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Human Development and Health

Home Parenteral Nutrition Therapy for Patients with Incurable Malignancy and Intestinal Failure

by

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ABSTRACT

In the UK, the prevalence of home parenteral nutrition (HPN) for patients with incurable palliative malignancy has historically been lower than countries with comparable health economies, but there is evidence to suggest a significant increase in the prevalence within the UK. Despite this increase, there has been lack of clarity regarding patient survival and quality of life, optimisation of patient selection and associated health economics.

This thesis examined the complex issues involved in the use of HPN for Intestinal Failure in the palliative phase of malignancy deriving information from: a systematic review of the existing medical literature on these topics; novel data generated through meta-analysis of survival data; a national questionnaire of clinician's attitudes to PN use in this context; analysis of a retrospective case series from University Hospital Southampton; identification of patient factors which effect survival; validation of newly developed survival prognostic tools; and a health economic assessment of this therapy.

Meta-analysis of survival data for palliative malignancy patients treated with HPN showed that survival was short, 55% and 74% mortality at 3- and 6-months respectively, with only 2% of patients alive at one year. There were insufficient and poor quality data on quality of life (QoL), although the available data indicate a probable positive impact of HPN treatment in this highly symptomatic patient group. The attitudes of UK based IF clinicians are increasingly positive towards HPN therapy for palliative malignancy, with an emphasis of treatment for improving QoL. Patient performance status at commencement of HPN is the best predictor of survival. Newly developed survival prognostication tools lack sensitivity and specificity. The cost of HPN treatment in the palliative malignancy patient group is high, with low cost effectiveness (£176,587 per quality adjusted life year), although comparable to HPN treatment for non-malignancy patients.

The cost effectiveness dramatically improves when patient selection favours better performance status with consequent longer survival, at a higher QoL.

The results presented in this thesis provide clinically relevant information that can help with informed decision making by clinicians and patients when considering commencing HPN therapy during the palliative phase of malignant disease. This thesis also presents the first health economic assessment of this treatment, which can aid commissionaires when planning funding of services to meet the increasing demands for this treatment.

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DECLARATION OF AUTHORSHIP

I, Mani Naghibi, declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

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I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. Parts of this work have been published

Signed: .....

Date: .....

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List of published works based on thesis

Peer reviewed journal publications

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International meeting oral presentations

- Tripartite conference, Birmingham, June 2014: Naghibi M, Leach Z, King A, Smith T and Stroud M. 'Home parenteral nutrition in the palliative phase of colorectal cancer? A tool to predict survival length'

National meeting oral presentations

- British Association of Parenteral and Enteral Nutrition Conference, Brighton, Oct 2016: Oke S, Ismail D, Stroud M, Smith T, Gabe S, Naghibi M. 'Application of a survival nomogram for palliative cancer patients on home parenteral nutrition: is it valid?'
- British Association of Parenteral and Enteral Nutrition Conference, Harrogate, Oct 2014: Naghibi M, Leach Z, Stroud M and Smith T. 'Home parenteral nutrition treatment during the palliative phase of malignancy – A UK single centre case series with analysis of survival prediction tools'
- British Society of Gastroenterology Conference, Manchester, June 2014: Naghibi M, Leach Z, King A, Smith T and Stroud M. 'Survival of patients with palliative inoperable gastrointestinal obstruction due to malignancy treated with home parenteral nutrition'

International meeting poster presentations

- European Society of Parenteral and Enteral Nutrition Conference, Vienna, 2016: Oke S, Ismail D, Stroud M, Smith T, Gabe S, Naghibi M. 'Application of a survival nomogram for palliative cancer patients on home parenteral nutrition: is it valid?'

National meeting poster presentations

- (Poster of distinction) British Association of Parenteral and Enteral Nutrition Conference, Harrogate, Oct 2014: Naghibi M, Smith and Elia M. 'Home parenteral nutrition treatment during the palliative phase of malignancy – A systematic review and meta-analysis of survival length in patients with inoperable bowel obstruction'
- (Poster of distinction) British Association of Parenteral and Enteral Nutrition Conference, Harrogate, Oct 2014: Naghibi M, Stroud M and Stroud M. 'Home parenteral nutrition treatment during the palliative phase of malignancy – A UK based survey of attitudes'

Abbreviations

ASPEN	American Society of Parenteral and Enteral Nutrition
BANS	British Artificial Nutrition Survey
BO	Bowel obstruction
CASP	Critical Appraisals Skills Program
CPS	Clinician prognostication score
CVC	Central venous catheter
CVC-BSI	Central venous catheter blood stream infection
ESPEN	European Society of Parenteral and Enteral Nutrition
FFNCC	French Federation of National Cancer Centres
HPN	Home parenteral nutrition
IBO	Inoperable bowel obstruction
ICER	Incremental cost effectiveness ratio
IF	Intestinal failure
IFU	Intestinal Failure Unit
JAMA	Journal of the American Medical Association
KPS	Karnofsky performance status
NHS	National Health System
PN	Parenteral nutrition

QALY	Quality adjusted life years
QoL	Quality of life
SBO	Small bowel obstruction
UHS	University Hospital Southampton
UK	United Kingdom
WHO	World Health Association
WWII	World War II

Chapter 1 - Introduction and Background

This thesis investigates the challenges and uncertainties that face the use of medium to longer term parenteral nutrition (PN) to prolong life or improve quality of life for patients with incurable malignancy.

1.1 Definitions

In this thesis the terms 'incurable malignancy' and 'palliative malignancy' refer to the malignant disease process that is not amenable to curative treatment, without implication of the patient's potential survival length. These term are often used interchangeably within clinical practice and in the medical literature.

Although, the term 'palliative' is not clearly defined in the medical literature, 'palliative care' is defined by the World Health Organisation (WHO) as "the approach that improves the quality of life of patients and their families, facing the problems associated with life-threatening illness, through the prevention and treatment of pain and other problems, physical, psychosocial and spiritual" (1).

PN is a treatment whereby macronutrients (amino acids, proteins, carbohydrates and fats), electrolytes, micronutrients (vitamins and trace elements) and hydration are supplied by means of a venous catheter device directly into the blood circulation. This high burden therapy carries a significant risk to the patient, hence this treatment is reserved for complete or supplemental nutrition for patients with inadequate oral or enteral nutrition intake, which is termed 'intestinal failure' (IF).

The definition of IF has developed since it was first coined by Fleming and Remington in 1981 as 'a reduction in the functioning gut mass below the minimal amount necessary for adequate digestion and absorption of food' (2). This definition has been refined to account for hydration, electrolytes, distinction between macro- and micronutrients and requirement for artificial supplementation. Most recently, in 2015, IF has been defined by the European Society of

Parenteral and Enteral Nutrition (ESPEN) as 'the reduction of alimentary tract function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth' (3).

Different classifications of IF have been proposed based on clinical presentation, aetiology, requirements and anatomy. Nightingale and Woodward proposed severe, moderate and mild IF depending on supplemental requirements of intravenous, enteral and oral, respectively (4). The classification most commonly used in current practice is based on the clinical presentation proposed by Shaffer in 2002 (5), sub-dividing in to three types:

- Type 1 IF - self-limiting intestinal failure as occurs following abdominal surgery
- Type 2 IF - occurring in severely ill patients with major resections of the bowel and septic, metabolic and nutritional complications requiring multidisciplinary intervention with metabolic and nutritional support to permit recovery
- Type 3 IF - chronic intestinal failure requiring long-term nutritional support

This classification has the advantage of encapsulating the likely immediate clinical stability, eventual clinical outcomes and length of parenteral support requirement in a simple and reproducible model. When IF is caused by malignant disease, this same classification can be used.

1.2 History of PN

The history of discoveries leading to the provision of safe and effective PN in the 20th century can be traced back to the landmark description of the relationship between arteries, veins and the heart by William Harvey in 1616, which led to pioneering intravenous experiments.

The first published study into the effects of intravenously administered compounds was carried out by Christopher Wren in 1658 (6), noting the effects of intravenous wine, ale and opium on dogs. Wren observed that the effects were similar when compared to oral ingestion. Over the next few decades many different infusates including vinegar, salts, blood and urine were experimented with varying success in animals and humans.

Courten, in 1678, noted that the infusion of olive oil intravenously led to fatal respiratory distress in dogs, leading to the conclusion that the alimentary tract altered these fats through digestion before entry into the blood circulation. Latta in 1831, achieved short term success in the treatment of Cholera using 'copious' volumes of intravenous salty water, but the mortality remained high due to haemolysis induced by non-physiological electrolyte concentrations (7).

The use of intravenous salt with appropriate electrolytes was shown to be effective in the treatment of shock by Landerer in 1887, with further evidence of efficacy in post-operative use of intravenous sucrose by Kausch in 1911. Based on the extensive basic science work on amino acids by Rose and Elman in the 1930s and 1940s, coupled with unprecedented technological advances triggered by World War II (WWII), the groundwork was set for the breakthroughs that were made in the field of artificial nutrition in the proceeding 50 years (7). In 1968, Dudrick et al, published the results of exclusive intravenous feeding of six beagle puppies for up to 6 months, showing comparable growth to matched littermates fed on conventional oral feed (8), followed by the first human supported for 44 days exclusively on intravenous nutrition by Wilmore and Dudrick in 1968 (9), which was in an infant with atresia of the entire small bowel.

The natural progression for this long-term hospital based treatment for a chronic disease was to develop the technique to allow safe long-term use at home, eventually termed Home Parenteral

Nutrition (HPN). Improvements in central venous catheter devices, asepsis, intravenous nutrient mixtures and, in many developed countries, a sophisticated network of community services that support patients have led to widespread access to HPN in many parts of the world.

1.3 Malignancy, nutrition and cachexia

Involuntary weight loss can often be the first symptom of a disease process in patients with malignancy. Depending on the site of malignancy, between 31-87% of patients have involuntary weight loss (10-13). In pancreatic malignancy, it has been shown that 85% of patients have weight loss at diagnosis, with 30% displaying severe weight loss of greater than 10% in the preceding 6 months (10).

Weight loss correlates with the stage of the malignancy, as well as the clinical outcome (14). Malnourished malignancy patients have been shown to have a poorer response to medical oncology treatments (15-17). There is also evidence that malnutrition also negatively influences length of hospital stay, readmission rates, symptom burden and quality of life in malignancy patients (18).

The causes of weight loss in patients with malignancy vary by the primary site and metabolic activity of the tumour, but common themes are reduced intake through inflammatory and cytokine driven loss of appetite (19-21) or obstructed gastrointestinal tract, increased resting energy expenditure in some cancers (22-24), insulin resistance leading to increased gluconeogenesis (25) and lipolysis (26, 27).

Cancer cachexia is the term used for ongoing weight loss despite supply of nutrients via the natural or artificial routes. This is a complex multifactorial syndrome that leads to progressive functional impairment (28).

The pathophysiology of cancer cachexia is characterised by reduced food intake and abnormal metabolism. The hallmarks are anorexia, early satiety, weight loss, muscle wasting, anaemia and in the late stages, oedema. The definition of cachexia overlaps with other diagnosis such as simple starvation, sarcopenia and malnutrition, but can be distinguished from them as cachexia is always caused by the presence of a disease process, which may be benign or malignant.

The current understanding of cancer cachexia suggests that the syndrome can be classified into pre-, peri- and refractory cachexia (28). Unlike malnutrition, the supply of additional nutrients through oral or artificial routes is not sufficient to reverse the progression of cachexia. To combat the progression of cachexia to the refractory stage early supplementation of nutrition need to be combined with therapies that can slow or stop the metabolic process contributing to its development.

We are in the early stages of understanding cancer cachexia metabolic pathways. It is apparent that the pathways are numerous and highly variable between tumours, even within tumour sites. One key clinical feature of cancer cachexia in some malignant disorders is the higher patient resting energy expenditure, above and beyond the direct effect of tumour mass (29). This has been linked to higher thermogenesis by increasing abundance of brown fat cells. In a murine lung cancer model tumour derived parathyroid hormone related protein (PTHrp) was shown to stimulate the conversion of white to brown fat cells, leading to greater resting energy expenditure. Blocking this PTHrp action halted this conversion and reduced muscle loss, with resultant improved functional status (29). Further studies have shown that substrates produced directly by cancer cells interact through phosphoinositide 3-kinase (PI3K) cell membrane signalling pathway of host muscle cells to down regulate growth through cycle progression and protein synthesis, leading to loss of muscle mass (30). These findings reveal potential sites for therapeutic agents in future, which can be used in combination with nutrient supply to combat cancer cachexia.

Additionally, many tumours are known to induce inflammation causing peripheral and centrally mediated catabolism and appetite suppression, with stepwise reduction in survival length in those with higher markers of inflammation (31). A systematic review of non-steroidal anti-inflammatory drugs (NSAIDs) and cancer cachexia, identified 11 out of 13 trials demonstrating stabilisation in weight or lean body mass where NSAIDs were used, though the studies were small with the risk of false positives (32).

These findings suggest that we may be able to manipulate the processes leading to weight loss associated with malignancy, with potential for effective utilisation of nutrient intake to positively influence clinical outcomes including response to anti-cancer medical and surgical treatments.

The ability to alter the type of nutrition supplied to cancer patients may also play a role in improving their utilisation of nutrients. Waterhouse and Kemperman in 1969 (33) demonstrated that fat is metabolised more efficiently than carbohydrates in cancer patients. The mechanism for this may be the increased reliance on mobilisation of fatty acids from fat deposits as the major source of energy in any semi-starved state. A number of further studies also observed the effective fat metabolism in malignancy patients (34-37). For example, the lipid clearance, after the administration of short chain and medium chain triglycerides, has been shown to be more effective in malignancy patients compared to healthy controls (36).

The potential effects on the immune system of fat based nutrition may also suggest advantages over carbohydrate predominant infusions. The effects of eicosapentaenoic acid (EPA) (C20:5n3), an omega-3 fatty acid, has been studied in vitro human cancer cells with potential benefits observed in increased apoptosis (38-40), inhibition of cancer cell invasion (41) and reduced cancer cell proliferation (42, 43). In vivo studies have shown the use of EPA reduces tumour microvascular density, probably through reduced vascular endothelial growth factor (VEGF), resulting in tumour growth deceleration (44).

The use of EPA in human malignancy patient studies has produced contradictory results, especially when used in isolation as the therapeutic agent. In the randomised trial by Fearon et al (45), 518 GI and lung cancer patients were randomised to control, 2g and 4g of oral EPA per day (standard western diet contains only 0.1g of EPA). In this study, no significant clinical benefit was observed in weight or lean body mass at 4 or 8 weeks in either treatment group. Only a modest 7% improvement in physical function in the 2g of oral EPA per day group compared to placebo was observed, with no significant effect for the 4g of oral EPA per day group.

When EPA was used in a multimodal trial, reflecting the multiple mechanisms contributing to cancer cachexia, the results were more promising. Kassa et al combined orally supplemented EPA with NSAIDs and physical exercise for incurable pancreatic and lung cancer patients. The preliminary results suggest improvement in weight in the treatment group (abstract 2016, personal communication, Ken Fearon, FRANC conference 2016).

1.4 Malignancy and PN

For patients with malignant disease the principle for use of PN for nutritional support is unchanged. When the preferred oral route for nutrition fails, the enteral route is used and finally parenteral feeding can be considered if provision by other routes is inadequate.

The journey of cancer patients after diagnosis will often involve a combination of either medical and/or surgical treatments. If cure is not achieved or is not achievable, the supportive palliative phase of treatment is instigated. At each of these stages there may be a role for short or long term nutritional support, which may involve parenteral support.

It is well documented in both benign and malignant conditions pre-operative inadequate nutrition leads to higher mortality, infections, length of stay and overall costs (46, 47). This was shown in a cohort of gastric and colorectal cancer in the study by Von Meyerfeldt (48). In this study 200 cancer patients were randomised pre-operatively to four different groups. Group 1, malnourished treated with PN; group 2, malnourished treated with EN; group 3, malnourished with no nutrition intervention and group 4, not malnourished with no nutrition intervention. The post-operative complications were the same for all four groups, suggestive that nutritional interventions were not of benefit. However, subgroup analysis showed improved outcomes when treated with EN or PN, only in those with significant malnutrition in groups 1 and 2 (weight loss of greater than 10% or BMI <19 with greater than 5 days of poor nutrition). This demonstrates that the use of PN for patients with malignancy is the same as those with benign disease and should be reserved for significant malnutrition when the oral and enteral route nutrition has failed.

In the 2009 ESPEN guidelines (18) the use of PN in the palliative phase of malignant disease can be utilised in two broad patient groups: those with severe and intractable IF as their main route of nutrition, and those receiving HPN as supplementation to existing oral and enteral routes. The degree of reliance and requirement on PN in the supplemental group is variable and often unclear in the literature.

When HPN was first attempted in the early 1970s, it was initially reserved for patients with severe, benign, life threatening IF, such as short bowel syndrome. Patients were selected if their disease was coupled with favourable physiology to cope with the burden of this treatment at home. As experience has grown with the use of HPN, the boundaries of possible indications and baseline physiology for HPN are being challenged, along with the use of HPN for incurable malignant conditions.

Over the last three decades the ethical issues surrounding HPN therapy for patients with palliative malignancy has become more acceptable in many parts of the world. This is reflected in the increasing use of HPN for this patient group. Due to the large number of all malignancy patients, the economic challenge will be that even a small increase in the percentage of all malignancy patients receiving HPN would represent a large increase in the total HPN population.

In 2015 the period prevalence of all HPN patients in the UK has been approximately at 2,350 (49). This represents a yearly prevalence rate of 40 per million in the UK compared to Denmark (80 per million, year 2017) (50), Italy (50 per million, year 2017) (51) and Canada (12 per million, year 2006) (52). Data reported to British Artificial Nutrition Survey (BANS) shows that 25% of new HPN registrations in the UK are for palliative malignancy, which is a significant increase from a previous prevalence of 8-10% (49). This translates to represent 105-116 new palliative cancer patients registered with BANS per year between 2013 and 2015 (49). Given cancer is the second most common cause for death in the UK (53), this still represents a small number of patients nationally, especially when considered in the context of total national cancer prevalence. In 2013 in the UK, there were 350,000 new cases of cancer, leading to 160,000 deaths, accounting for 26% of all deaths (53).

In the UK the two cancers that are most likely to cause IF and potentially require HPN in the palliative phase are bowel and gynaecology. The Cancer Research UK data report bowel cancer rates as those including small and large bowel, but these do not including oesophageal and stomach, which are reported separately. In 2013, bowel and gyaecological cancers alone

accounted for 41,000 and 16,000 cases, respectively. This led to 16,000 and 8,000 cancer deaths, respectively (53).

