid and electrolytes and may occur in severely malnourished patients receiving artificial refeeding” [22]. The National Institute for Health and Care Excellence recommends: “PN should be introduced progressively and closely monitored, usually starting at no more than 50% of estimated needs for the first 24-48 hours” [75]. The median PN start dose in this study was 15 kcal/kg/day and made up approximately 45% of the median estimated energy requirements (data not shown). This was in line with the recommendations.

4.3.4.2 Energy provided by PN compared to estimated energy requirements

With respect to energy intake, guidelines recommend providing 25-30 kcal/kg/day [22, 54]. The median energy provided by the highest PN dose in this study population was 28 kcal/kg/day, which was 5 kcal/kg/day lower than their estimated energy needs, but in line with the recommendations for nutrition in cancer patients [22, 54]. These data on PN dosages indicates that most of the patients receive less than calculated energy needs from PN. For patients with one or more pauses in treatment, the overall dose of PN given is lower. Because of a lack in the documentation of pauses in this study, it is difficult to establish the accurate amount of PN received in patients when including all pauses in treatment. Also, it would have been interesting to look at differences between reasons for indications and amount of PN given across the groups, as one may think that patients with a GI-malfunction may receive higher doses compared to patients able to eat in addition to the PN treatment. One systematic review stated that there is a lack of knowledge regarding the optimal PN treatment in patients with incurable cancer “as the energy requirement and whether these patients have an anabolic potential in response to energy balance is uncertain” [12]. The clinical practice indicates that most of the patients with incurable cancer receive less than estimated energy needs from PN treatment, they have one or more pauses in treatment, and many have an oral food intake in addition to PN treatment.

4.3.5 Duration of parenteral nutrition

The data suggest that duration of PN treatment in patients with incurable cancer varies from a few days to several months, with a median (Q1-Q3) of 44 (18-99) days. The mGPS at PN start was higher in the group receiving PN >2weeks-≤1month compared to patients receiving PN ≤2 weeks (p=0.04). This indicates that mGPS may not have an impact on whether to initiate PN or not in this population since mGPS reflects in a way the degree of malnutrition and can change upon treatment [76]. The distribution of pauses in treatment varied across the groups and indicates that several of the patients have one or more pauses during treatment. Pauses may, as previously mentioned, say something about patient's tolerance to the PN treatment, but may also be caused by catheter-related complications, such as blocked catheters, catheter-related infections (e.g., locally at the injection site or sepsis) and central vein thrombosis [77]. Not surprisingly, there was an association between duration of PN and survival from PN start. Patients receiving PN for a longer period also survive longer. Several factors may impact on survival in cancer patients such as site and stage of cancer disease, patients response to anti-cancer treatment, impaired nutritional status and patient age [54]. The data suggest that palliative cancer patients are a heterogeneous group with different expected survival from the time their cancer cannot be cured.

4.3.6 Reasons for discontinuation of parenteral nutrition

The results suggest that reasons for discontinuation of PN treatment are differentiated among patients with incurable cancer and that over one-third of the population receive PN close up to death. Patient is terminal or has a short/very short expected survival was reported as a reason for discontinuation of PN in 50 (37.6%) of the patients, which indicates that patients receive PN treatment close to death. A patient's condition may change rapidly at this phase of the disease trajectory, and it seems that the practice regarding PN therapy is challenging and far from easy. Complications of PN treatment were reason for discontinuation of PN treatment in 16 (12.0 %) of the patients, indicating that some of the patients do experience complications during treatment. PN is contraindicated if complications and no perceived benefits from treatment occur [54]. Other reasons for discontinuation of PN were patient does no longer benefit from PN or rapidly progressive disease. This may indicate that patients have reached a terminal stage of their disease and will not have any benefit from the treatment. In this phase of the disease, the treatment focus is symptom relief, and according to the guidelines, PN or fluid treatment is not recommended [22, 78]. Patients with incurable cancer will sooner or later

die from their disease, and medical nutrition therapy, such as PN, cannot change this. It is therefore essential to improve the knowledge of when PN is contraindicated and when to terminate treatment where the burden outweighs the benefits.