The cause of IF related to malignancy is most commonly bowel obstruction (BO), followed by fistulation, short bowel resulting from surgery, infarction or dysmotility. BO is estimated to occur in 10 - 28% of colorectal cancers and 5 - 50% of ovarian cancers (54). This would suggest 4,100 - 11,500 colorectal and 1,600 – 8,000 ovarian cancer BO cases per year in the UK. Although the BO may not lead to type 3 IF at first presentation (as surgical, oncological or radiological treatments may initially be effective), there is a significant proportion of patients where the BO reoccurs and type 3 IF is established (55-57).

When type3 IF occurs in the context of palliative malignancy, the life expectancy of the patient is dramatically reduced. Without parenteral support the immediate cause of death would be dehydration rather than tumour progression or, if hydration is maintained, malnutrition. Nevertheless, in the majority of such cases optimal palliative care without commencement of PN would be the most appropriate intervention. Commencement of risky, expensive and burdensome PN would be neither ethical nor acceptable to the patient. The challenge is, therefore, to optimally select patients with end stage malignancy in whom the benefits outweigh the disadvantages of treatment. However, the proportion of patients suitable for HPN treatment in the end stage of malignancy is unknown but based on the overall numbers of IF cases in malignancy described above, there is a potential to over stretch current HPN service capacity, with a significant health economic burden.

Advocates for the use of palliative HPN in malignancy argue that it can extend survival and facilitate other modalities of treatment such as palliative chemoradiotherapy. Others, however, argue that the treatment is expensive, with a high burden and unknown effects on quality of life for patients and family members during an already limited survival length. Reliable data are therefore needed on the potential length of survival and quality of life for patients with IF in the context of incurable cancer treated with HPN.

Given current knowledge on the safety of HPN and its clear life extending advantages when used on cancer patients with complete IF, it would be unethical to conduct experimental clinical trails with controls randomized to non-PN treatment (18). Whilst conversely, if supplemental PN (i.e. its administration in addition to oral/enteral nutrient intake) were used in individuals without complete IF, it could be argued that it is unethical to expose patients to the risk of PN at all. The survival advantage of HPN therapy in incurable malignancy patients must therefore be inferred from observational cohort studies rather than controlled trials and as a result, current data on survival length and quality of life in this patient group are inconsistent and variable, so consequent clinical decision making is very difficult.

Furthermore, health systems such as the National Health Service (NHS) in the UK that function in a resource limited economy need to consider the cost of therapies. Resources need to be managed to allow the greatest benefit to society. To allow comparison of different treatments economic units such as cost per quality adjusted life years (QALY) have been used. HPN use for benign indications has been subjected to this economic assessment, but its use for incurable cancer is yet to be assessed.

In addition to the cost, to be able to appreciate the scale of the economic burden posed by this treatment, an understanding of the prevalence for use of HPN in patients with palliative malignancy is also needed. This raises a challenge caused by a number of factors, such as incomplete reporting of HPN indications to national or regional databases as well as mixed reporting of both malignancy and benign patient groups. Furthermore, even within the malignant PN patient grouping, there are three distinct sub-groups, which are not always distinguished from each other: short-term PN support during radical therapy; HPN for ‘cured’ malignancy with subsequent IF caused by radical therapies; and long-term PN during the palliative phase of illness.

1.5 PN and 'feeding the tumour'

Some concerns have been expressed that nutrients supplied by PN could adversely influence the clinical outcome of patients by feeding tumour growth and therefore hasten death or reduce efficacy of anti-cancer treatments, even in the palliative phase of malignancy.

There is contradictory evidence on this, with animal models suggesting tumour growth but human studies have not suggested clinical relevance for survival length (18, 58).

Animal models have shown that tumour growth accelerates in periods of nutrition repletion (59-61), and tumour growth is retarded in periods of protein-calorie depletion (62, 63), but there is unease about drawing conclusions to apply to human tumour states. The relative weight of tumour to animal ratio, is significantly higher in animal studies, as high as 1:5, while this rarely exceeds 1:100 in humans (18). The relative period of feeding in the natural history of the tumour also tends to be far longer in animal models and the rate of tumour growth is faster by up to 20 times (64).

If tumour turnover is stimulated by PN, it might also provide an opportunity for treatment. Many chemotherapy agents target the cell cycle in the S-phase (DNA replicating) and the M-phase (mitosis). PN induced increases in proliferation rates of cells could therefore increase chemotherapy exposure of S- and M-phases of the cycle and hence improve effectiveness. The improved anti-tumour effects of chemotherapy during tumour stimulation by PN were reported in a rat model by Torosian et al (61, 65, 66).

There is, however, no consensus in studies of human tumour cell proliferation and in a review by Bossola et al in 2011 (58), 11 human studies were identified in which PN was given for between 5 and 18 days, with 6 reporting increased tumour growth and 5 no effect. Two studies, reporting PN stimulating proliferation, also reported the inhibition of proliferation by the concurrent use of chemotherapy.

In the study of Jin et al (67) 92 patients with operable gastric cancer and malnutrition were randomised into four groups: PN alone; PN and chemotherapy (PNCT); chemotherapy alone; and control with neither PN or chemotherapy. The PN alone group showed greater proliferation, with higher proportion of cells in S-phase, while the PNCT group did not show this trend (though a non-significant increase was observed). This suggests that the proliferation stimulated by PN was combated by the chemotherapy, suggesting a favourable result with PNCT. Survival differences were not described, but the nutritional status of the PN patients, with or without chemotherapy, was improved.

The clinical relevance of potential cell proliferation, due to PN, would be on survival but few studies allow this comparison to be made, as most are retrospective and non-controlled. Furthermore, in many cases intestinal failure induced malnutrition would always be a significant cause of death in the non-PN group.

The most clinically relevant study is the work of Lundholm et al (68), where 309 patients with incurable solid organ tumours where randomised to two groups: a treatment group who received indomethacin, erythropoietin (EPO) (as required to maintain normal haemoglobin) and nutrition (oral supplements, unless <90% achieved, in which case supplemental HPN was used until premorbid or patient's wishes to stop, EN not used); and a control group who received the same indomethacin and EPO protocol, but without any nutritional support. Of the 139 patients in the treatment group, approximately 50% received HPN for a mean duration of 46 days (+/- 3 days standard error). Chemotherapy was not used for any patient in this study. On an intention-to-treat basis the survival in both groups was the same. This suggests that nutrition supplied did not have an unfavourable effect on outcome regardless of potential effect on proliferation. Furthermore, in the as-treated analysis survival of patients in the nutrition treatment group was improved ($p<0.001$), the median was approximately 50 days longer (Figure 1). Personal communication with the author reveals that the sub-group analysis of the HPN patients against those with similar non-PN nutrition intake within the treatment group was not carried out, but it

is assumed that if the HPN group had shorter survival this would have reduced the overall survival of the treatment group, whereas the opposite has been observed. Furthermore, in addition to the survival non-inferiority, the nutrition treatment group exhibited improved body composition and exercise tolerance.

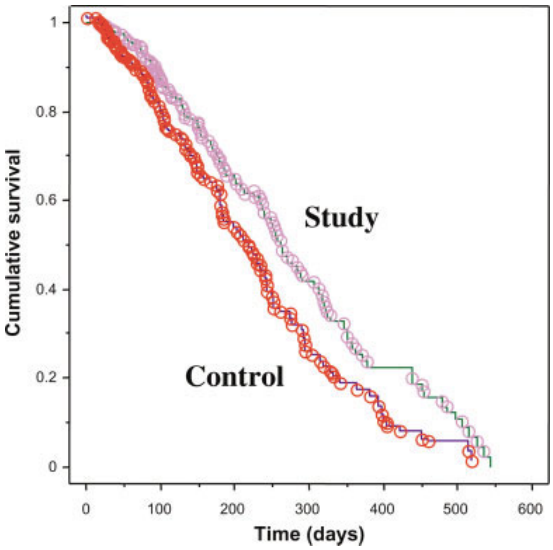

Figure 1 Survival data for as-treated analysis, comparing control vs. treatment groups. Reproduced from Lundholm et al (68)

The cellular evidence for increased tumour proliferation appears to be contrary to the survival data in human studies. The direct randomisation of patients into PN against non-PN for palliative cancer patients is increasingly unlikely as the evidence grows for survival benefits in PN treated patients. The ethical considerations of this become irrelevant when the patient is suffering from intestinal failure, in the context of high performance status and willingness for treatment, when dehydration or malnutrition are the leading cause of morbidity and mortality.

The debate regarding tumour cell proliferation is more relevant in the treatment of curative cancer patients that require nutritional support, where the increased proliferation may have survival prognostic consequences beyond just immediate tumour size, but rather from increased potential for micro-metastasis.

1.6 Prevalence and guidelines for HPN and malignancy

Table 1, summarises the published data for prevalence rates across the world for PN use in malignancy patients. For the reasons outlined above, these data can be difficult to evaluate and in addition, the prevalence rates are expressed in different time periods (i.e. variable period prevalence or point prevalence). Nevertheless, despite these limitations, it is clear that the practice of using HPN for incurable malignancy is common but varies considerably even between countries with comparable health systems.

The lowest reported rates appear to be in the UK (49, 69) and highest in Italy and North America (51, 70), with evidence of increasing prevalence in all parts of the world, including the UK (55, 70, 71).

The variation in the prevalence suggests that there are different practices between countries with similar potential provision for HPN, and hence that the different prevalence may be caused by the attitude of clinicians towards this therapy. This in turn must be influenced by many complex factors, although these have not been investigated to date.

These variations in clinician attitude lead to variable patient selection, despite national and international guidelines. The French Federation of National Cancer Centres (FFNCC) 2003 Standards, Options and Recommendations (72) supported PN in the palliative phase of malignancy for patients with Karnofsky Performance Status index greater than 50% or World Health Organisation performance status of 2 or higher. The American Society of Parenteral and Enteral Nutrition (ASPEN) 2009 guidelines (73) states that the use of PN in the terminal phase of malignancy is rarely indicated, but can be considered if four patient domains are met, these are set out in Figure 2. In the same year the European Society of Enteral and Parenteral Nutrition (ESPEN) 2009 (18) guidelines were published suggesting wider appropriate usage based on similar domains, also set out in Figure 2.

In both the ASPEN and ESPEN guidelines there is a focus on expected survival length (>40-60 days and >2-3 months respectively). This is challenging to apply as clinician prediction of survival has been consistently shown to be inaccurate with bias towards overestimation in the majority of cases (74-78). This is reflected in the largest case series of palliative malignant patients treated with HPN (79) which reports a 50% mortality before 3 months. All the guidelines also refer to decisions being based on performance status, but only the FFNCC give objective cut-off measurements.

Only the ASPEN guideline stipulates that enteral routes must have failed before PN is used, while ESPEN supports the use of supplemental PN as well as for failed enteral feeding. Support for supplemental PN in the ESPEN guideline, however, was based partially on a study that was later retracted (80) because the trial was not conducted in the manner described in the publication. The ASPEN guideline is the only one of the three to comment on financial implications, perhaps due to the very different routes of funding in the United States.

The heterogeneity of the guidelines is an indicator of uncertainty of best practice, variable attitudes and most of all, paucity of evidence based data.

There is scope for unification of selection criteria through clinically applicable patient selection tools that may predict better outcomes based on baseline patient factors, though currently these are yet to be optimally developed.

French Federation of National Cancer Centres (2003) (72)

(1) Karnofsky performance status >50

(2) or, World Health Organisation >2

American Society of Enteral and Parenteral Nutrition (2009) (73)

(1) Must be physically and emotionally capable of participating in their own care

(2) Should have estimated life expectancy of >40-60 days

(3) Require strong social and financial support at home, including a dedicated in home lay carer

(4) Must have failed trials of less invasive medical therapies such as appetite stimulants and enteral feeding

European Society of Enteral and Parenteral Nutrition (2009) (18)

In intestinal failure and incurable malignancy, long-term PN should be offered, if:

(1) enteral nutrition is insufficient

(2) expected survival due to tumour progression is longer than 2–3 months

(3) it is expected that PN can stabilise or improve performance status and quality of life

(4) the patient desires this mode of nutritional support

There is probable benefit in supporting incurable cancer patients with weight loss and reduced nutrient intake with ‘‘supplemental’’ PN.

Figure 2 French, American and European guidelines regarding parenteral nutrition therapy in palliative malignancy

Table 1 Prevalence of malignant conditions as indication for home parenteral nutrition

Study	Country	Terminology of cancer indication	Total HPN patients	Number of HPN patients with cancer as indication	Proportion of HPN with cancer as indication	Period or point prevalence (years)	Data source
Vafa et al, 2010 (81)	Belgium	Advanced cancer	125	60	48%	*Period* prevalence (1987-2007)	Single academic centre database
Soo and Gramlich, 2008 (70)	Canada	Advanced cancer	158	38	48%	*Period* prevalence (Jan – Dec 2006)	North Alberta Home Total Parenteral Nutrition program database
Cazzaglio et al, 1997 (82)	Italy	Terminal malignancy	125	75 ('Majority considered terminal')	43%	*Period* prevalence (1983-1990)	Italian Home Parenteral Nutrition registry
Wanden Berghe et al, 2011 (71)	Spain	Palliative cancer	148	29	20%	*Period* prevalence (Dec 2009 – Dec 2010)	Nutricion Artificial Domiciliaria y Ambulatoria (NADYA) database
Gillanders et al, 2011 (83)	Australia and New Zealand	Cancer	124	19	15%	*Period* prevalence (July 2010 – July 2011)	Australian Society of Parenteral and Enteral Nutrition (AuSPEN) database
Jirka et al, 2011 (84)	Czech republic	Cancer	138	51	37%	*Period* prevalence (2010)	National Home Parenteral Nutrition registry *(Poster abstract)*
Takagi et al, 1995 (85)	Japan	Malignant	231	93	40%	*Period* prevalence up to 1990 (start not reported)	National survey
Baxter et al, 2003 (69)	Scotland	Malignancy	72	7	10%	*Period* prevalence (Aug 2010 – Aug 2011)	Managed Clinical Network Database
Smith et al, 2011 (49)	UK	Cancer	523	42	8%	*Point* prevalence 31/12/2010 (Percentage of new registrations during 2010 – 14%)	British Artificial Nutrition Survey (BANS) database
Howard et al, 1995 (86)	USA	Neoplasm	4520	2122	47%	Period prevalence (1985 – 1992)	North American Home Parenteral Nutrition database

Chapter 2 - Aims, Objectives and Hypothesis

2.1 Aims and objectives

The aims and objectives of this thesis are to address the areas of uncertainty in the treatment of incurable cancer patients with HPN.

I have investigated the survival for this patient group through a systematic review of the literature with extraction of individual patient data to allow meta-analysis. The survival of incurable cancer patients treated with HPN at University Hospital Southampton is also reported in a case series with comparison to international data.

Quality of life of patients with incurable cancer treated with HPN is also explored from a systematic review of the literature allowing a summary of current understanding and highlighting of the areas that require further investigation with proposals for future research methods.

The thesis also examines factors that could aid in selection of palliative malignancy patients with IF for HPN therapy by identifying baseline patient factors which predict survival. This is addressed through both the systematic review and the case series, and in particular, I have examined the potential use of recently developed cancer survival prognostic tools, examining their validity using data from our case series.

A UK survey of intestinal failure clinicians' attitudes towards HPN therapy for patients with incurable cancer is also included, granting insights into both positive and negative opinions on the appropriateness of using HPN in the palliative phase of malignancy as well as the perceived barriers to treatment and particularly highlighting factors that have led to the lower prevalence rates observed in the UK.

The final aim of this was to carry out the first health economic assessment of palliative HPN which is presented in Chapter 7. This was carried out using the current industry standard, incremental

cost effectiveness ratio (ICER) model, with critical assessment of whether this model is the most appropriate when considering end of life treatments for a limited number of patients.

The overall objective of this thesis is to provide reliable clinical and economic data regarding HPN treatment for patients with palliative malignancy to aid in patient selection and to improve the quality of information communicated with patients and their family members when discussing treatment options.

2.2 Hypotheses

The hypothesis for the following chapters of the thesis are as follows:

- Chapter 3 –
    - There is significant variability in survival length data for incurable malignancy patients treated with HPN, limiting the clinical application when considering commencing therapy for future patients
    - It is possible to optimise patient selection to favour those patients likely to survive longer by identifying baseline patient specific factors
    - The quality of life for incurable malignancy patients treated with HPN will be acceptable to the majority of patients
- Chapter 4 –
    - The use of HPN therapy for incurable malignancy patients with intestinal failure will increase their survival length compared to those not utilising HPN
- Chapter 5 –
    - The averages of survival length of incurable malignancy patients treated with HPN at University Hospital Southampton will be comparable to the international published data identified in the systematic review of this thesis
    - The prognostic tools applied retrospectively to this cohort will be able to predict the survival length of patients in this case series
- Chapter 6 –
    - The attitudes of the intestinal failure clinicians in the UK will represent the trend of increasing HPN utilisation in this patient group
    - Intestinal failure clinicians in the UK will place equal emphasis on improving survival length and quality of life of patients by utilising HPN therapy in this patient group
- Chapter 7 –
    - The cost of HPN for incurable malignancy patients is high

- The cost effectiveness of HPN for incurable malignancy patients is comparable to the use of this therapy in patients with benign causes of intestinal failure

Chapter 3 - Systematic literature review of survival time and quality of life for patients with inoperable bowel obstruction caused by palliative malignancy treated with HPN

3.1 Introduction

This chapter presents a systematic review of the existing literature on survival time and quality of life (QoL) in palliative patients with incurable malignancy treated with HPN. This chapter will test the hypotheses set out in Chapter 2.

The survival time of non-PN patients with palliative inoperable bowel obstruction (IBO) can vary due to a number of factors such as anatomical location of obstruction, grade of obstruction, tumour staging, tumour grade, baseline performance status, chemoradiotherapy and confounding co-morbidities. Chakraborty et al reported in 2011 (87) on the natural history of 35 patients with palliative malignant bowel obstruction undergoing multimodal treatments including surgery, stenting, PN, chemotherapy and palliative symptom control. 14 patients (43%) were given short-term PN and only one patient was discharged with HPN. For all PN patients, median length of PN was only 13 days (range 3 – 83 days). PN was used to support patients peri-operatively (9 patients, 26%) or -chemotherapy (5 patients, 14%). The survival length of PN and surgically treated patients were not reported separately. The survival median of the entire cohort was 80 days (2.6 months), with one and two-year survival of 17% and 9% respectively. 26 (74%) patients were discharged home. It may be suggested that PN was not used to significantly prolong the patient's life (expect in one HPN case), but rather for short term support during surgical or chemotherapy treatments. Therefore, although 26% this cohort underwent surgery, suggesting a less advanced malignancy patient group, it may serve as the best surrogate control group available to compare the additive effect of HPN in IBO patients for this systematic review. Hence, if the more advanced malignancy IBO patient population was treated with HPN and their survival

length was equal to or greater than observed by Chakraborty et al, then there would be implied survival improvement due to PN treatment.

Another potential surrogate control group is the survival outcomes demonstrated by the tragic events of the Leningrad siege (88), Warsaw ghetto (89) and Irish hunger strike (90), where the length of survival of starved (though not water deprived) non-malignant individuals did not exceed 73 days (2.4 months). Hence survival in non-PN palliative malignancy IBO patients would not be expected to exceed this, and would be considerably less due to the catabolic malignant state, increased risk of dehydration, poorer baseline caused by the underlying disease. Though the IBO that occurs in palliative malignancy is of variable grade and can be intermittent, so that variable but insufficient nutrient intake is achieved by some patients.

Bowel obstruction is estimated to occur in 2% of all cancers (54), and in 3-11% of terminal cancers, including non-abdominal primary cancers (91). There is greater propensity in colorectal and ovarian cancers, with reported prevalence of 10 - 28% and 5 - 50% respectively (54, 91, 92). The obstruction can be caused by the primary tumour, metastasis or a benign cause in the context of malignant disease (i.e. adhesions).

There is significant variation in the literature regarding the proportion of malignant bowel obstruction patients amenable to attempted surgical resolution, and the subsequent effect on survival length and quality of life. Individual narrative reviews have concluded both favourably for surgical intervention (55) or a conservative surgical role (92, 93), with more recent reviews advocating an individual patient decision, favouring conservative treatment (94). It is necessary to keep in mind that radiological and surgical techniques have developed over the last few decades, which could influence the likelihood to operate in this patient group, with additional advances in oncological therapies that would positively influence the decision towards surgery.

Henry et al (95) in 2012 advocated a more cautious approach, while considering the patient factors that can predict better or worse outcome from surgery. A nomogram was devised using

these variables by Henry et al to predict likely success of surgery. Factors leading to less favourable outcomes were: complete small bowel obstruction (SBO) (cf. partial SBO or large bowel obstruction), non-gynaecological primary, ascites, low albumin and raised white cell count. Feuer et al (56) additionally identified age >65 years, malnutrition and general decline in functional status at baseline, as markers of poor prognosis in a systematic review on this topic.

In bowel obstruction short-term PN is often used to support patients undergoing surgery, but the initial intention to use short-term PN is sometimes converted to long-term PN through complications of surgery (entercutaneous fistula, short bowel syndrome) or inability to resolve the bowel obstruction. Even in cases of successful initial surgery and weaning from PN, recurrent bowel obstruction is common (10 - 50%) (56) rendering patients inoperable and due to previous experiences with PN these patients may be more likely to pursue HPN in the long-term.

In addition to the potential survival benefits of HPN for palliative malignancy, the QoL of patients during HPN therapy is also of paramount importance. This chapter will also aim to systematically review the evidence for changes in QoL during treatment with HPN. Due to the same issues regarding defining the palliative phase, the IBO patient population was again studied.

QoL is a measure of the impact of disease and treatment on physical, psychological, social and beliefs of the patient. QoL measurements must be made by the person experiencing the state being measured. QoL is not a static measure, it changes depending on timing and the manner it is measured, with high inter and intra-reporter variability.

A review of the QoL of patients treated with HPN for benign indications was published by Baxter et al in 2006 (96). They found that there was a general lack of QoL data even in the benign HPN group. Additionally, there was a lack of standardised and scientifically validated tools appropriate to HPN treatment. Furthermore, the interpretation of QoL data was highly dependent on disease burden before starting HPN. In those patients who had suffered high burden symptoms such as fistulating Crohn's disease, the start of HPN was associated with a significant improved QoL

scores. Conversely those patients who had sudden intestinal failure thrust upon them by acute illnesses such as small bowel infarct, the start of HPN was associated with low QoL scores. When these patient groups were followed up for a number of years their QoL scores tended to converge, but this requires a period of time not afforded to most palliative malignancy patients.

The QoL control group for comparison would again be the non-PN malignant IBO patients, who have been offered PN treatment but declined. There is no QoL data available in this patient group.

3.2 Methods

3.2.1 Eligibility criteria

This systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (97).

Although palliative care has been previously defined, there is no accepted definition for the start of the palliative phase. In some disease processes the point at which the focus of treatment is placed on symptom control, rather than cure is clear and in others this time point is challenging to pin point.

For this systematic review it was essential to be able to define the start of the palliative phase to allow definition of the patient population. The following two criteria were used; (i) confirmed diagnosis of terminal malignancy and (ii) bowel obstruction that is deemed as inoperable, hence termed palliative inoperable bowel obstruction (IBO).

In order to identify relevant trials, a broad search strategy was implemented using pre-determined inclusion and exclusion criteria (Table 2). Included participants were adults, ≥18 years old, with a confirmed diagnosis of active malignancy during the palliative phase of disease (no further curative treatment available). A distinction was not made between patients where the mechanical cause of IBO was directly due to the malignant tumour, its metastasis or a benign process parallel to malignancy.

This definition of the population for this systematic review as palliative IBO patient population has two main advantages. Firstly, IBO indicates a clear starting point for the palliative phase of illness, which is often supported by radiological evidence. Secondly this clinical situation is the most common indication for the use of HPN for patients in the palliative phase of malignant disease (79), hence encompassing the majority of such patient.

Once the definition for the 'treatment' patient group is set, a control population is needed to allow comparison of survival lengths and quality of life between these cohorts. The control population in this case would be palliative malignant IBO patients, suitable for but not receiving HPN. Survival data for this control population does not exist, but surrogate groups may be used.

HPN was defined as initiation of PN with intention to discharge to a home environment, even if home discharge with PN was not ultimately achieved.

IBO caused by malignancies such as neuroendocrine, pseudomyxoma peritonei and desmoid tumours were excluded because these tumours behave very differently (more favourable long-term outcome) than other types of malignancies causing gastrointestinal obstruction. Duplicate studies of the same patients were excluded.

Table 2 Inclusion and exclusion criteria for identifying relevant studies via search strategy

Inclusion criteria	Exclusion criteria
≥18 years old Confirmed diagnosis of malignancy in the palliative phase of disease with inoperable bowel obstruction treated with PN Intention at time of commencing PN was to discharge to a home environment, regardless of eventual outcome ± Palliative chemoradiotherapy English language ≥ Year 1970	Bowel obstruction caused by pseudomyxoma peritonei and desmoid tumours Lack of survival or QoL data Data from letters or abstracts, case reports or case series ≤ 4

3.2.2 Search strategy

The search strategy was undertaken using four databases; MEDLINE, EMBASE, CINAHL and Web of Knowledge databases, between 1st – 3rd April 2013. The search was limited to the English language and publications from 1970 onwards. The following broad search terms were used to identify relevant papers: *cancer**, *malig**, *parenteral* and *nutrition*. A manual search of references of key articles was also carried out.

The first pass of studies was carried out by reviewing title and/or abstract. If the article was potentially suitable for inclusion, the full article was retrieved for more detailed assessment.

3.2.3 Quality assessment

The quality and risk of bias assessment of included articles were carried out using the Critical Appraisal Skills Programme (CASP) (98). The questionnaire was adapted to the topic of this review as not all aspects of the CASP assessment were relevant to this topic.

3.2.4 Data extraction

3.2.4.1 Kaplan-Meier graphs

Where possible data were extracted from Kaplan-Meier (KM) graphs by enlarging graphs to approximately A4 landscape format. The number of patients in each survival curve on the graph was established from the text or figure legend (or personal communication in one case (99)). To calculate the number of patients represented by each 'step' on the curve, the total height of the Y-axis was measured and the smallest 'step' was assumed to represent one patient. According to this 'single patient measurement' the number of patients in each remaining 'step' was assessed to estimate their patient number. The total number of patients estimated by this method was compared to that declared by the author. If these numbers did not match, the smallest 'step' was assumed to be 2 patients and the process repeated until a correct total was reached.

Once the correct height on the Y-axis was established for each patient, the length of survival per patient was estimated by calculating the point on the X-axis that correlates with the death of that patient, as demonstrated below in Figure 3.

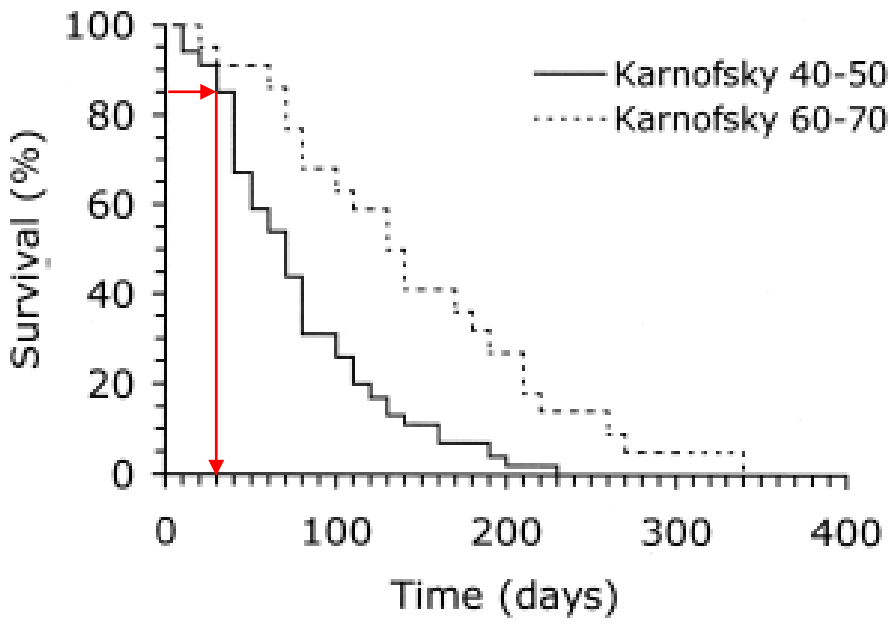

Figure 3 Kaplan-Meier graph from Pasanisi et al 2001 (100). Arrows indicate those patients represented by the proceeding 'step' had an estimated survival of 40 days

3.2.4.2 Corrections applied to KM graph data extraction

In two of the four studies that represented their patient survival data with KM graphs (Brard et al (101) and Chermesh et al (99)) the death of each patient was represented by a single 'step', but in the other two studies (Pasanisi (100) and Bozzetti (102)) the KM graphs grouped survival data into time periods, i.e. Pasanisi (100) represented survival on the KM graph by categorising patients into 10 day categories and Bozzetti (2002) (102) used categories of 1 month (Figure 4).

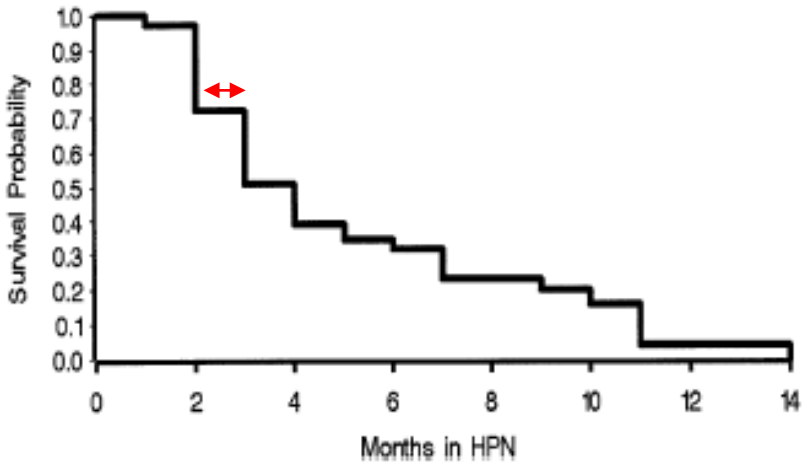

Figure 4 Kaplan Meier graph from Bozzetti et al (2002) (102) for survival outcomes grouped into monthly time periods, indicated by the red arrow

Using the above described technique for extracting survival data would lead to an over estimation if all patients represented by each 'step' are assumed to die at the top end of the category. Therefore, the midpoint of the step was taken as the mean for all patients represented in that step. In the case of Pasanisi (100) the first 'step' represents three patients who died within 10 days of commencing PN, hence the survival estimate for each of these patients was recorded as 5 days. For Bozzetti (102) the midpoint of each month was taken as the length of survival for each 'step'.

Where months are given in whole numbers for survival a calculation to convert to days was used, taking into account lunar years, as follows, 365.25 divided by 12. Therefore, each month represented 30.4 days.

3.2.4.3 Scatter diagram

Data were extracted from a single scatter diagram in the study of Soo et al 2008 (70). The Y-axis of the scatter diagram represented the length of survival and the X-axis represented the age of the individual patient. By measuring the height of each dot on the scatter diagram length of survival was estimated for each patient.

3.2.5 Validation of extracted data

Patient level survival length data extracted from Kaplan-Meier or scatter plot graphs were validated by comparing the average values supplied by the author (mean and/or median where available) and those calculated from the extracted data.

3.2.6 Quality of life

Reported measures of QoL were extracted and evaluated, taking particular account of QoL measures based on validated tools, collected directly and prospectively from patients, and where baseline measurements were available so that changes over time could be assessed. Whenever there was variability in the tools used to assess and report QoL, a narrative description of the results was provided.

3.3 Results

3.3.1 Studies meeting inclusion criteria

The search strategy of all four databases identified 13,440 references, which reduced to 8,262 studies once duplicates were removed. Due to the broad search terms 8042 (97%) of the references were excluded based on title and abstract as not relevant to this study. The full article of the remaining 220 references were reviewed in further detail. The majority of articles excluded at this stage were due to lack of original data i.e. reviews and commentaries or insufficient survival or QoL data and lack of separate reporting of palliative malignancy patients with IBO. After applying the inclusion and exclusion criteria, the number of studies was reduced to 12 (see flowchart in Figure 5 for details).

Two studies published in 1995 by Mercadante (103, 104) were considered to contain relevant data but with probable duplication of some survival data. One of these studies (103) reported the survival length of 13 patients, with raw data provided for each patient's survival length, without QoL data. The other study (104) reported QoL data and only mean survival length on 25 patients, without extractable information on survival length of individual patients. Neither study reported the source of patients in detail, but it is reasonable to assume that the survival length data for some of the patients in these studies have been reported twice given the near identical time period of the study and comparable survival length data. Therefore, the study with raw survival length data (103) was utilised for the patient level analysis of survival length and the study level data of QoL data (104) was utilised to summarise QoL in a narrative manner.

3.3.2 Quality assessment of included papers

Table 3 summarises the assessment of the quality of the included studies using the Critical Appraisal Skills Programme (CASP) checklist (98). The CASP checklist is a structured approach to critical appraisal of evidence based medicine, devised initially in 1993 by the Research and Development department of the Oxford Regional Health Authority. This tool is comprised of 12

questions used to ascertain the validity, robustness, risk of bias and relevance of the study to the chosen topic of systematic review.

The CASP tool allows for adaption for relevance to the topic of each systematic review, which are described in the footnote of Table 3. The three questions in the CASP tool requiring descriptive narrative were Q7, Q8, and Q12 ('What are the results?', 'How precise are the results?' and 'What are the implications of this study for practice?', respectively) are described in detail in the Results section of this chapter.

Results of the quality assessment using the adapted CASP tool suggest a potential risk of bias for some of the studies, but many of the criteria were met by the majority of the studies with sufficient confidence to include in the systematic review.

Table 3 Quality and risk of bias assessment using the Critical Appraisal Skills Program

Study	Q1	Q2	Q3	Q4 – For survival outcomes	Q4 – For QoL outcomes	Q5	Q6	Q9	Q10	Q11
August et al, 1991 (105)	Y	Y	Y	Y	N	N (c, d)	Y	Y	Y	Y
Mercadante, 1995* (103)	Y	Y	Y	NA	N	N (c, d)	Y	Y	N†	N¥
Mercadante, 1995* (104)	Y	N**	Y	Y	NA	N (c, d)	Y	Y	N†	N¥
Pironi et al, 1997 (74)	Y	N**	Y	Y	N	N (d)	Y	Y	Y	Y
Abu-Rustum et al, 1997 (106)	N¥	N**	Y	Y	NA	N (c)	Y	Y	Y	Y
Pasanisi et al, 2001 (100)	Y	Y	Y	Y	NA	N (c, d)	Y	Y	Y	Y
Bozzetti et al, 2002 (102)	Y	N**	Y	Y	Y	Y	Y	Y	Y	Y
Duerksen et al, 2004 (107)	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y
Brard et al, 2006 (101)	Y	Y	Y	Y	NA	N (c)	Y	Y	Y	Y
Fan, 2007 (108)	Y	N**	Y	Y	NA	N (d)	Y	Y	Y	Y
Soo and Gramlich, 2008 (70)	Y	Y	Y	Y	NA	N (c)	Y	Y	Y	Y
Chermesh et al, 2011 (99)	Y	Y	Y	Y	NA	N (c, d)	Y	Y	Y	Y

Two Mercadante studies published in 1995, see above description in Results section for clarification. Q1 – Did study address a clearly focused issue (¥denotes no clear focus of study, but results relevant to this review), Q2 – Was cohort recruited in acceptable way (**denotes representativeness of population not state), Q3 – Was the exposure accurately measured to minimise bias? (exposure was taken to be HPN), Q4 – Was outcome accurately measured to minimise bias (NA – denotes not applicable were outcome not given), Q5 – Have the authors identified all important confounders (we prioritised 4 confounders as (a) age, (b) origin of malignancy (c) metastasis (d) chemoradiotherapy – the above lists the confounder not reported in study, Q6 – Was follow up of subjects complete, Q9 – Do you believe the results, Q10 – Can the results be applied to the local population (†Denotes results cannot be applied locally – see results in Section 3 for clarification), Q11 – Do the results fit with other available evidence (¥Denotes results do not fit with other evidence – see Results in Section 3 for clarification). Q7, Q8 and Q12 were not scored because they are addressed in detail in the Results and Discussion

3.3.3 Study outcomes

The primary outcome in all 12 studies was survival length, while four studies also reported QoL (74, 102, 104, 105). Secondary outcome measures of studies included identifying predictive factors of survival time, effect on survival time of patients if PN combined with chemotherapy and hospital re-admission rates.