4.3.7 Survival

The data suggest that survival in patients with incurable cancer receiving PN is heterogeneous and quite varied ranging from a few weeks to several years, and that PN is used in patients with a short survival (1 to 2 months). This is an interesting observation, as PN usually is not indicated if expected survival is less than 1-3 months [22, 78]. This suggests that initiation of PN may not only be based on available evidence [22] alone but that also ethical aspects such as possible physiologic and/or psychological benefits may have an impact on the clinical decision. Active feeding is regarded as essential in some cultures [22]. According to guidelines on ethical aspects of artificial nutrition and hydration, “there are no clear criteria to ascertain the beginning of the dying phase. Therefore, a nutritional intervention in this phase of life should be followed in an individualized manner” [79]. PN may be administered in patients with short survival and withdrawn if no benefits are achieved or complications occur [79]. In cases where GI malfunctions are listed as an indication for treatment, the use of PN in patients with a short survival may be supported. According to guidelines, the risk of PN is regarded to outweigh its benefits for patients with a prognosis of fewer than 2 months [22]. Is there a chance that the nutritional intervention is started too late in the disease trajectory? This study design prevents us from evaluating this aspect. Does the PN improve survival or does it only serve as a burden for the patient? The initiation of PN treatment in patients with short survival and if these patients can take advantage of the nutrition provided are questions for debate and more research is urgently needed.

The mGPS was widely distributed across the groups defined by survival from PN start. This is an interesting observation since mGPS is related to survival and helps stratify prognosis groups [24], suggesting that patients with a short survival from PN start would have a higher mGPS compared to patients surviving longer. The data implies that mGPS might not be appropriate as a prognostic factor regarding PN treatment as the active nutritional treatment given in this study can improve mGPS by increasing albumin levels by amino acid supplementation and reducing CRP by e.g., anti-inflammatory omega 3 fatty acids [22, 23], which is given in quite high doses in PN, and thereby changing the patients prognosis. To our knowledge, no studies have

evaluated the change in this prognostic score by nutritional treatment. This will be evaluated in the whole data set if prospective data on CRP and albumin is available in the PATNIC-study.

5 Conclusion

The overall aim of this study was to describe the current practice of PN therapy in patients with incurable cancer, receiving PN at Haukeland University Hospital, Bergen from 2011-2018.

The most common reported indication for PN start was insufficient oral and/or enteral intake followed by GI malfunctions/subileus. Food registrations was only conducted in 15 patients prior to PN treatment and showed a low oral intake in all patients, supporting indication of nutritional treatment with PN according to guidelines. Estimations of energy needs in patients with incurable cancer receiving PN were higher than the recommendations from the ESPEN guidelines on nutrition in cancer patients, and currently used estimates might lead to overtreatment in patients if fully nourished.

Most of the patients received PN on a daily basis, but some patients did receive PN every other day or less. PN infusion through central vein was most common and most of the patients received PN through cyclical infusions. Median starting dose was approximately 50% lower compared to the estimated energy needs and in line with recommendations for initiation of PN. The median energy provided by the highest PN dose was lower than estimated energy needs and most of the patients received less energy from PN compared to the estimated energy needs. For patients with one or more pauses in PN treatment the overall dose of PN given is lower.

The data suggests that duration of PN treatment in patients with incurable cancer varies from a few days to several months. Survival in patients with incurable cancer receiving PN is heterogenous and quite varied ranging from a few weeks to years. Patients receiving PN for a longer period of time also survive longer. Discontinuation of PN was based on expected survival, complications related to treatment as well as tolerance to PN.

6 Future perspectives

This study provides data on how PN is administered in patients with incurable cancer in terms of dose, duration and termination in clinical practice. Results from this thesis describes how PN treatment is used in palliative care. Future studies should investigate which patients that might have a benefit from PN treatment and who will not. The level of evidence on effects of

PN on clinical outcomes such as health-related QoL, physical function, nutritional status, survival and adverse events is weak, due to few high quality trials [12].

Two ongoing RCTs are currently awaited [38, 80], whereof one investigating supplemental PN at the palliative phase of advanced cancer [38], and one investigating early supplemental PN in metastatic gastric cancer patients at nutritional risk undergoing first-line chemotherapy [80]. In both studies, the control group receive nutrition exclusively by the oral route by counseling and supplements [38, 80]. In both of the studies, the exact dose of PN ordained is not described in the protocol, as PN is adapted according to residual oral intake [38, 80]. In one of the studies, the PN will account for at least 1000 kcal/day and 6 g of nitrogen, on 5 days of 7 [38]. Both studies use estimations of energy needs [38, 80], which is related to uncertainties due to individual differences in REE, and poses a risk of under- or overestimation a patient's requirements.