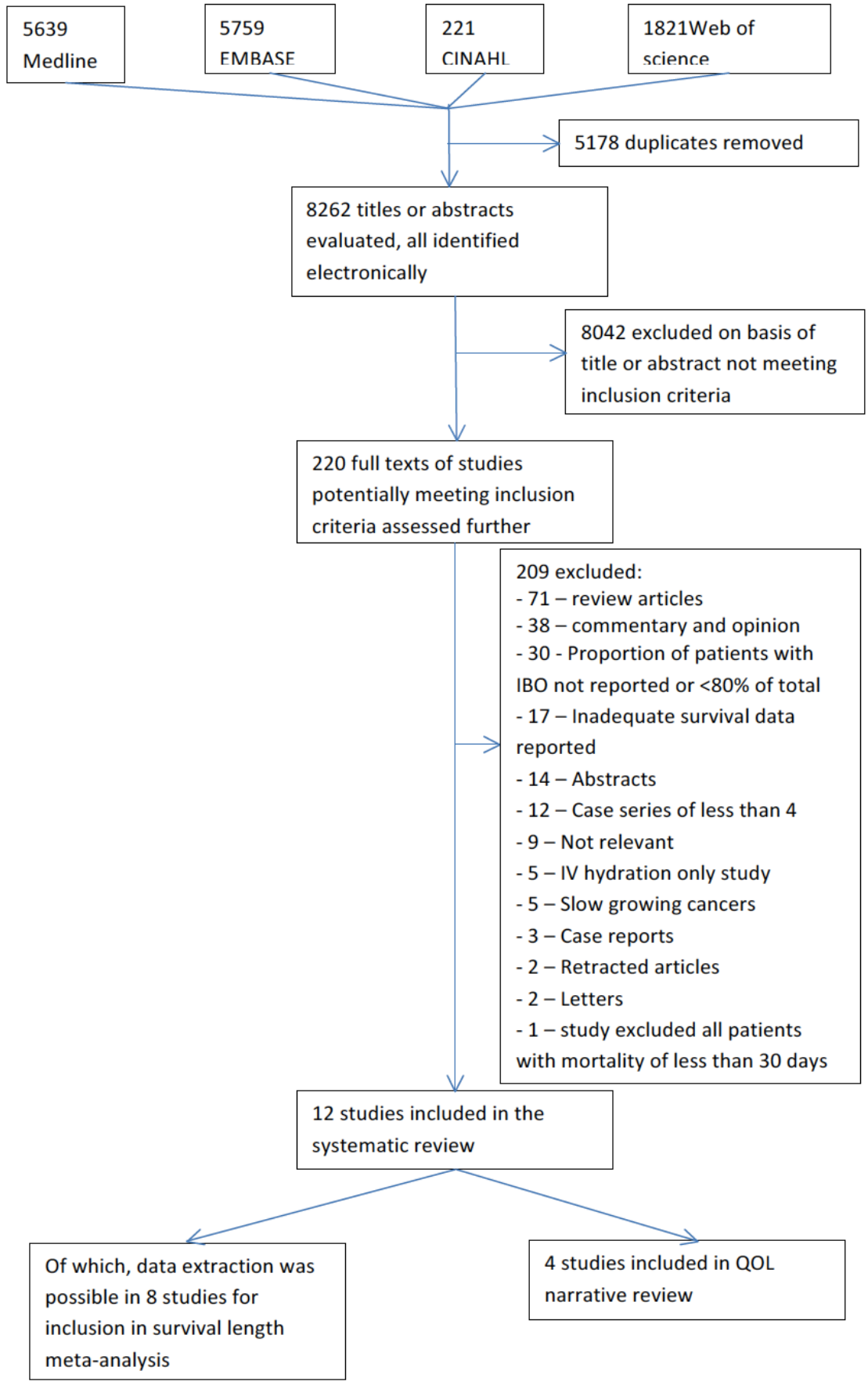

Figure 5 Flow diagram of study selection process

Table 4 Summary of study characteristics, patient demographics, survival length and quality of life data reporting

	Study characteristics					Patient demographics and conditions							Survival data (days)			
Study	**Period of study**	**Country**	**Single/ multiple centres**	**Source of data for survival length**	**Definition of length of survival**	**No. treated with HPN with survival data**	**% patient with IBO**	**Age mean or median (range/ SD)**	**% male**	**Underlying malignant condition (%)**	**Nutrition status/ weight (kg) at baseline**	**Palliative chemo-radiotherapy received during HPN**	**Mean**	**Median**	**Range**	**QoL data**
August et al, 1991 (105)	1980-1989	USA	Single	Raw data for each patient	From discharge with HPN to death	17	100%	Median 58 (33-79)	18%	Gynaecological (59%) Gastro-intestinal tract (41%)	Not reported	Not stated	72	53	5-208	Yes
Mercadante 1995* (104)	1990-1994	Italy	Multiple	Average reported only	From diagnosis of intestinal obstruction	25	100%	Mean 61 (35-65)	52%	Gastro-intestinal (52%) Gynaecological (28%) Other (20%)	Not reported	Not stated	19	Not stated	3-53	Yes
Mercadante 1995* (103)	5 year period – dates not stated	Italy	Multiple	Raw data for each patient	From diagnosis of intestinal obstruction	13	100%	Mean 53 (32-71)	38%	Gynaecological (15%) Gastro-intestinal tract (62%) Other (20%)	Not reported	Not stated	30	15	3-121	No

	Study characteristics					Patient demographics and conditions							Survival data (days)			
Study	**Period of study**	**Country**	**Single/ multiple centres**	**Source of data for survival length**	**Definition of length of survival**	**No. treated with HPN with survival data**	**% patient with IBO**	**Age mean or median (range/ SD)**	**% male**	**Underlying malignant condition (%)**	**Nutrition status/ weight (kg) at baseline**	**Palliative chemo-radiotherapy received during HPN**	**Mean**	**Median**	**Range**	**QoL data**
Pironi et al, 1997 (74)	1990-1996	Italy	Multiple	Average reported only	Not defined	29	100%	Not stated	Not stated	Gastro-intestinal tract (62%) Head & neck (10%) Lung (3%) Genitourinary (14%) Other (10%)	"Protein-energie mal-nutrition in 82%"	Not stated	85	56	14-343	Yes
Abu-Rustum et al, 1997 (106)	1990-1995	USA	Single	Average reported only	From insertion of venting gastro-stomy to death	11	100%	Mean 55 (32-75)	0%	Gynaecological (100%)	Not reported	100%	Not stated	89	Not stated	No
Pasanisi et al, 2001 (100)	1995-1999	Italy	Multiple	Extracted from Kaplan Meier graph	Not defined	76	100%	Mean 57 (+/- 14 SD)	29%	Gynaecological (24%) Gastro-intestinal tract (58%) Other (18%)	Mean weight 54.2 (+/- 9 SD), Mean BMI 20.8 (+/- 3.7 SD)	Not stated	98	74	6-301	No

	Study characteristics					Patient demographics and conditions							Survival data (days)			
Study	**Period of study**	**Country**	**Single/ multiple centres**	**Source of data for survival length**	**Definition of length of survival**	**No. treated with HPN with survival data**	**% patient with IBO**	**Age mean or median (range/ SD)**	**% male**	**Underlying malignant condition (%)**	**Nutrition status/ weight (kg) at baseline**	**Palliative chemo-radiotherapy received during HPN**	**Mean**	**Median**	**Range**	**QoL data**
Bozzetti et al, 2002 (102)	3 year period – dates not stated	Italy	Multiple	Extracted from Kaplan Meier graph	From PN in hospital to death	48	84%	Median 54 (29-82)	41%	Gynaecological (19%) Gastro-intestinal tract (53%) Other (28%)	Median weight - 53 (35-78)	Not stated	156	91	30-426	Yes
Duerksen et al, 2004 (107)	1997-2002	Canada	Single	Raw data for each patient	From PN in hospital to death	9	100%	Mean 45 (35-57)	67%	Gastro-intestinal tract (89%) Other (11%)	Not reported	56%	166	84	27-433	No
Brard et al, 2006 (101)	1994-2002	USA	Single	Extracted from Kaplan Meier graph	From diagnosis of intestinal obstruction	28	100%	Mean age 54 (+/- 9.8 SD)	0%	Gynaecological (100%)	Not reported	64%	90	74	16-485	No
Fan, 2007 (108)	2000-2006	China	Single	Averages reported only	From PN in hospital to death	115	100%	Mean 51 (31-74)	46%	Gastro-intestinal tract (70%) Other (30%)	Mean 9kg weight loss	Not stated	**	**	Not stated	No

	Study characteristics					Patient demographics and conditions							Survival data (days)			
Study	**Period of study**	**Country**	**Single/ multiple centres**	**Source of data for survival length**	**Definition of length of survival**	**No. treated with HPN with survival data**	**% patient with IBO**	**Age mean or median (range/ SD)**	**% male**	**Underlying malignant condition (%)**	**Nutrition status/ weight (kg) at baseline**	**Palliative chemo-radiotherapy received during HPN**	**Mean**	**Median**	**Range**	**QoL data**
Soo and Gramlich, 2008 (70)	1999-2006	USA	Multiple	Extracted from scatter graph	Not defined	38	87%	Mean 49 (+/- 14 SD)	29%	Gynaecological (37%) Gastro-intestinal tract (42%) Other (21%)	Not stated	39%	164	89	8-1004	No
Chermesh et al, 2011 (99)	2003-2009	Israel	Single	Extracted from Kaplan Meier graph	Not defined	28	82%	Mean 60 (+/- 12.7 SD)	53%	Gynaecological (32%) Gastro-intestinal tract (43%) Other (25%)	BMI 20.4 (+/- 4.8 SD)	Not stated	130	140	20-783	No

*Two Mercadante studies published in 1995 (103, 104), see results Section 3 for clarification. **In Fan (108) survival length mean and median terminology is interchange and both reported as 198 days without qualification. IBO – inoperable bowel obstruction. BMI – body mass index, HPN – home parenteral nutrition, QoL – quality of life

3.3.4 Patient characteristics

Of the 12 studies, the mean age of patients was reported in 9 studies (70, 99-101, 103, 104, 106-108), with a range of means between 45-61 years. The median age was reported in 2 studies only (102, 105) (54 and 58 years) while one study did not report either mean or median age (74). The age range from all studies was 33 to 82 years.

Only one study (74) did not reported the gender distribution of the patients, with an overall predominance of females (64%). The underlying primary malignancy was gynaecological in 25% of patients (accounting for the female predominance), gastrointestinal tract in 53% and other sites in 22%. IBO was reported as 100% of patients in 9 studies (100, 101, 103-108) and a range of 82-87% in the other three studies (70, 99, 102), equating IBO in 96% of patients included.

3.3.5 Study level survival length results

Amongst the 12 studies four different definitions of survival length were used, depending on the starting point of measuring: from diagnosis of 'terminal intestinal obstruction' (101, 103, 104), from insertion of venting gastrostomy (106), from the start of PN in hospital (102, 107, 108), and from the date of discharge from hospital (105). Four studies did not define the start of the survival period (70, 74, 99, 100). In general HPN treatment was continued until death or a few days before death.

Of the 12 included studies, none provided summary measures of variability of survival at monthly intervals (i.e. standard deviation or standard error). The data on median, mean and range of survival lengths are summarised in Table 4. One study used the terms median and mean survival interchangeably (108). The range of median survivals was variable between 15-140 days (excluding reference (104), where the median was not stated). In all but one study (99) the mean was higher than the median, indicating positively skewed data. The range of survival varied from 3-1004 days, and only nine patients (2%) survived longer than one year.

3.3.6 Patient level survival length data extraction validation

It was possible to extract survival data for individual patients in eight studies, that was presented as raw data (103, 105, 107), Kaplan Meier (99-102) or scatter graph (70).

To validate the graphically extracted data, the individual extracted patient data were used to calculate average survival for each study and compared to the corresponding average values reported by the authors. For example, in the study of Pasanisi et al (100) the author reported the median survival as 74 days, the median survival length based on the manually extracted data (from the Kaplan-Meier graph) was 75 days, hence validating the extraction procedure. Pasanisi et al (100) did not report mean survival length, hence this could not be used to validate the extracted data further.

Table 5 demonstrates the extracted survival averages by comparing them to the authors described averages.

Table 5 Validation of extracted data by comparison of study reported mean/median survival (days) to those acquired by data extraction

Study	Source of data extraction	Author's Mean	Data extraction mean (where relevant)	Author's median	Data extraction median
Pasanisi et al, 2001 (100)	Kaplan Meier graph	Not reported	-	74 days	75 days
Bozzetti et al, 2002 (102)	Kaplan Meier graph	Not reported	-	3.0 months	3.1 months
Brard et al, 2006 (101)	Kaplan Meier graph	Not reported	-	74 days	71 days
Soo and Gramlich, 2008 (70)	Scatter graph	164 days	158.6 days	89 days	89 days

3.3.7 Patient level survival length data results

Using the validated extracted data graphs of the survival patterns of each study over the first six months were produced, including 95% confidence intervals (CI), as shown in Figure 6. These demonstrate the large ranges of confidence intervals at each monthly interval in each study, which is due to the small numbers of patients in each. For example, in Figure 6, for August et al, the 95% CI for proportion of patients dead at 1 month is between 15-60%. Large ranges for CI of the survival proportion at each month interval exist for all the studies included in the systematic review, rendering the data of little clinical use, except the knowledge that there is potential for great variability. Therefore, data amalgamation was needed for meta-analysis, described in Chapter 4.

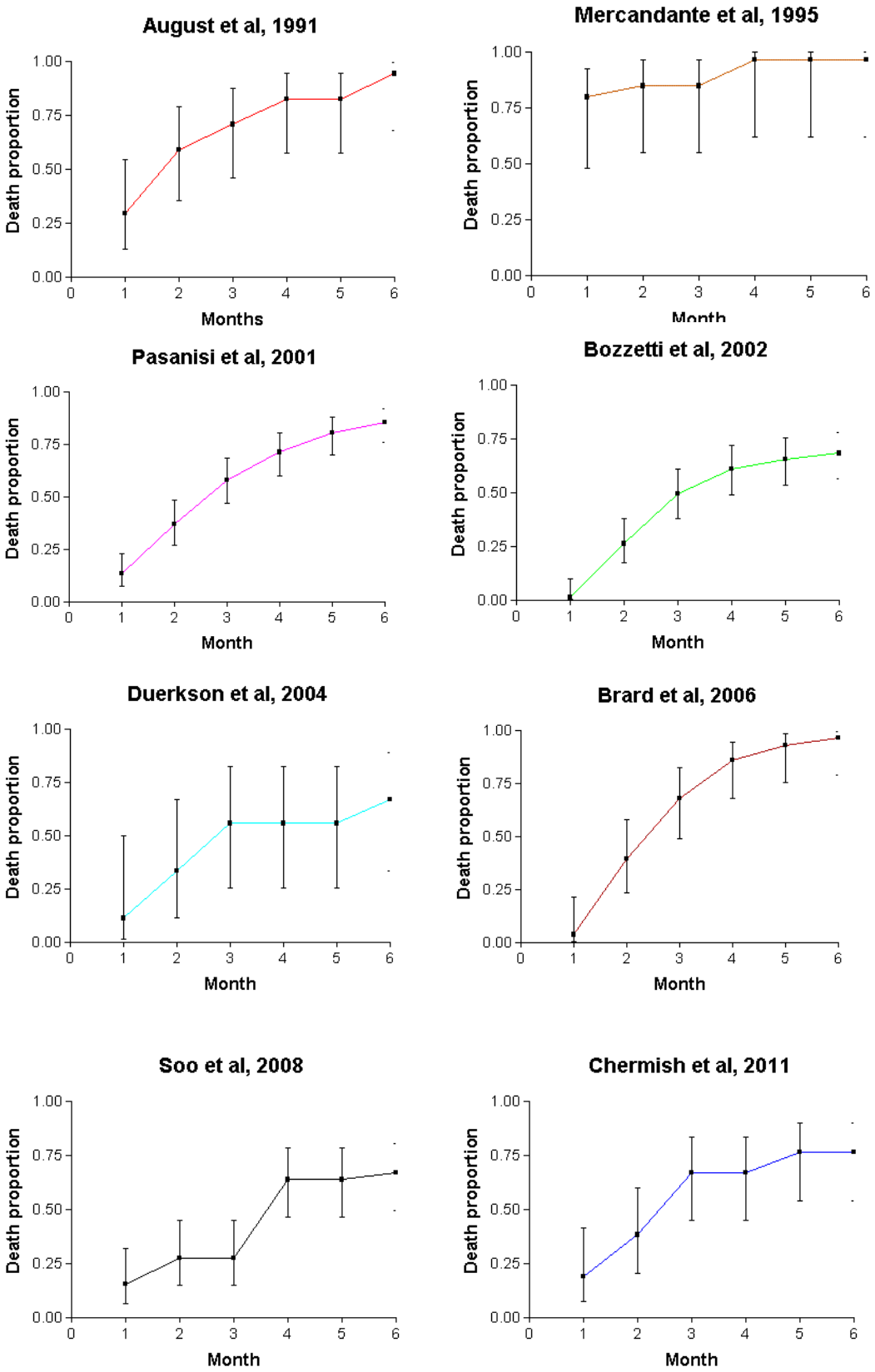

Figure 6 Survival pattern in each study over the first six months (70, 99-103, 105, 107). Vertical bars represent the 95% confidence interval at monthly intervals

To allow for further assessment of this data a KM graph of all included studies was also produced, as shown in Figure 7. This graphical representation shows a broadly comparable survival pattern in most studies, with the exception of one study Mercadante (103) (represented by the dotted line). This study involved a particularly short survival time which can be explained by selection criteria leading to a lower threshold for initiating HPN in patients with more severe or advanced disease, described in discussions Section 3.3 below. The remaining studies show an almost linear decline in survival between 0 and 100 days, with approximately 50-75% mortality at 100 days.

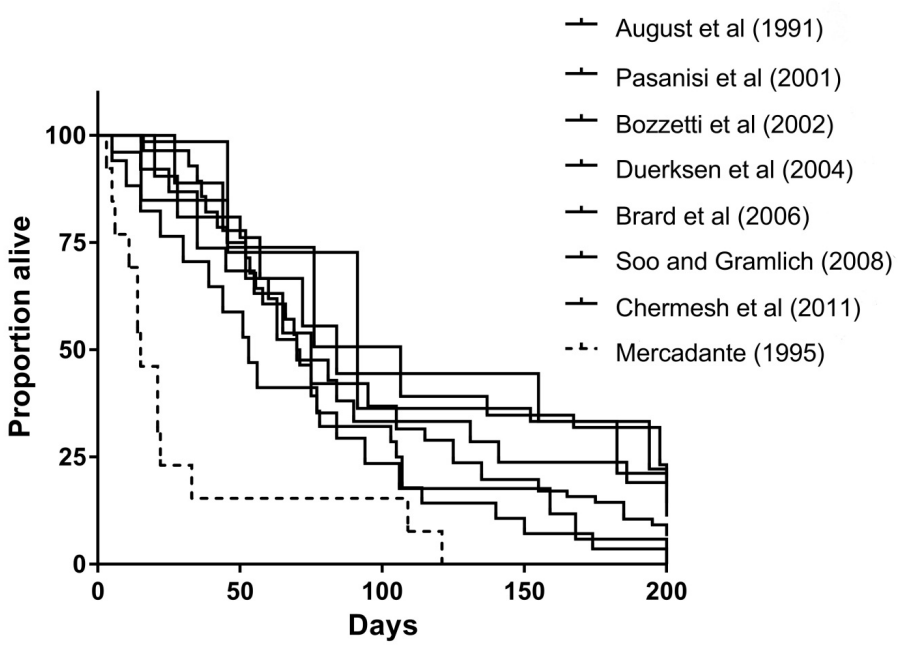

Figure 7 Kaplan Meier survival curves using patient level data from the 8 included studies, demonstrating the difference between the broadly similar survival for seven studies in the first 100 days and the shorter survivals in Mercadante (103)

3.3.8 Quality of life results

Four studies (74, 102, 104, 105) were identified by the search strategy relating to QoL for patients treated with HPN within the palliative phase of malignant IBO, totalling 140 patients. The results are summarised in Table 6. Different tools were used by all four studies and results reported in different ways, hence meta-analysis was not possible. A narrative description is provided below instead.

Table 6 Summary of quality of life study characteristics and results

Study	N	Source of data	Prospective/ Retrospective	Baseline/ post-treatment/ both	Type of assessment	Description of findings
Bozzetti et al, 2002 (102)	69	Patient	Prospective	Both	RSCL* (includes symptoms, activity levels, psychosocial and overall well being)	96% of patients reported symptoms 80% of the time Transient benefit in physical symptoms, followed by decline 2-4 months before death 58% said they were "well" or "very well" (related to overall health), despite needing help with activities of daily living
Mercadante, 1995 (104)	25	Patients	Prospective	Both	Symptoms	Improved symptom control one week after starting PN, though confounded by other palliative treatments
August et al, 1991 (105)	17	Patient, family and Clinician review of medical notes	Prospective and Retrospective	Post-treatment	Effect of treatment	65% benefit from PN, 18% may have benefited and 18% did not benefit
Pironi et al, 1997 (74)	29	Clinician review of medical notes	Retrospective	Post-treatment	Effect of treatment	66% accepted PN well, 24% displayed annoyance at PN and 10% scarcely tolerated PN

*RSCL – Rotterdam Symptom Check List

Two studies (102, 104) assessed QoL using information provided solely and directly from the patients, and the two others (74, 105) used a mixture of information from patients, family members and clinician's opinion based on patient's notes. Only one of these studies (102) reported QoL using a validated tool.

In the study of Bozzetti et al (2002) (102), the Rotterdam Symptom Check List (RSCL) (four domains and a totalled score) was used to assess QoL. The authors conclude from the results that QoL is stable until the last two months before death and showed improvement for 40% in the first month of HPN. The findings of this study were used heavily to influence the ESPEN 2009 guidelines (18) recommending predicted survival of greater than 2-3 months in order to support PN for this patient group. However, graphical results presented in the article were difficult to interpret because they were presented as median scores obtained from a different number of patients, at various time points between 0 and 10 months before death. There was no obvious trend in median results for the 'psychological' and 'well-being' domains and there was substantial variability within all domains at the same time points. In addition, there was substantial variability in three individual domains ('physical', 'activity' and 'total QoL scores') at various time points during the last few months before death, with some of them showing better scores at 2-3 months than an at 4 months before death, the worst being at 1 month before death. Although it is not possible to draw conclusions without access to the raw data, the graphically presented data in this article do not entirely concur with the conclusions drawn by the authors. This and the implications for ESPEN 2009 guidelines (18) is discussed further in the discussion Section 1.1.

It is noteworthy that in the study of Bozzetti et al (2002) (102), despite the high symptom burden (96% of patients reported symptoms 80% of the time) 58% reported feeling "well" or "very well" within the context of an overall assessment of their QoL at baseline.

In the study of Mercadante (104) improvements were reported after commencing PN therapy, but these may have been confounded by variables that were introduced at the same time as starting PN, such as decompression of stomach with nasogastric tubes in 7/25 (28%) patients and administration of anti-secretory treatment to most patients. Although these additional palliation treatments were not commented on in the above Bozzetti et al (2002) (102) article, it is reasonable to assume that their patients also underwent these symptom control methods. This may also explain the improvements observed in that study in the first month.

August et al (105) and Pironi et al (74) also reported favourable improvements in QoL with the commencement of PN, 65% and 66% respectively. The methods of QoL assessment in both these studies are unvalidated and discussed further below.

3.4 Discussions

The results of this systematic review show that there are limited data on the length of survival of patients with incurable malignancy and IBO treated with HPN. The current data show that the survival is short, with 75% of the patients dying between 50-100 days and only 2% of patients alive after one year.

In keeping with the first hypothesis for this chapter, the small numbers of patients in each study led to wide confidence intervals for survival proportions at monthly time points, making the interpretation of these data difficult; hence the clinical application is limited.

This systematic review demonstrates that the survival length will depend heavily on patient selection criteria applied. This is demonstrated by the significantly lower survival lengths observed in the study of Mercadante (103). The selection criteria in this study were not set out in detail, but inferred from the author's quote "the family can induce the team and patient to start or continue PN, even if the patient is, at some level, opposed". The authors conclude that PN should not be denied on the basis of anticipated life expectancy or beliefs of the clinician. This selection process is not supported by current mainstream practice and ESPEN 2009 (18) and other national and international guidelines (72, 73), accounting for the lower survival lengths observed in this study.

In keeping with the second hypothesis made for this chapter baseline patient factors were identified to potentially guide patient selection for favourable survival lengths. The patient characteristics identifiable at baseline to aid in prognostication of survival length were performance status, type of malignancy and the use of palliative chemoradiotherapy. These factors are discussed in more detail in Chapter 4 where data amalgamation methods allow for greater confidence in the interpretation of results.

In addition to the small patient numbers the survival length data for this patient group is limited by a number of other factors. Many studies were excluded early in the search due to mixed reporting of benign and malignant HPN patient survival. Where only malignant patients were

reported, there was mixed reporting of patients with and without IBO. Where data were reported separately for malignant IBO patients, only summaries of survival length data (such as median, mean and range) were supplied without raw or graphical reporting of data. Where the data were presented graphically, allowing data extraction, different graphical methods were used (such as KM and scatter graphs) and there was variation between the type of KM graphs (i.e. grouping of patients vs. individual patient data).

The extraction of data from graphical representation also introduces possible errors. The method depends on accurate reporting by the author of the study on how many patients are included in each KM graph. Where this was not stated in the text or the legend of the KM graph the presumed number were the total patients in the study or treatment arm. In this circumstance it is possible the author censored survival data of a number of patients, therefore influencing the total in each graph, causing a knock on effect on the estimated extracted survival lengths. This is demonstrated by the KM graph for Chermesh et al (99). The text of this article reports the total number of patients in the study as 28, but does not report the number of patients in each arm of the KM graph. Through personal communications with Dr Irit Chermesh the exact numbers were determined, hence allowing accurate data extraction.

The extraction of data in this systematic review was validated in all the included studies (see Table Section 3.3.6 and Table 5), hence despite the potential errors described above the impact of errors in data extraction can be considered minimal.

Further limitations were introduced by variable definition of the starting point that survival length was measured from. In the 12 included studies there were four different definitions of starting points and four of studies that did not report their definition of survival length. The periods of time between the earliest reported starting point (onset of IBO) and the latest (discharge from hospital with HPN) can reasonably be expected to vary between two weeks and a few months. In the context of the already short survival lengths in this patient group, this additional variation, introduces a further limitation to the interpretation of data.

The third hypothesis for this chapter was that quality of life for incurable malignancy patients treated with HPN would be acceptable to the majority of patients. Due to paucity of studies and understanding for this topic, with only four studies meeting the inclusion criteria, this hypothesis remains untested. Only narrative summary conclusions could be made on the basis of these data, which show that patients are highly symptomatic with a probable decline in QoL throughout treatment. Based on the data presented in this chapter it is difficult to judge if their QoL improves at the commencement of HPN or if a reliable survival length is required for HPN treatment to be considered worthwhile for the patient's QoL.

This conclusion is contradictory to that of the ESPEN 2009 guidelines (18), which relies heavily on the QoL results of Bozzetti et al (2002) (102), which was included in this systematic review. In this study, the authors interpret their results as stability or improvement in QoL in the majority of patients until the last two months of life, hence the recommendation for an expected survival length of 2-3 months to allow the patient to experience some benefit from HPN before this decline. The difficulties in interpretation of these results are described in the Results section, but in summary this 'tipping point' is not appreciated with any clarity from the results presented in the Bozzetti et al study.

All four QoL studies used a different method to assess QoL. Three of these methods were based on the interpretation of the QoL as judged by the nutrition support team, which is not a validated method and has risk of bias. Additionally, the judged improvements in QoL on commencing HPN may also be attributed to the introduction of other simultaneous treatments such as gastric decompression and medical management of IBO. Without a control group the additive effects of HPN cannot be reliability assessed.

Given the finding that a significant portion of patients (50-75%) are not surviving beyond three months across all the included studies and stabilisation or improvement of QoL cannot be reliably demonstrated, it can be argued that the ESPEN 2009 guidelines (18) are not representative of the majority of palliative HPN practice over the last 25 years presented in this chapter. As

demonstrated in this chapter the quality of data for these recommendations are poor, as acknowledged by Grade C level of recommendations. The next chapter explores meta-analysis methods based on these extracted data to increase the reliability of survival length in this patient group.

Chapter 4 - Meta-analysis of survival data for patients with inoperable bowel obstruction caused by incurable malignancy and treated with HPN

4.1 Introduction

As described in the previous chapter the duration of survival of incurable cancer patients with inoperable bowel obstruction treated with HPN is short, but variable, and the current understanding is limited by small numbers of patients in each study leading to lack of confidence in the clinical application of the data.

The aims of this chapter are to quantify the variability between the survival patterns of the studies and to amalgamate extracted data to be used in meta-analysis to gain a more reliable understanding of survival lengths.

Meta-analysis of data utilises a number of statistical methods to combine data from different sources to increase the power of the dataset. To carry out a reliable meta-analysis all relevant data should be collected and considered for entry into the statistical modelling to reduce the risk of bias. The collection of all relevant data is carried out through a systematic review using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement (97) described in the previous chapter.

The basis of carrying out meta-analysis is that there is common truth in all scientific studies on the same topic, with inherent sample measurement errors in each study. Therefore, statistical methods are used to give weighted average of the entire known data, with the aim of getting a result closest to the truth despite variability in methods used to measure outcomes in each separate study. Conceptually meta-analysis is the process of carrying out research on previous research to reach conclusions with greater confidence than the individual studies were able to supply.

While the use of statistical methods to gain more accuracy from known data was used as early as the 17th century in astronomy, the first modern publication using this method was by Karl Pearson in 1904 (109) to report on enteric fever inoculation methods. The term meta-analysis was coined by Gene Glass in 1976 (110) who is credited with the wide use of this technique.

Despite the advantages provided by the use of meta-analysis techniques, however, the results from meta-analysis of several small studies have been shown not to be predictive of large randomised controlled single studies (111). Additionally, a well conducted meta-analysis of poorly conducted studies will still result in inaccurate conclusions. Hence, some statisticians have argued that subjective weighting should be given to studies with flawed methodology, while others argue that this investigator subjectiveness defeats the underlying reason for carrying out the meta-analysis.

Further potential for the introduction of bias is described by the term 'the file drawer problem'. This is a wider reaching problem for evidence based medicine, where there is publication bias against negative studies, which would affect the conclusions of a meta-analysis but are not available for inclusion. In the example of the topic for this meta-analysis, those centres with longer survival length in palliative malignancy IBO patients may be more likely to publish their data, as the shorter survivals may attract peer criticism.

Once the quality of data from individual studies has been assessed and pre-set entry criteria have been met, the most suitable meta-analysis method needs to be applied to the data. The appropriate method used will depend on the variability, i.e. heterogeneity, of the data. The two main methods are the fixed and random effects models.

The fixed effect model is used when there is an assumption that all the separate studies investigated the same population using the same entry criteria and the same outcome measures. In many circumstances this assumption is not possible due to variability in study designs and populations, but if this assumption can be made each study's results are weighted proportionally to their size.

In the random effects model the above assumption cannot be made. As in the case of the topic for this chapter's meta-analysis, the patients are diagnosed with palliative malignancy IBO, but the underlying malignancies, patient selection, PN regimen and other factors are sufficiently different to suggest the need to use the random effects model. Statistical analysis can be used to formally assess heterogeneity between related studies.

4.2 Methods

The search strategy, inclusion criteria, data extraction and validation methods for the studies included in these meta-analysis are described in Chapter 3.

To determine the type of meta-analysis most appropriate for these data the variability of survival pattern between the studies was investigated using two methods: initially the proportion of patients alive at each monthly time point was compared between each study using chi-squared test of proportions; then the entire Kaplan-Meier curves of each study were compared with each other using the log-rank test. These tests would determine if the extracted data from the different studies should be considered to have originated from the same population or different population.

The extracted patient level data were then used to undertake overall meta-analysis and to undertake separate analysis using specific patient characteristics, such as type of malignancy to determine if these characteristics can be used at baseline to predict survival.

4.2.1 Statistics

Differences in survival between studies were analysed using chi-squared and the log rank test obtained from the Kaplan Meier analysis using SPSS (version 21, Chicago, USA) and GraphPad Prism (version 6, California, USA). Random effects meta-analyses were undertaken using Comprehensive Meta-analysis (CMA version 2, Biostat Inc, NJ, USA). A p-value of <0.05 was considered significant in a two tailed test.

4.3 Results

4.3.1 Chi-squared test of proportions for variability of survival patterns between studies

Table 7 shows the results of the chi-squared test of proportions of patients who were alive at month 1. This table shows that at month 1 the proportion of patients alive in the study of Mercadante (103) is statistically different from all other seven studies, while Duerksen et al (107) and Brard et al (101) have no statistical differences with any other study at this time point.

Table 7 Chi-squared test of proportions of alive patients at month 1. Statistically significant test highlighted in bold and underlined, demonstrating a difference in survival proportion at month 1 between two studies

At month 1	August et al, 1991	Mercadante 1995	Pasanasi et al, 1997	Bozzetti et al, 2002	Duerksen et al, 2004	Brard et al, 2006	Soo and Gramlich 2008	Chermesh et al, 2011
August et al, 1991	NA	**0.010**	**0.100**	**0.001**	0.292	0.013	0.232	0.455
Mercadante, 1995	***0*.010**	NA	**0.000**	**0.001**	**0.002**	**0.000**	**0.000**	**0.001**
Pasanasi et al, 1997	**0.100**	**0.000**	NA	***0*.008**	0.863	0.159	0.781	0.497
Bozzetti et al, 2002	**0.001**	**0.001**	**0.008**	NA	0.085	0.505	**0.006**	**0.002**
Duerksen et al, 2004	0.292	**0.002**	0.863	0.085	NA	0.384	0.759	0.593
Brard et al, 2006	0.013	**0.000**	0.159	0.505	0.384	NA	0.130	0.077
Soo and Gramlich, 2008	0.232	**0.000**	0.781	**0.006**	0.759	0.130	NA	0.708
Chermesh et al, 2011	0.455	**0.001**	0.497	**0.002**	0.593	0.077	0.708	NA

The above analysis was also carried out for each monthly interval up to six months. Table 8, shows the results of those studies that showed no statistical difference at any of the first 6 month intervals in their proportion of alive patients. This table demonstrated that Duerkson et al (107)

survival pattern over the first six months is the most representative of this patient group as it has no statistical differences with five out of seven studies at all six monthly intervals.

Table 8 demonstrates that while there are similarities between studies there is sufficient variability to suggest the need to use the random effects model for data amalgamation and meta-analysis.

Table 8 Variation in survival patterns over the first six months. Ticks represent no differences in survival proportion at any month between studies

Months 1 to 6	August et al, 1991	Mercadante, 1995	Pasanasi et al, 1997	Bozzetti et al, 2002	Duerksen et al, 2004	Brard et al, 2006	Soo and Gramlich, 2008	Chermesh et al, 2011
August et al, 1991	NA		✓		✓			
Mercadante, 1995		NA						
Pasanasi et al, 1997	✓		NA		✓	✓		
Bozzetti et al, 2002				NA	✓			✓
Duerksen et al, 2004	✓		✓	✓	NA		✓	✓
Brard et al, 2006			✓			NA		✓
Soo and Gramlich, 2008					✓		NA	
Chermesh et al, 2011	✓		✓		✓	✓		NA

4.3.2 Log-rank test for variability of survival patterns between studies

Further analysis of the variability between the survival patterns of the studies was done by analysing the entire survival curve of each study against all other studies using the log-rank test. Figure 8 shows the entire study periods, demonstrating visual variability between the studies.