The primary aim of the ALIM-K study is to evaluate the influence of PN on health-related QoL deterioration free survival of one of the 3 targeted scores of European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 15 Palliative (QLQ-C15-PAL): global health-related QoL, physical functioning and fatigue, and preliminary data was presented at American Society of Clinical Oncology conference 2018 [80]. Trends towards better QoL, physical function and fatigue as well as less adverse events in favor of control arm was reported, and the authors conclude that PN did “not provide clinical benefit for advanced cancer patients with numerically reduced overall survival and increased toxicity” [81].

Reported complications and side effects of modern PN treatment have been low, but have predominantly been reported as catheter-related infections [12]. Treatment is safer as the hygiene protocols have improved and such complications are thus no longer a central concern in PN treatment. Many of the patients do already have inserted central catheters for infusion of chemotherapy and PN does not involve any extra invasive procedures for these patients. However, side-effects such as ascites, oedema and dyspnoea due to high fluid volume administration are understudied but often reported as a concern from clinicians working in palliative cancer care when patients receive higher doses of PN. This indicates that we not only need to know more about effects of PN on survival, physical function and QoL but also symptom burden of various doses as well as patients' actual energy needs in terms of basal metabolic rate.

The recent Lancet oncology commission on integration of oncology and palliative care states that: “To facilitate better patient involvement in cancer care and improved patient-centred outcomes, the patient’s voice must be heard by their medical team during shared decision-making, in terms of symptoms, functions, QoL, and preferences for information provision” [2]. To be able to provide the best nutritional care for patients living with incurable cancer, it is essential to focus on the patient’s perspective in terms of symptom burden, wishes, nutritional needs and doses of PN that are tolerated.

References

1. World Health Organization. Cancer: World Health Organization; 2018 [updated 12.09.2018; cited 2019 21.08]. Available from: <https://www.who.int/news-room/fact-sheets/detail/cancer>.
2. Kaasa S, Loge JH, Aapro M, Albreht T, Anderson R, Bruera E, et al. Integration of oncology and palliative care: a Lancet Oncology Commission. *Lancet Oncol*. 2018;19(11):e588-e653.
3. World Health Organization. Noncommunicable diseases: World Health Organization; [updated 01.06.2018; cited 2019 28.08]. Available from: <https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases>.
4. Cancer Registry of Norway. Cancer in Norway 2018 - Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway; 2019.
5. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours: John Wiley & Sons; 2016.
6. The National Cancer Institute. Advanced cancer: The National Cancer Institute; [29.08.2019]. Available from: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/advanced-cancer>.
7. Cancer Control: Knowledge into Action: WHO Guide for Effective Programmes: Module 5: Palliative Care. Geneva: World Health Organization
Copyright (c) World Health Organization 2007.; 2007.
8. Norwegian Institute of Public Health. Public Health Report: Health Status in Norway 2018. Oslo; 2018.
9. Ferrell BR, Temel JS, Temin S, Alesi ER, Balboni TA, Basch EM, et al. Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2017;35(1):96-112.

10. World Health Organization. Cancer - Palliative Care: WHO definition of Palliative Care: World Health Organization; [cited 2019 21.08]. Available from: <http://www.who.int/cancer/palliative/definition/en/>
11. Howie L, Peppercorn J. Early palliative care in cancer treatment: rationale, evidence and clinical implications. *Ther Adv Med Oncol*. 2013;5(6):318-23.
12. Tobberup R, Thoresen L, Falkmer UG, Yilmaz MK, Solheim TS, Balstad TR. Effects of current parenteral nutrition treatment on health-related quality of life, physical function, nutritional status, survival and adverse events exclusively in patients with advanced cancer: A systematic literature review. *Crit Rev Oncol Hematol*. 2019;139:96-107.
13. Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A. Quality of life of patients with lung cancer. *Onco Targets Ther*. 2016;9:1023-8.
14. Holmenlund K, Sjogren P, Nordly M. Specialized palliative care in advanced cancer: What is the efficacy? A systematic review. *Palliat Support Care*. 2017;15(6):724-40.
15. Zhi WI, Smith TJ. Early integration of palliative care into oncology: evidence, challenges and barriers. *Annals of Palliative Medicine*. 2015;4(3):122-31.
16. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer. *New Engl J Med*. 2010;363(8):733-42.
17. Stene GB, Helbostad JL, Amundsen T, Sorhaug S, Hjelde H, Kaasa S, et al. Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. *Acta Oncologica*. 2015;54(3):340-8.
18. Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. *Am J Clin Nutr*. 2010;91(4):1133s-7s.
19. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011;12(5):489-95.
20. von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. *J Cachexia Sarcopeni*. 2010;1(1):1-5.
21. von Haehling S, Anker SD. Prevalence, incidence and clinical impact of cachexia: facts and numbers-update 2014. *J Cachexia Sarcopeni*. 2014;5(4):261-3.
22. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr*. 2017;36(1):11-48.

23. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. *Clinical Nutrition*. 2017;36(5):1187-96.
24. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. *Cancer Treat Rev*. 2013;39(5):534-40.
25. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. *Nat Rev Clin Oncol*. 2013;10(2):90-9.
26. Fearon KCH, Glass DJ, Guttridge DC. Cancer Cachexia: Mediators, Signaling, and Metabolic Pathways. *Cell Metabolism*. 2012;16(2):153-66.
27. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. *Nat Rev Dis Primers*. 2018;4:17105.
28. Baracos VE. Cancer-associated cachexia and underlying biological mechanisms. *Annu Rev Nutr*. 2006;26:435-61.
29. Jordhoy MS, Fayers P, Loge JH, Saltnes T, Ahlner-Elmqvist M, Kaasa S. Quality of life in advanced cancer patients: the impact of sociodemographic and medical characteristics. *Br J Cancer*. 2001;85(10):1478-85.
30. Jordhoy MS, Inger Ringdal G, Helbostad JL, Oldervoll L, Loge JH, Kaasa S. Assessing physical functioning: a systematic review of quality of life measures developed for use in palliative care. *Palliative Med*. 2007;21(8):673-82.
31. Sorensen JB, Klee M, Palshof T, Hansen HH. Performance status assessment in cancer patients. An inter-observer variability study. *Br J Cancer*. 1993;67(4):773-5.
32. West H, Jin JO. Performance Status in Patients With Cancer. *JAMA Oncology*. 2015;1(7):998-.
33. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma. With particular reference to bronchogenic carcinoma. *Cancer*. 1948;1(4):634-56.
34. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-55.
35. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition – An ESPEN Consensus Statement. *Clinical Nutrition*. 2015;34(3):335-40.

36. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clinical Nutrition*. 2017;36(1):49-64.
37. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. *Clin Nutr*. 2019;38(1):1-9.
38. Pazart L, Cretin E, Grodard G, Cornet C, Mathieu-Nicot F, Bonnetain F, et al. Parenteral nutrition at the palliative phase of advanced cancer: the ALIM-K study protocol for a randomized controlled trial. *Trials*. 2014;15.
39. Guttormsen AB, Helsedirektoratet Avdeling ernæring. Nasjonale faglige retningslinjer for forebygging og behandling av underernæring. Oslo: Helsedirektoratet, Avdeling ernæring; 2009 [cited 2020 02.03]. Available from: <https://www.helsedirektoratet.no/retningslinjer/underernaering/Forebygging%20og%20behandling%20av%20underernæring%20-%20Nasjonal%20faglig%20retningslinje.pdf?download=false>.
40. Sobotka L, Wanten G, Camilo M. Techniques of nutritional support - Parenteral nutrition - Metabolic complications of parenteral nutrition. In: Sobotka L, Allison SP, Forbes A, Ljungqvist O, Meier RF, Soeters PB, editors. *Basics in clinical nutrition*. 4th ed. Prague: Galén; 2011. p. 411-7.
41. Pertkiewicz M, Dudrick SJ. Techniques of nutritional support - Parenteral nutrition - Different systems for parenteral nutrition (AIO vs. MB). In: Sobotka L, Allison SP, Forbes A, Ljungqvist O, Meier RF, Soeters PB, editors. *Basics in clinical nutrition*. 4th ed. Prague: Galén; 2011. p. 370-2.
42. Hellerman Itzhaki M, Singer P. Advances in Medical Nutrition Therapy: Parenteral Nutrition. *Nutrients*. 2020;12(3).
43. Staun M, Pironi L, Bozzetti F, Baxter J, Forbes A, Joly F, et al. ESPEN Guidelines on Parenteral Nutrition: home parenteral nutrition (HPN) in adult patients. *Clin Nutr*. 2009;28(4):467-79.
44. Pertkiewicz M, Szczygieł B, Sobotka L, Dudrick SJ. Techniques of nutritional support - Parenteral Nutrition - Composition of nutritional admixtures and formulas for parenteral nutrition. In: Sobotka L, Allison SP, Forbes A, Ljungqvist O, Meier R, Pertkiewicz M, et al., editors. *Basics in clinical nutrition*. 4th ed. Prague: Galén; 2011. p. 400-10.

45. Carpentier Y, Sobotka L, Soeters P. Substrates used in Parenteral and Enteral Nutrition - Carbohydrates. In: Sobotka L, Allison SP, Forbes A, Ljungqvist O, Meier RF, Soeters PB, editors. Basics in clinical nutrition. 4th ed. Prague: Galén; 2011. p. 252-7.
46. Carpentier Y, Sobotka L. Substrates used in Parenteral and Enteral Nutrition - Energy. In: Sobotka L, Allison SP, Forbes A, Ljungqvist O, Meier RF, Soeters PB, editors. Basics in clinical nutrition. 4th ed. Prague: Galén; 2011. p. 247-52.
47. Carpentier Y, Sobotka L. Substrates used in Parenteral and Enteral Nutrition - Lipids. In: Sobotka L, Allison SP, Forbes A, Ljungqvist O, Meier RF, Soeters PB, editors. Basics in clinical nutrition. 4th ed. Prague: Galén; 2011. p. 257-61.
48. Fell GL, Nandivada P, Gura KM, Puder M. Intravenous Lipid Emulsions in Parenteral Nutrition. *Adv Nutr.* 2015;6(5):600-10.
49. Wanten GJ, Calder PC. Immune modulation by parenteral lipid emulsions. *Am J Clin Nutr.* 2007;85(5):1171-84.
50. Jones CJ, Calder PC. Influence of different intravenous lipid emulsions on fatty acid status and laboratory and clinical outcomes in adult patients receiving home parenteral nutrition: A systematic review. *Clinical Nutrition.* 2018;37(1):285-91.
51. Sriram K, Lonchyna VA. Micronutrient supplementation in adult nutrition therapy: practical considerations. *JPEN J Parenter Enteral Nutr.* 2009;33(5):548-62.
52. Vanek VW, Borum P, Buchman A, Fessler TA, Howard L, Jeejeebhoy K, et al. A.S.P.E.N. position paper: recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. *Nutr Clin Pract.* 2012;27(4):440-91.
53. Mitchell J, Jatoi A. Parenteral Nutrition in Patients With Advanced Cancer: Merging Perspectives From the Patient and Healthcare Provider. *Seminars in Oncology.* 2011;38(3):439-42.
54. Bozzetti F, Arends J, Lundholm K, Micklewright A, Zurcher G, Muscaritoli M. ESPEN Guidelines on Parenteral Nutrition: Non-surgical oncology. *Clinical Nutrition.* 2009;28(4):445-54.
55. McGeer AJ, Detsky AS, O'Rourke K. Parenteral nutrition in cancer patients undergoing chemotherapy: a meta-analysis. *Nutrition.* 1990;6(3):233-40.
56. Haukeland University Hospital. About the hospital: Haukeland University Hospital; [updated 06.08.2019; cited 2020 17.04]. Available from: <https://helse-bergen.no/en/about-the-hospital>.

57. Haukeland University Hospital. Research: Haukeland University Hospital,; [updated 20.03.2020; cited 2020 19.04]. Available from: <https://helse-bergen.no/en/research#clinical-trials-for-industry>.
58. WMA. Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects 64th WMA Association October 2013 11.09.2019. Available from: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>.
59. Staunton C, Slokenberga S, Mascalonzi D. The GDPR and the research exemption: considerations on the necessary safeguards for research biobanks. *Eur J Hum Genet.* 2019;27(8):1159-67.
60. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-83.
61. Bruera E, Kuehn N, Miller MJ, Selmsler P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care.* 1991;7(2):6-9.
62. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc EWG. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr.* 2003;22(3):321-36.
63. Worster A, Haines T. Advanced statistics: Understanding medical record review (MRR) studies. *Academic Emergency Medicine.* 2004;11(2):187-92.
64. Sarkar S, Seshadri D. Conducting record review studies in clinical practice. *J Clin Diagn Res.* 2014;8(9):JG01-4.
65. Gregory KE, Radovinsky L. Research strategies that result in optimal data collection from the patient medical record. *Appl Nurs Res.* 2012;25(2):108-16.
66. Kaji AH, Schriger D, Green S. Looking Through the Retrospectroscope: Reducing Bias in Emergency Medicine Chart Review Studies. *Ann Emerg Med.* 2014;64(3):292-8.
67. Orrevall Y, Tishelman C, Permert J, Lundstrom S. A National Observational Study of the Prevalence and Use of Enteral Tube Feeding, Parenteral Nutrition and Intravenous Glucose in Cancer Patients Enrolled in Specialized Palliative Care. *Nutrients.* 2013;5(1):267-82.
68. Purcell SA, Elliott SA, Baracos VE, Chu QSC, Sawyer MB, Mourtzakis M, et al. Accuracy of Resting Energy Expenditure Predictive Equations in Patients With Cancer. *Nutr Clin Pract.* 2019;34(6):922-34.