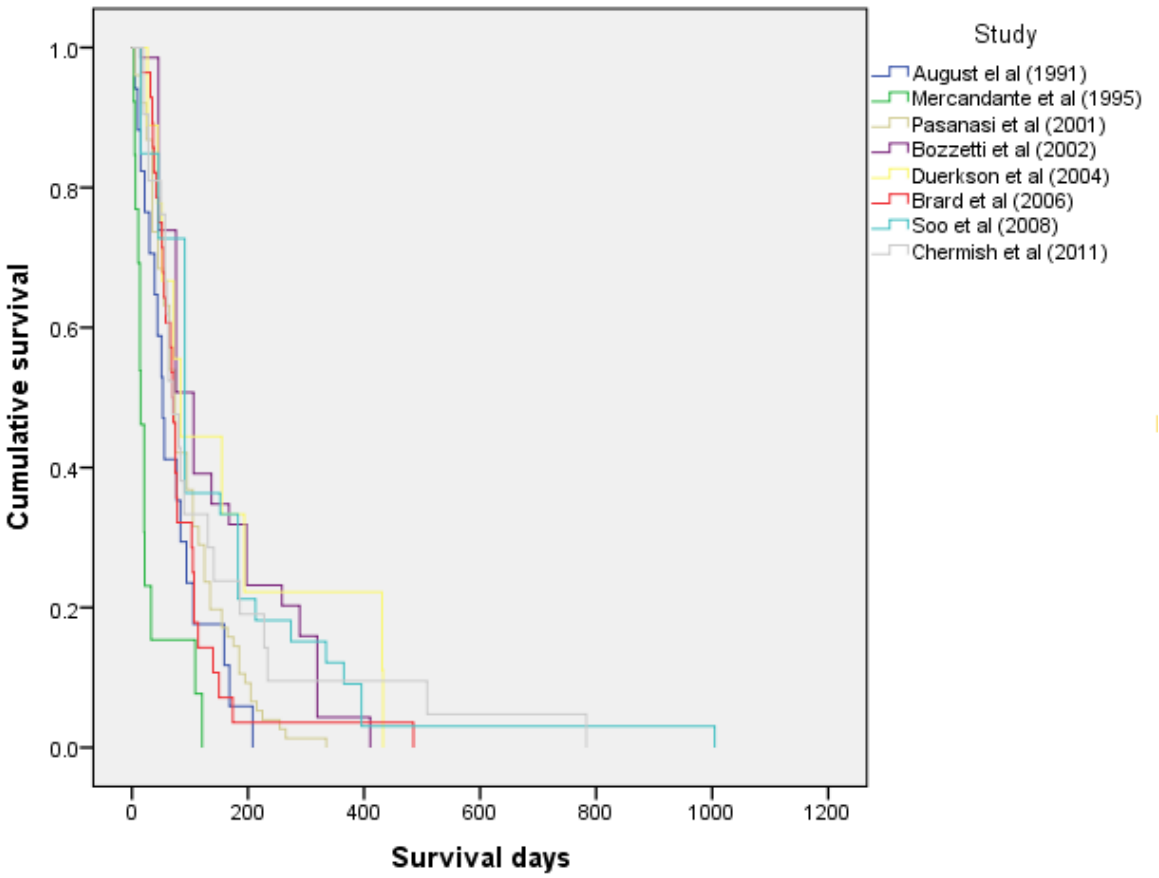

Figure 8 Kaplan-Meier curve for all eight included studies for the entire length of study

Further evidence of variability between the study's survival patterns is shown by comparing the study's KM curves directly with each other. Table 9 shows the results of the log-rank test of this head-to-head comparison. The results are identical to that produced by the chi-squared method, despite the log-rank taking into account the whole study and not just the first six months. These results further reinforce the need to use a random effects meta-analysis test.

Table 9 Variation in survival patterns over the entire period of the studies. Ticks represent no differences in survival pattern between the studies Kaplan-Meier curves

At month 1	August et al, 1991	Mercadante, 1995	Pasanasi et al, 1997	Bozzetti et al, 2002	Duerksen et al, 2004	Brard et al, 2006	Soo and Gramlich, 2008	Chermesh et al, 2011
August et al, 1991	NA		✓		✓			
Mercadante, 1995		NA						
Pasanasi et al, 1997	✓		NA		✓	✓		
Bozzetti et al, 2002				NA	✓			✓
Duerksen et al, 2004	✓		✓	✓	NA		✓	✓
Brard et al, 2006			✓			NA		✓
Soo and Gramlich, 2008					✓		NA	
Chermesh et al, 2011	✓		✓		✓	✓		NA

4.3.3 Meta-analysis of survival length

The results from the study of Mercadante (103) were excluded from the analysis as they were not considered to reflect current clinical practice (discussed further in Chapter 3 -). Without the study of Mercadante, using the remaining 7 studies (70, 99-102, 105, 107) (244 patients, 92.6% with IBO), the meta-analysis amalgamated data has a median survival of 83 days (95% CI 67 – 100 days), with the mean of 116 days.

A series of random effects meta-analysis of survival at monthly time points were carried out. The results are presented in Figure 9 demonstrating the mortality to be 14%, 36%, 55%, 69%, 74% and 78% at 1, 2, 3, 4, 5, and 6 months respectively.

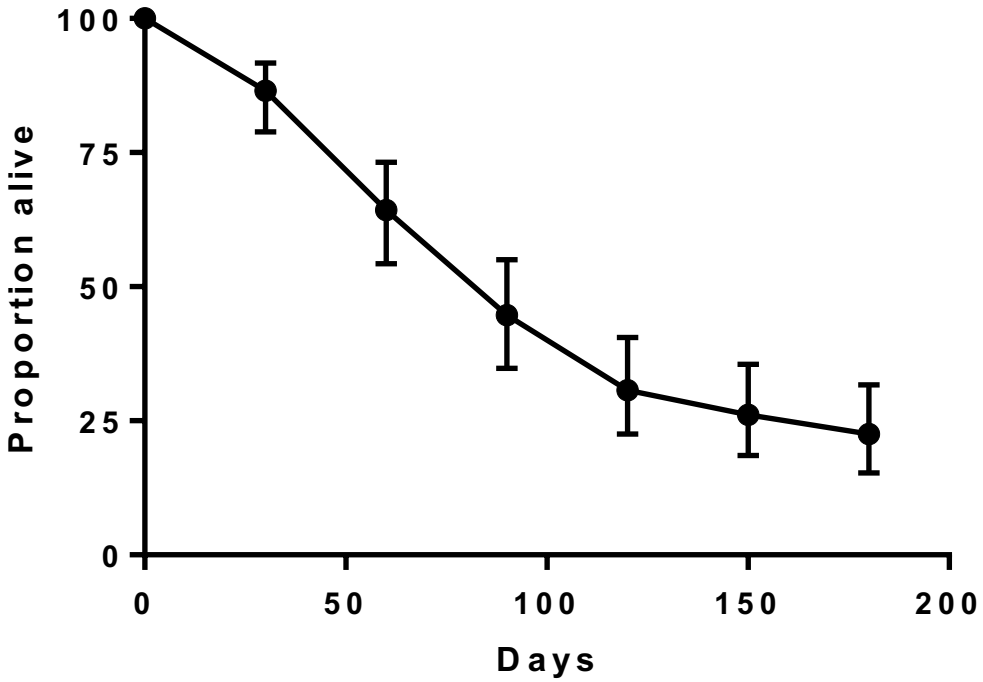

Figure 9 Proportion of patients alive at monthly intervals during the first six months (n=244). Each point shows the mean and 95% confidence interval at each month, established using a random effects meta-analysis of extracted survival data from the included studies (7 studies, 244 subjects) (70, 99-102, 105, 107)

4.3.4 Analysis of survival length by patient characteristics

Survival length by type of malignancy, performance status and concomitant palliative chemoradiotherapy was examined using individually extracted data. Since these subject characteristics could only be extracted from some studies, the analyses below were based on a total of 130 patients or less.

4.3.4.1 Type of malignancy

Survival data for type of primary malignancy were available for 53 patients from 3 studies (100, 105, 107). Gastrointestinal malignancy patients (n=15) from 2 studies (105, 107) were found to survive longer than those with gynaecological malignancy (n=38) from 3 studies (100, 105, 107) with a median survival 106 days vs. 57 days respectively (p= 0.012, log rank test) (Figure 10 (a)).

4.3.4.2 Performance status

Survival data and baseline performance status, assessed using the Karnofsky performance score (KPS) (range 0-100), were available for 81 patients, from two studies (100, 107). Patients with a higher performance status, defined as KPS>50, (n=27) were found to survive longer than those with a KPS<50 (n=54) with a median survival 183 days vs. 91 days respectively (p= 0.01, log rank test) (Figure 10 (b)).

Soo and Gramlich (70) did not report the survival length of individual patients in a way that could be matched with performance status, but a summary statement in the paper also indicated significantly higher survival in patients with KPS>50 compared to those with KPS≤50 (median survival 183 vs. 91 days; p= 0.01, the number of patients in each group was not reported).

4.3.4.3 Concomitant palliative chemoradiotherapy

Survival length in the context of concomitant palliative chemoradiotherapy was established for 37 patients from two studies (101, 107). There was no significant difference between the survival length of patients receiving palliative chemoradiotherapy (n=22) and those not receiving it (n=15) (median survival 75 vs. 52 days respectively; p=0.535, log-rank test) (Figure 10 (c)).

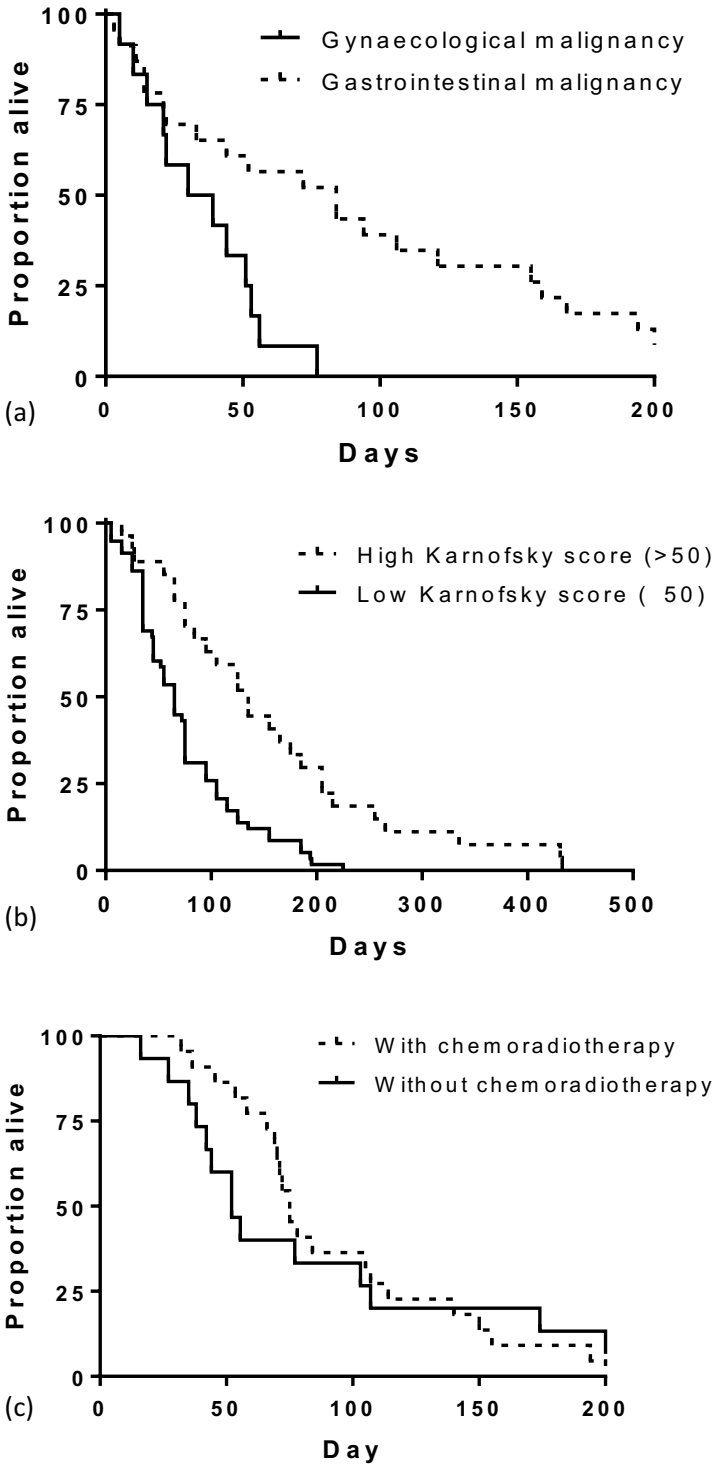

Figure 10 (a), (b) and (c) – Kaplan Meier survival curves, based on extracted data, by patient characteristics demonstrating statistically significant difference in survival depending on (a) type of malignancy (p= 0.012) and (b) performance status (measured by Karnofsky performance score) (p= 0.01) and lack of a difference for patients who underwent (c) concurrent palliative chemoradiotherapy during parenteral nutrition treatment (not significant)

4.4 Discussion

Using random effects meta-analysis the survival pattern of incurable cancer patients with inoperable bowel obstruction treated with HPN can be defined, showing a median survival of 83 days (2.7 months) with over half of patients dying within 3 months. The amalgamation of data leads to tighter 95% confidence intervals giving greater confidence.

Although similarities in survival patterns exist between the eight studies, especially over the first 100 days as demonstrated in Chapter 3, the analyses described in this chapter quantify the degree of variability. This variability may have been caused by variability in patient selection process and different definitions of survival length by authors, along with variation in intrinsic patient characteristics.

The data amalgamation carried out in this chapter suggest that the baseline performance status and type of underlying malignancy influences the survival length and hence may be useful in selecting patients likely to survive for longer with HPN treatment.

The use of palliative chemoradiotherapy was not associated with longer survival but there was insufficient information to ascertain which, if any, of the palliative chemoradiotherapies could lead to longer survival or whether different types of malignancies respond better than others. This topic requires further research.

Since the search period of the systematic literature review, a further large study of survival lengths for patients with incurable cancer treated with HPN has been published by Bozzetti et al (2014) (79). This study would not have met the inclusion criteria for this review because there was mixed reporting of survival length of patients with and without IBO (approximately two-thirds of patients had bowel obstruction, further comment was not made about the indication for HPN in the remaining third). Despite this, this multi-centred international series (n=414) reported strikingly similar survival outcomes as those produced by the above meta-analysis.

The median survival in the study of Bozzetti et al (2014) (79) was 91 days (cf. 83 days in this meta-analysis), with 3 and 6-month mortality of 50% and 77% (cf. 55% and 78% in this meta-analysis). The prospective nature of this trial and the strikingly similar results compared to the retrospective meta-analysis in this chapter give confidence that, if current patient selection criteria are used, the survival outcomes that can be expected are as described as above.

Additionally, the Bozzetti et al (2014) (79) trial results also provide confidence in the methodology of the meta-analysis described above with respect to data extraction, validation and appropriate statistical modelling use as well as evidence that the meta-analysis was not unduly effected by 'the file drawer problem', since unpublished survival data suggesting shorter survival times would have unduly pushed the meta-analysis survival data upwards.

The results of the meta-analysis also enable comparison of survival length to the potential control population described in Chapter 3. Chakraborty et al (87) described the survival of 35 patients with palliative malignant BO, 34% of the patients did undergo surgery. The patients in Chakraborty et al (87) were described as a group and the non-surgical patients were not described separately. This patient group is therefore, at best, a surrogate for the inoperable group described in this meta-analysis. The survival median for patients described in Chakraborty et al (87) was 80 days, which is similar to that found in this meta-analysis. It can be assumed that the operable nature of 34% of the Chakraborty et al (87) patients represents a better disease and co-morbidity status and the use of HPN in only one patient, is additional evidence that the Chakraborty et al patient population had lower grades of BO and stages of malignancy. If this assumption is correct, the use of HPN in the IBO patient group in this meta-analysis can be interpreted as prolonging the patients' lives, which would be in keeping with the hypothesis for this chapter. Due to the lack of a control group for the HPN treated patients this hypothesis remains incompletely tested, but these results add evidence to the hypothesis that HPN increases survival in the context of malignant IBO and intestinal failure.

The lack of a control group for HPN treated palliative malignant IBO patients is unlikely to be resolved as PN treatment is widely available and accepted in developed countries where the above data are collected. The study of patient survival with palliative malignant IBO not treated with HPN can only be achieved if those patients offered HPN choose not to have the treatment, while receiving all the additional palliative treatments afforded to the HPN population. The reasons for the refusal may or may not be interlinked with their underlying performance state and hence limit the comparison even in this circumstance.

Baseline performance status in addition to the Glasgow Predictive Score (based on serum albumin and C-reactive protein), were identified in the study of Bozzetti et al (2014) (79) as patient characteristics that can aid in survival length prognostication. The utilisations of these factors for patient selection are further discussed in Chapter 5.

Using these data clinicians can have greater confidence when counselling patients and family members regarding the likely survival outcomes when commencing HPN for patients with incurable malignancy, especially in the context of IBO.

As discussed in Chapter 1 of this thesis, there is evidence that PN can lead to proliferation of tumour cells, but despite this, survival improvement has been observed in palliative patients treated with PN (67). The presence of IBO in the palliative phase should further distance the clinician's concerns regarding tumour proliferation as mortality will be caused by dehydration and malnutrition rather than tumour burden.

Chapter 5 - Case series and assessment of survival time predictive tools in patient selection for palliative malignancy HPN therapy

5.1 Introduction

The average and median survival time for cancer patients with intestinal failure treated with HPN have been described in Chapters 3 and 4, but there have been no UK based case series on survival times for such patients. In this chapter, the primary aim was therefore to report a retrospective analysis of such patients treated by the University Hospital Southampton Intestinal Failure team. The secondary aim was to retrospectively apply two prognostic tools to assess their value in patient selection through their accuracy in predicting survival length.

The application of the ESPEN 2009 guidelines (18) poses a challenge for physicians, as patient selection is partly based on the clinician's prediction that the patient is likely to survive greater than 2-3 months with HPN. This is due to a perceived, though controversial, assumption that represents the minimal period for the patient to benefit from treatment with regards to QoL. Discussion of this assumption has been presented in Chapter 3, predominantly based on the results of one QoL study reported by Bozzetti et al (2002) (102).

Clinician prediction of survival (CPS) has been shown to be inaccurate with a bias for overestimation (74, 112, 113). Development of reliable survival length predictive tools would aid clinicians in minimising the risk of under or over treatment with HPN in the palliative phase.

Two predictive tools for survival length were chosen for analysis. The first was chosen because it was developed in a highly relevant patient group in the case series by Bozzetti et al (2014) (79), utilising the combination of Karnofsky Performance Status (KPS) and the Glasgow Prognostic Score (GPS) at commencement of HPN. KPS is a validated subjective score of performance whilst GPS is based on the patient's blood concentrations of C-reactive protein and albumin. In the study

of Bozzetti et al (2014) (79) 414 patients were categorised according to KPS (up to 50 or above 50) and then sub-divided further into three tiers by GPS (0, 1 or 2). Patients were therefore categorised into six sub-groups, (most favourable, four intermediate groups and least favourable) with statistically significant differences in intergroup survival times at 3 and 6 months.

The Palliative Prognostic Score (PaP) was chosen due to its widely accepted application in palliative care. The PaP was developed (114) and has been validated (115) in large groups of palliative malignancy patients with varied underlying malignancies. Although the design of this tool was not based on patients with IF or HPN therapy, we hypothesised that the use PN would replace the patient's inability to gain nutrients and hydration and hence HPN would return the patient's survival to the same trajectory had IF and HPN not been necessary. The PaP score uses weighted scores for four subjective indices (CPS, KPS, presence of anorexia and presence of dyspnoea) as well as white blood cell count and lymphocyte percentage to categorise patients into three sub-groups with statistically significant differences in survival at 1, 2 and 3 months.

5.2 Methods

A retrospective search was conducted for all patients commenced on HPN in the palliative phase of malignancy by the University Hospital Southampton IF team, dating from inception of HPN services in January 1990 until January 2014. All patients were commenced on PN with the intention of long-term treatment in a home environment although all cases were included regardless of whether discharge home was actually achieved.

Decisions to start HPN were carefully considered on an individual patient basis, with assessment involving the patient, family and the multidisciplinary intestinal failure Team. Key features of the selection process were a good performance status at baseline, exhausted attempts at providing enteral nutrition or surgical reversal of IF, and patient consent despite awareness of prognosis and burden of treatment.

Retrospective review of the patient records included medical, nursing, dietetic and electronic notes to collect data on patient demographics, type of underlying malignancy, presence of metastasis, gastrointestinal anatomy, need for venting gastrostomy, use of concurrent chemoradiotherapy, PN-related complications and survival time.

Cases were also retrospectively classified using the recently developed ESPEN classification of IF in adults according to functional, pathophysiological and clinical status (116).

Survival time was defined from the date of commencing PN in hospital until date of death. Survival patterns were illustrated using Kaplan-Meier graphs and differences in sub-group survival patterns were statistically analysed using log-rank tests and unpaired t-tests with significance at 95%. Analyses were performed using GraphPad Prism (version 6, California, USA).

Both the PaP score and the KPS/GPS model were retrospectively calculated for each patient. Subjective data were assigned and agreed through Nutrition Support Team multidisciplinary

discussion of each case. Blood test indices required for both prognostic tools were applied from blood results on the date of commencing PN or the preceding week.

For the PaP tool, weighted overall scores for each patient were calculated to allow classification into one of three PaP groups. The KPS/GPS model categorised patients into six sub-groups; the most and least favourable and four intermediate groups.

5.3 Results

20 patients were identified who were treated with long-term PN during the palliative phase of malignancy with the intention to discharge to a home environment. This represented 19% of the total of 104 patients commenced on HPN during this period for all indications. Patient characteristics are described in Table 10.

All patients demonstrated complete, irreversible type 3 IF as the indication for HPN therapy. The mean age of the patients at the time of commencing PN was 54 years (median 56 years; range 34 to 74 years) (Table 10). The majority of patients were female, 12 (60%). The underlying primary malignancy was gastrointestinal (GI) in 12 (60%) and gynaecological in 5 (25%), pseudomyxoma in 2 (10%), and unknown in 1 (5%) patient. There was evidence of metastasis in 18 (90%) patients. Four (20%) patients underwent concurrent palliative chemoradiotherapy therapy (for symptom control) after commencing HPN. Of the 20 patients, 16 (80%) required PN while 4 (20%) required only parenteral fluids.

The first patient to commence HPN during palliative malignancy was in the year 2005, after which there was a trend towards increasing numbers per year with zero to three patients commenced yearly up to and including the year 2012, and nine patients commencing HPN in the year 2013 (Table 10).

In accordance with the recent ESPEN classification (3) of IF in adults, all patients were 'functionally classified' as type 3 IF (chronic condition, requiring PN long term). Their ESPEN 'pathophysiological classification' was 'mechanical obstruction' in 17 (85%) patients (5 of these patients had 'high-grade' obstruction requiring gastric venting tube and 12 due to 'sub-complete' obstruction not requiring venting tube, though failing sufficient enteral feeding), 'short bowel' in 3 (15%) patients secondary to surgery to relieve malignant BO with a resulting proximal jejunostomy, and 'intestinal fistula' in 1 (5%) patient, caused by malignant broncho-oesophageal fistula, who was

unable to tolerate oral or tube feeding. Data for ESPEN 'clinical classification' based on energy and volume requirements were available for 13 (65%) patients and are detailed in Table 11, which shows there was a tendency for high volume and energy requirements. All 4 patients classified in the lower energy sub-categories (classified as A and B, 0-10 Kcal/kg/day) were receiving parenteral fluids only with minimal energy supply from glucose, while all the other patients were classified in the high sub-category (classified as D, >20Kcal/kg/day).

All patients commenced PN in hospital using a long term central venous catheter. Successful discharge to a home environment was achieved in 17 (85%) patients; 2 of these patients expressed a wish to be discharged to a hospice long term for social reasons (hospice admission lengths of 43 and 119 days). Of the remaining 3 (15%), 1 patient was readmitted only one day after discharge and her health consequently deteriorated. Two further patients died in hospital during their index PN admission due to deterioration in health while discharge plans were being made. 33% of total survival length for all patients was spent in hospital (range 6-100%). The mean percentage time spent in hospital was 43% and median was 37% (though lower in those successfully discharged, 35% and 34% respectively).

Table 10 Patient demographics, characteristics and survival length

Patient number	Age at start of HPN	Sex	Calendar year of commencing HPN	Primary malignancy	Presence of metastasis	Long term gastric venting	PN or IVI fluid only	ESPEN clinical classification¥	Concurrent palliative chemotherapy or radiotherapy	Days as inpatient after starting PN	Days in home environment after starting PN	Overall survival (days)
1	47	M	2006	Rectal	Yes	No	PN	-	No	28	133	169
2	59	F	2007	Ovarian	Yes	No	PN	-	Chemotherapy	122	119	241
3	40	F	2006	Unknown	Yes	Yes	PN	D3	No	71	150	225
4	47	M	2009	Pseudomyxoma	Yes	No	PN	D3	No	16	13	29
5	61	F	2009	Rectal	Yes	No	IVI	B3	No	22	27	68
6	68	F	2010	Ovarian	Yes	No	IVI	B3	Chemotherapy	14	100	114
7	48	F	2010	Colonic	Yes	Yes	PN	D3	No	31	83	114
8	49	F	2011	Pseudomyxoma	No	No	IVI	A1	No	69	116	185
9	55	F	2010	Ovarian	Yes	Yes	PN	-	Chemo/radiotherapy	30	5	37
10	41	F	2013	Colonic	No	No	PN	D2	No	28	43*	74
11	41	M	2012	Small bowel (adenocarcinoma)	Yes	Yes	PN	D4	No	129	119*	248
12	34	M	2013	Oesophageal	Yes	No	PN	D3	No	15	26	41
13	58	F	2013	Appendix	Yes	No	PN	D3	No	47	1	56
14	67	F	2013	Endometrial	Yes	No	PN	-	No	25	64	89
15	53	M	2013	Gastric	Yes	No	PN	-	No	25	0	32
16	55	FF	2013	Ovarian	Yes	No	IVI	B3	No	44	55	99
17	62	M	2013	Colonic	Yes	No	PN	-	No	54	0	65
18	74	M	2013	Colonic	Yes	No	PN	D4	No	204	385	589
19	56	F	2013	Colonic	Yes	Yes	PN	D4	No	21	123	149
20	58	M	2005	Small bowel (carcinoid)	Yes	No	PN	-	No	29	429	458

*Entire period spent in hospice, ¥European Society of Parenteral and Enteral Nutrition (ESPEN) clinical classification (where data available), see Results section and Table 11 for further information

Table 11 European Society of Parenteral and Enteral Nutrition (ESPEN) 'clinical classification' of intestinal failure in adults, based on energy and fluid volume requirements per day (116). Table demonstrates the number of patients classified in each sub-category (data available in 13 patients)

Intravenous energy (Kcal/kg/day)	**Intravenous fluid volume** (ml/day)			
	≤1000 (Classification **1**)	**1001-2000** (Classification **2**)	**2001-3000** (Classification **3**)	**≥3000** (Classification **4**)
0 - (Classification **A**)	1			
1-10 - (Classification **B**)			3	
11-20 - (Classification **C**)				
>20 - (Classification **D**)		1	5	3

Four (20%) patients each had one confirmed central venous catheter blood-stream infection (CVC-BSI), translating to a rate of 1.52 per 1000/PN days, consistent with the Southampton IF department's overall HPN CVC-BSI rate of 1.42 per 1000/PN days for all patients.

At the time of commencing PN, 18 (90%) patients were judged to have a performance status corresponding to KPS >50 and only 2 (10%) patients with KPS ≤50 (Table 12). The performance status was KPS ≥80 in 13 (65%) patients, and compared to those with KPS <80 the percentage time spent in hospital was lower (30% vs 43% respectively, p=0.0467, t-test). 19 (95%) patients were judged to have a CPS >12 weeks, with only 1 patient judged to have a CPS 3-4 weeks (Patient 12).

Patient 12 was assessed and offered HPN therapy during the palliative phase of malignancy in spite of his poor performance status and short expected survival, which was due to exceptional circumstances. The cause of Patient 12's IF was broncho-oesophageal fistula secondary to an aggressive recurrent oesophageal adenocarcinoma, with failed attempts at placing a covered stent and enteral tube feeding. At the time of commencing PN he was only 34 years-old and expecting the birth of his first child within 2 months. He survived a total of 41 days from starting PN, 26 days were at home. He died a few days after his son was born.

The median survival of the remaining 19 patients was 106 days (3.5 months), with a mean of 154 days (5.1 months) (range 29 to 589 days), 3 and 6-month survival was 55% and 30% respectively. The overall survival pattern is demonstrated by Kaplan-Meier graph in Figure 11. Comparison of the survival length of patients with GI (n=12) compared to gynaecological malignancy (n=5) was not statistically significant (p=0.7752, log-rank test).

The 9 patients classified in the higher energy ESPEN sub-category (classification D, all PN fed) survived for a mean of 164 days, compared to a mean 117 days in the 4 patients classified in the lower energy sub-categories (classification A and B, all parenteral fluid only), their median survival

was similar at 102 and 107 days respectively, with no significant statistical difference when comparing the survival curves for high vs. low energy patients (p=0.6380, log-rank test).

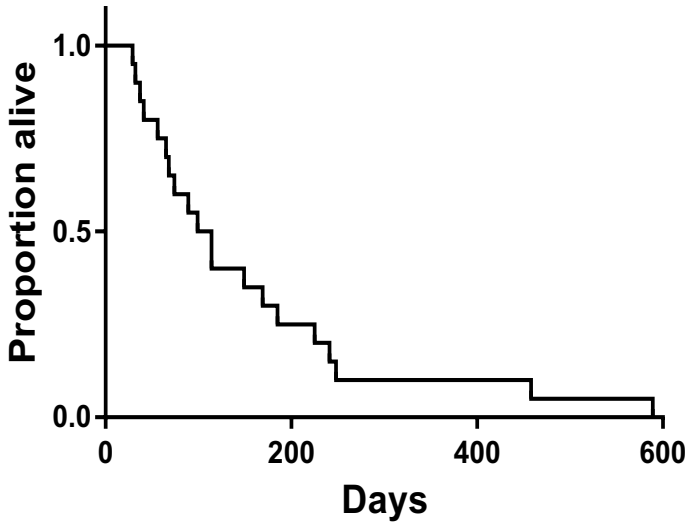

Figure 11 Kaplan-Meier survival curve demonstrating the survival pattern of n=20 malignancy patients with intestinal failure treated with home parenteral nutrition

Table 12 Prognostic predictive scores per patient. KPS – Karnofsky Prognostic Score, GPS – Glasgow Predictive Score, PaP – palliative prognostic score

Patient number	KPS	GPS	KPS/GPS group	PaP Group
1	80	0	Most favourable	A
2	80	2	Intermediate*	A
3	90	2	Intermediate*	A
4	90	2	Intermediate*	A
5	60	2	Intermediate*	A
6	90	1	Intermediate	A
7	80	2	Intermediate*	A
8	90	2	Intermediate*	A
9	50	NA**	NA**	A
10	70	2	Intermediate*	A
11	80	NA**	NA**	A
12	40	2	Least favourable	C
13	70	NA**	NA**	A
14	90	2	Intermediate*	A
15	90	1	Intermediate	A
16	70	2	Intermediate*	A
17	60	2	Intermediate*	A
18	90	2	Intermediate*	A
19	90	2	Intermediate*	A
20	80	1	Intermediate	A

*12 patients in same intermediate group of KPS>50/GPS=2, ** NA – Due to lack of blood results data within one week of commencing PN

When the criteria for the PaP score were applied 19 (95%) patients were categorised into the most favourable PaP group A, zero patients into PaP group B and one (5%, Patient 12) patient into the least favourable PaP group C (Table 12). The observed survival of the 19 patients categorised into PaP group A was higher than that predicted; 18 (95%) patients survived up to 30 days (PaP group A predicts 82%), 15 (79%) survived up to 60 days (PaP group A predicts 55%) and 11 (58%) survived up to 90 days (PaP group A predicts 32%) (Table 13). Patient 12 was appropriately categorised into the least favourable PaP group C (survival length 41 days). 5 patients had ultra-short survival (less than 2 months), 4 were categorised as PaP group A.

Table 13 Palliative prognostic score (group A) predicted survival compared to witnessed survival at monthly time points

Time	**Predicted survival at monthly time points**	**Percentage survival in this case series at monthly time point**
1 month	82%	95% (n=18)
2 months	55%	79% (n=15)
3 months	32%	58% (n=11)

Blood results were not available to apply the GPS score in 3 (15%) patients as they had been commenced on PN at other centres before transfer to University Hospital Southampton IFU, hence the KPS/GPS classification was completed in 17 (85%) patients. As demonstrated in Table 14, one (5%) patient was categorised into the most favourable group (KPS>50/GPS=0) (Patient 1, survival length 169 days), three (18%) and 12 (71%) patients into two of four intermediate sub-groups and one (5%) patient into the least favourable group (KPS≤50/GPS=2) (Patient 12, survival length 41 days).

Table 14 KPS/GPS model sub-groups with associated predicted survival percentages, the number of patients categorised into each sub-group and observed survival percentage at 3 months

KPS/GPS sub-groups	3 month predicted survival	Classification of sub-group	Number of patients categorised into sub-group	Percentage observed survival at 3 months
KPS>50 and GPS=0	79%	Most favourable	1	NA*
KPS>50 and GPS=1	58%	Intermediate	3	NA*
KPS>50 and GPS=2	56%	Intermediate	12	58%
KPS≤50 and GPS=0	60%	Intermediate	0	NA*
KPS≤50 and GPS=1	36%	Intermediate	0	NA*
KPS≤50 and GPS=2	33%	Least favourable	1	NA*

* NA – Not applicable due to small numbers in sub-group

The only KPS/GPS sub-group with sufficient numbers to allow comparison with the predicted survival length outcomes was the intermediate KPS>50/GPS=2. Of the 12 patients in this intermediate subgroup, 58% were alive at 3 months compared to 56% in the original model. Three patients who had ultra-short survived (less than 2 months) were each grouped in separate intermediate groups.

5.4 Discussion

The results of this chapter demonstrate short but variable survival lengths in 20 palliative malignant IF patients treated with HPN, with median survival of 99 days, and 55% and 30% survival at 3 and 6 months respectively. This compares closely to the survival data reported in Chapter 3 and Chapter 4, which is in keeping with the first hypothesis for this chapter.

The majority of patients were classified in the ESPEN 'Clinical classification' (116) as requiring high volumes and energy requirements. This represents their inability to use the oral/enteral route for either, both suggestive of severe IF, which without PN support would have led to death within days or weeks, strongly suggestive that HPN extended the patients survival.

At University Hospital Southampton there was a noteworthy increase in the yearly prevalence of palliative malignancy HPN patients in 2013. This is in keeping with British Artificial Nutrition Survey (BANS) 2016 report (49) showing a significant increase in this indication for HPN in the UK. BANS data demonstrates that 25% of all new HPN patients are for palliative malignancy, which is significant increase from pre-2013 data. There are many reasons for this increase including greater awareness of this potential treatment, especially amongst colorectal and gynaecology specialities, but the improved provision of HPN services through the HPN Framework have also led to quicker discharge facilities favouring the palliative cancer patient group.

The secondary aim of this study was to evaluate two survival time predictive tools in this patient population. The results suggest that the KPS/GPS model is more likely to be a suitable prognostic tool, though there are inadequate numbers of patients to fully assess either tool. Hence, the second hypothesis that the prognostic tools would be of value in patient selection is not supported.

In KPS/GPS model, where there are six sub-groups, through chance there was a clustering of 60% of patients on one of the intermediate sub-groups, which allowed comparison with the original

study in this sub-groups. In this intermediate sub-group (KPS>50 and GPS=2) a similar proportion were alive at 3 months compared to that predicted.

When the PaP score was applied, all but one patient was categorised in the most favourable prognostic group (group A). The survival times for these 19 patients were longer than predicted by the PaP score. Although this longer survival could be ascribed to chance in view of our limited numbers, it could also be explained by three other factors. Firstly, the PaP model is not based on a similar patient group and hence may not be applicable and hence it underestimates in this case series. Secondly, the patient selection process undertaken in our department favours selection of longer surviving patients even if compared to those generally categorised into the most favourable sub-group of the PaP score. Thirdly, the patients in the original PaP study were either oral or enterally fed, which may have been insufficient, while the PN use in our cases is more likely to meet the nutritional requirements of the patients leading to longer survival.

Both tools were shown to have low sensitivity, but high specificity for patients with ultra-short survival (less than 2 months). This suggests that if a patient is classified in an unfavourable prognostic sub-group the clinician can have greater confidence in guiding the patient's decision regarding not commencing HPN, allowing for goal driven decisions to be made.

The above results show that survival length prediction tools have potential use in the challenging practice of patient selection for HPN in the palliative phase of malignancy to avoid under- and overtreatment with HPN. Based on our results it is not possible to validate or discount either of these prognostic tools. The KPS/GPS model at 3 months appears to fit the survival pattern better, with a suggestion for high specificity for ultra-short survival, although poor sensitivity. The better predictive value of the KPS/GPS is probably due to the model originating from a highly relevant patient group.

Modifications are required to improve reliability of both tools. In the systematic review of survival prediction tools by Vigano et al (117), the solitary use of CPS was discouraged, but incorporation of CPS into predictive scores was recommended. The weighted addition of CPS to the KPS/GPS

model may contribute to improving reliability, which would in turn require formal prospective validation. Currently the use of prognostic survival tools should be as part of a diligent assessment, based on clinical acumen and multidisciplinary discussion involving the patient and family.

Chapter 6 - Attitudes towards HPN use in the palliative phase of malignancy

6.1 Introduction

Commencing HPN treatment for an individual patient with palliative malignancy is influenced by many factors. The prevalence of this indication varies widely across Europe and the rest of the world, these variations have been reported in detail in Chapter 1. The causes of these variations are multifactorial with complex interdependence of these factors, which included historical use of treatment, availability of treatment, health economics and established referral pathways from associated specialities such as Oncology, Surgery and Palliative Medicine. But in many countries where there are comparable health economies and access to HPN, the most influential factors will be based on attitudes of clinician and to a lesser extent patients and family. These attitudes are influenced by cultural, religious, media and public opinion regarding the dying process.