69. Van Soom T, El Bakkali S, Gebruers N, Verbelen H, Tjalma W, van Breda E. The effects of chemotherapy on energy metabolic aspects in cancer patients: A systematic review. *Clin Nutr.* 2019.
70. Martin L, Kubrak C. How much does reduced food intake contribute to cancer-associated weight loss? *Curr Opin Support Pa.* 2018;12(4):410-9.
71. Virizuela JA, Cambor-Alvarez M, Luengo-Perez LM, Grande E, Alvarez-Hernandez J, Sendros-Madrono MJ, et al. Nutritional support and parenteral nutrition in cancer patients: an expert consensus report. *Clinical & Translational Oncology.* 2018;20(5):619-29.
72. Fresenius Kabi. Innholds- og tilsetningsguide Smofkabiven: Fresenius Kabi; [updated 03.2020; cited 2020 07.05]. Available from: https://www.fresenius-kabi.com/no/documents/SmofKabiven_Innholds-og-tilsetningsguide.pdf.
73. Bruera E, Hui D, Dalal S, Torres-Vigil I, Trumble J, Roosth J, et al. Parenteral hydration in patients with advanced cancer: a multicenter, double-blind, placebo-controlled randomized trial. *J Clin Oncol.* 2013;31(1):111-8.
74. Hui D, Dev R, Bruera E. The last days of life: symptom burden and impact on nutrition and hydration in cancer patients. *Curr Opin Support Palliat Care.* 2015;9(4):346-54.
75. National Collaborating Centre for Acute Care. National Institute for Health and Clinical Excellence: Guidance. London: National Collaborating Centre for Acute Care (UK) National Collaborating Centre for Acute Care.; 2006. Available from: <https://www.nice.org.uk/guidance/cg32/resources/nutrition-support-for-adults-oral-nutrition-support-enteral-tube-feeding-and-parenteral-nutrition-pdf-975383198917>.
76. Chang P-H, Wang C-H, Chen EY-C, Yang S-W, Chou W-C, Hsieh JC-H, et al. Glasgow prognostic score after concurrent chemoradiotherapy is a prognostic factor in advanced head and neck cancer. *Chin J Cancer Res.* 2017;29(3):172-8.
77. Sobocki J, Sitges-Serra A, Dudrick SJ. Techniques of nutritional support - Parenteral nutrition - Complications associated with central venous catheter insertion and care. In: Sobotka L, Allison SP, Forbes A, Ljungqvist O, Meier RF, Soeters PB, editors. *Basics in clinical nutrition.* 4th ed. Prague: Galén; 2019. p. 411-7.
78. Aass N, Haugen DF, Rosland JH, Jordhøy M, Dønnem T, Knudsen AK. Nasjonalt handlingsprogram for palliasjon i kreftomsorgen. Oslo: Helsedirektoratet; 2015.
79. Druml C, Ballmer PE, Druml W, Oehmichen F, Shenkin A, Singer P, et al. ESPEN guideline on ethical aspects of artificial nutrition and hydration. *Clin Nutr.* 2016;35(3):545-56.

80. Caccialanza R, Cereda E, Klersy C, Brugnatelli S, Borioli V, Ferrari A, et al. Early intravenous administration of nutritional support (IVANS) in metastatic gastric cancer patients at nutritional risk, undergoing first-line chemotherapy: study protocol of a pragmatic, randomized, multicenter, clinical trial. *Therapeutic advances in medical oncology*. 2020;12:1758835919890281.
81. Bouleuc C, Anota A, Cornet C, Grodard G, Vuillemin AT, Pazart L, et al. Multicenter randomized controlled trial for advanced cancer patients receiving parenteral nutrition (PN) versus oral feeding (OF): Results of AlimK study. *Journal of Clinical Oncology*. 2018;36(15_suppl):10029-.

Appendices

- Appendix 1: Approval from REC
- Appendix 2: Collaboration agreement
- Appendix 3: Data collection manual