The topic of palliative HPN creates divisive opinions in the medical literature, with both advocate and opposing opinions expressed. It is worth noting that the opinions published in the medical literature appear to have lagged behind the opinion implied by the day-to-day practice of the intestinal failure clinicians in many countries.

Dr Federico Bozzetti, has been a vocal advocate of this therapy over the last three decades. He is widely published on this topic and his views represent the more enthusiastic opinions on this topic. His works include multiple studies on QoL and survival length in this patient group (14, 79, 89). He was also the Chair and lead author for European Society of Parenteral and Enteral Nutrition (ESPEN) society's guideline on PN in non-surgical malignancy in 2009 (18) which included PN for patients in the palliative phase of malignancy. In 1987, in his study regarding the effects of PN on nutrition parameters in advanced malignancy he concluded that "the effect of TPN on the nutrition status of patients with cancer is cautiously optimistic" (118). Later in 2001 when the changes in nutritional parameters proved challenging in terms of improvement in clinical outcomes he commented that "when there is uncertainty regarding benefits of HPN to the

patient, a pragmatic 'try and see' approach can be taken" (119). Although his enthusiasm has not diminished with time, his opinions have become more aligned with the mainstream, expressing in 2011 "what we see in clinical practice is that there are 'some' incurable cancer patients who die prior from starvation rather than tumour progression who would benefit for PN" (120).

Opposing authors have argued that the lack of convincing evidence for this treatment makes it unethical to continue providing it as great cost. This opinion was forcibly expressed in the emotively titled "Must every cancer patient die with a central venous catheter?" by Buchman in 2002 (121) and "To live or not to live?" by Arends in 2010 (122). Both these articles favour conservative management of advanced cancer patients without the use of parenteral support.

In the last few decades the involvement of patients and their relatives in the decision process regarding palliative HPN has also changed due to clinician's changing attitudes. This level of involvement has varied between countries based on many cultural factors, but the changes have been most pronounced in publications from Italy. In the study of Bozzetti et al (2002) (102) on QoL for palliative HPN patients a significant proportion of patients (30/69, 43%) were not aware of their cancer diagnosis and the greater majority (63/69, 91%) were not aware of their prognosis when commenced on palliative HPN. Similar evidence of this now dated approach was also demonstrated by Mercadante (103) where the role of the family in commencing HPN was described as "the family can induce the team and patient to start or continue PN, even if the patient is at some level oppose to the treatment". Although this attitude may now cause concern in some clinicians, through personal communications with IF physicians in Italy, I have been made aware of elements in Italian culture that need to be considered and particularly that the influence of the Roman Catholic Church is significant, supporting a principle of the sanctity of life and its preservation at all costs and hence more aggressive end of life treatments.

More recent publications reflect a change in these attitudes and the ESPEN 2009 guideline group (18) stress the importance of patient participation as one of the four conditions that should be met to support the use of HPN in palliative malignancy. Again through further personal

communication with IF clinicians in Italy, the prevailing attitude is that more clinicians are now informing the patient of their diagnosis and prognosis prior to commencing HPN.

The article by Whitworth et al published in 2004 “Doctor, does this mean I am going to die” (123) represents the changing attitudes of clinicians in the increasing involvement of patients regarding the decision making process of palliative HPN.

To appreciate the significance of any of the attitudes expressed in the medical literature a number of factors regarding the context of the published opinion need to be considered in parallel. These factors are country of origin (i.e. prevailing local culture), year of publication and relation to significant other publications or guidelines released near the time of expressed opinion.

Although it is challenging to succinctly summarise the prevailing opinion on this controversial topic, the apparent change in attitudes over the last few decades have undoubtedly been a softening of opposition and acceptance of sub-groups of patients in the palliative phase of malignancy that can benefit from HPN.

There are no published data regarding surveyed opinions of clinicians towards this treatment within or outside the UK. This chapter explores the attitude of intestinal failure clinicians in the UK, aiming to identify clinician’s knowledge of international guidelines, explore aspects of positive and negative opinions, highlight potential barriers to treatment and potentially identify differences in principles of practice between UK and comparable countries.

6.2 Methods

A questionnaire was designed to assess clinicians' attitudes in relation to four distinct aspects of palliative HPN. These were: the role and experience of the clinician; clinician's awareness of international guidelines; attitudes towards indications; and attitudes towards the treatment as a whole.

The questions were optimised through consultation with members of the Nutrition Support Team at University Hospital Southampton and were further critiqued by Dr Emma Parsons (personal communication) who has extensive experience regarding surveys of attitudes towards nutritional therapies.

Survey Monkey™ was used to design the online survey. Online functions were used to direct the flow of the survey depending on the answers provided (named 'Question Logic' function) and to enforce compulsory answers to questions of high importance, although a 'Do not know' or equivalent option was provided for every question. Participants were also invited to leave comments.

For a full version of the survey please refer to Appendix A.

Members of three professional UK nutrition societies were invited by email correspondence to participate in the online survey during the period of 1st November 2013 and 1st April 2014. The three societies were the British Intestinal Failure Alliance (BIFA), British Dietetic Association (BDA) and National Nutrition Nurses Group (NNNG). Two reminder invites were sent during the period of the study. The professions represented by these associations are Gastroenterologist, Colorectal, Biomedical, pharmacists, nurses other medical, surgical and paramedical specialities with self-expressed interest in IF/nutrition and general dietitian members of the BDA who were asked to partake if they had prior experience with HPN services.

Results were analysed using Microsoft Excel 2010 and graphically represented utilising graph functions of Survey Monkey™.

6.3 Results

The survey was returned by 70 respondents, with 52 (74%) completing >90% of questions. The most prevalent professions were dietitians and gastroenterologists with 29 (41%) and 23 (33%) respondents respectively (Figure 12), although dietitian respondents had the highest level of incomplete questionnaires.

Geographical location of respondent was an optional entry, which was completed by 42 (60%) of respondents with all four nations of the UK represented. England represented the majority of respondents (79%), followed by Scotland (12%), Wales (7%) and Northern Ireland (4%).

Half of the respondents (53%) reported practicing within Regional IF Units, with 13% at National IF Centres and 24% at District General Hospitals. 21 out of 23 (91%) gastroenterologists reported being primarily responsible for decisions regarding commencing HPN in their organisation compared to: 7 out of 29 (24%) dietitians; 1 out of 8 (13) nurses; 3 out of 6 (50%) surgeons; 2 out of 3 (67%) clinical biochemists and 2 out of 3 (67%) pharmacists.

The level of experience with HPN services amongst respondents was high with 56% of respondents reporting >10 years of experience, see Figure 13. Clinicians practicing in the national IF centres reported higher experience with a mean of 20 previous palliative HPN patients compared to mean of 8 patients for regional IF centres and 3 in District General Hospitals. 80% of respondents indicated awareness of European Society of Parenteral and Enteral Nutrition (ESPEN) 2009 guidelines regarding palliative HPN.

When considering the indications for use of HPN in the palliative phase of malignancy, 89% of respondents would support the use of HPN therapy to improve quality of life (QoL) alone and 75% to improve performance status (PS) alone, irrespective of potential to prolong life, while only 13% would support palliative HPN if it was considered life prolonging. Only 9 (18%) out of 51 respondents who gave an answer regarding predicting the survival length of patients felt confident in their estimation.

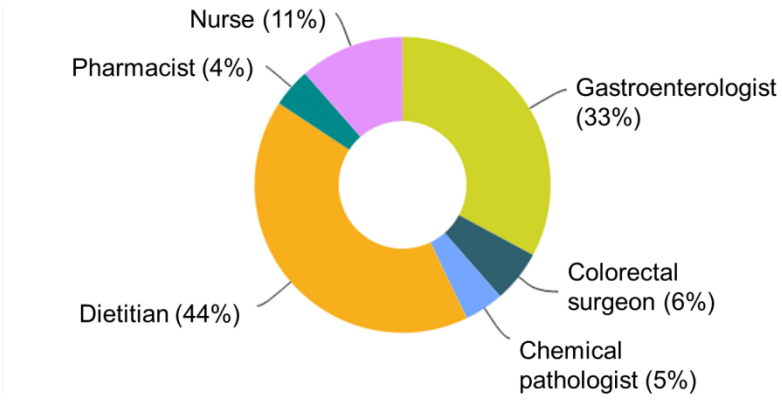

Figure 12 Professions of survey respondents

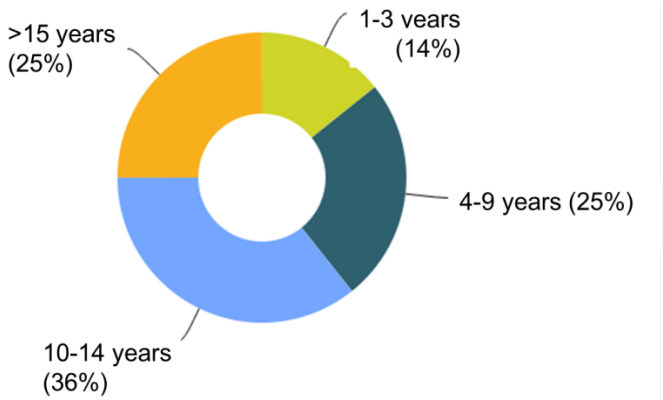

Figure 13 Life time experience of survey respondents with home parenteral nutrition services for both benign and malignancy indications

The majority (47 respondents, 87%) reported supporting the use of palliative HPN only in the presence of IF, although 19 (35%) did report use of 'supplemental' HPN without the presence of IF. Where respondents indicated experience with supplemental palliative HPN, further questions regarding indications were posed. The strongest indications for supplemental HPN were for dehydration and QoL, while family's preferences were considered a 'common indication' by 42%.

When asked about their interpretation of patient's experience with palliative HPN, 63% of respondents perceived a positive effect on QoL, 54% perceived improvement in PS and 44%

perceived a probable extension of survival length due to HPN therapy. Only 6% believe PN would adversely affect tumour growth. Table 15 describes further attitudes explored in this section of the survey.

Table 15 Attitudes towards effects of home parenteral nutrition therapy on palliative malignancy patients

Factors influencing attitudes	**Agree or strongly agree (%)**	**Neither agree nor disagree (%)**	**Disagree or strongly disagree (%)**	**NA (%)**
Palliative HPN would prevent weight loss	40	15	44	0
HPN affects tolerability of palliative chemoradiotherapy	37	45	14	4
Able to predict palliative HPN patient survival (≥2-3 months)	15	23	56	6
Able to predict HPN therapy effect on patient's QoL	44	29	27	0
The risk of HPN complications too high in this patient group	13	19	67	0
The equipment burden is too great in this patient group	10	19	71	0
Palliative HPN is not cost effective	17	37	44	2

Respondents were also asked to choose three perceived barriers to commencing HPN in palliative malignancy patients from a predetermined choice of six with the addition choice of 'other' and free text. Figure 14 shows the results of this section with the two most commonly perceived barriers being 'lack of clearly defined indications' (50%) and 'risks greater than benefits' (50%). Despite these barriers, 57% of respondents reported awareness of increasing utilisation of HPN for palliative malignancy patients in their department.

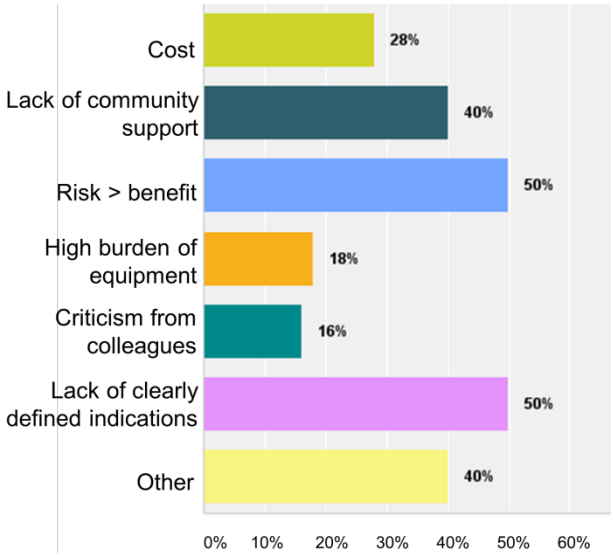

Figure 14 Perceived barriers for home parenteral nutrition for palliative malignancy patients as reported by survey respondents

6.4 Discussion

This is the first survey of attitudes of UK intestinal failure clinicians towards HPN therapy in the palliative phase of malignancy. The results show variable attitudes, with a general trend towards supporting this treatment for selected patient groups, which is in keeping with the the first hypothesis for this chapter.

This survey was purposefully aimed at the intestinal failure community, but advocate or opposing clinicians would not have received an invitation to participate unless they were a member of the relevant societies, this may have introduced a bias. Additionally, the attitudes of those clinicians involved in the care of advanced cancer patients, but not affiliated directly to their nutritional care, were not sought in this survey. These include oncologists, surgeons not affiliated with HPN services, gynaecologists, general practitioners and elderly care physicians, all of who care for advanced cancer patients. To gain a more profound understanding of the reasons leading to the lower UK prevalence the engagement of those specialities who may actively or passively withhold referral to HPN services would also be relevant.

The predominantly positive attitudes expressed in this survey would be consistent with evidence that the prevalence of palliative HPN in the UK is increasing (49), but it is clear from this self-reported survey that variation exists between the level of support. Not surprisingly those practicing in the larger centres, especially national IF centres had higher experience of this indication for HPN. Additionally, national and regional IF centre clinicians will naturally gain greater experience due to the centralisation of HPN therapy.

The ESPEN 2009 guidelines (18) aimed to set out indications for palliative HPN use. This survey demonstrates that within the UK intestinal failure community awareness of ESPEN 2009 guidelines is high, but despite this, ‘lack of clear indications’ was reported as the joint highest barrier to commencing treatment. As explored in Chapter 1, one of the four conditions set out in the ESPEN 2009 guidelines requires the clinician to predict the survival length of the patient as

greater or equal to 2-3 months as part of the conditions for commencing HPN, but this survey confirms that only a small proportion of clinicians feel able to make this judgement confidently.

Concerns regarding high complication rates were also reported as a barrier to commencing palliative HPN, although the majority of respondents also indicated in a separate part of the survey that they 'disagreed' or 'strongly disagreed' when asked if 'risk of HPN complications are too high in this patient group'. This may indicate that although clinicians are aware that the evidence from published studies suggests only a modestly higher rate of complications compared to the benign HPN population, this remains a factor that inhibits their decision to commence HPN in palliative cancer patients due to the significant impact complications would have on an already short survival length.

There was a greater importance placed by the survey participants on perceived improvement in patient's QoL and performance status, compared to perceived increase in survival length. Furthermore, there was greater support reported for HPN treatment to improve QoL and performance status, rather than just for survival length extension. This is contrary to the second hypothesis for this chapter that hypothesised equal emphasis would be placed by clinicians on improving length of survival and QoL.

This hints that within the surveyed clinicians there is a stronger motivation to improve the quality of remaining life, rather than simply to increase the survival length, though this may have been due to the wording of the question, which may have suggested the prolonged life would not be associated with benefits of QoL and performance status (Appendix A).

One of the factors identified as a potential cause for the difference in rates of palliative HPN utilisation observed between UK and Europe has been the higher rates of supplemental HPN use (i.e. use of PN without the presence of complete intestinal failure). Currently palliative supplemental HPN in Europe accounts for approximately 33% of cases (79). The results of this self-reporting survey shows that 35% of respondents have used supplemental HPN therapy in palliative malignancy patients, but the majority (87%) do not currently support HPN use without

the presence of intestinal failure. There are no published data available from the UK to estimate the proportion of palliative patients receiving supplemental HPN, but this survey suggests a generally negative attitude towards this therapy in the UK.

Given the lower prevalence of palliative HPN use in the UK, the predicted attitudes in this survey may have been more negative than those demonstrated, but this survey was carried out in a period of time when the topic of palliative HPN has become prominent in the intestinal failure community, coinciding with increasing patient numbers in many centres, which in itself would suggest a turn in the tide of opinion. The positive attitudes demonstrated in this survey are therefore in keeping with the recent increased prevalence. Further surveys after a period of time would allow for comparison and trends in attitudes.

Currently differences of attitudes between UK and non-UK clinicians regarding palliative HPN can only be inferred indirectly. Conducting this survey in other countries would allow more detailed comparison.

Chapter 7 - Health economics of home parenteral nutrition in the palliative phase of malignant disease

7.1 Introduction

The costs of all medical therapies are relevant when considered in the context of a health economy with limited financial resources. When comparing the cost of treatments, the absolute costs, may be misleading because of the variable impact of treatments on survival length and QoL. Incremental cost effectiveness ratio (ICER) is currently the most prevalent measure of the cost of a treatment per quality adjusted life year, allowing for direct comparison of a wide variety of treatment with variable impacts.

In addition to allowing comparison of different treatments, ICERs also allow for thresholds to be set when treatments are assessed for economically viability. While there is debate about the existence of a fixed ICER thresholds used by the National Institute of Clinical Excellence (NICE) in England and Wales, there is evidence that £30,000/QALY is often used as a cut off threshold (124, 125). It has been demonstrated that treatments associated with ICER over £30,000/QALY only have an 8% probability of approval (126). Comparable thresholds are used in several other countries, but controversy exists about the threshold that should be used, for example, in the Netherlands a threshold of up to Euros 80,000/QALY has been proposed according to severity of disease (127).

In the UK health systems where thresholds are used, when the ICER for a desired treatment is above the threshold, the justification for that treatment needs to be strong, with increasing justification needed with higher ICERs. In the England and Wales, criteria have been set by NICE for appraisal of 'end of life' treatments that exceed £30,000/QALY. These are: a limited number of patients expected to require the treatment, the treatment should be expected to extend life by greater than three months, the extended survival length is experienced at a QoL anticipated for a healthy individual at a similar age and health economic assessment models would need to be carried out.

Models estimating the health economics of HPN for benign disease are available (128, 129), but these calculations have not been carried out for HPN in palliative malignancy indications. The only detailed analysis of the health economics of benign indication HPN was carried out in the study of Richards and Irving in 1996 (128). In their model they calculated the absolute cost of HPN over the first year to be £44,288 with a corresponding ICER of £85,825/QALY. The ICER value reduced to £68,975/QALY after 4 years due to the health economic concept of 'discounting' with longer survival.

The cost implication is one of many factors that should inform the decision regarding commencing HPN in a palliative malignancy patient group. The aim of this chapter is to carry out the first examination of these costs through a model based on palliative malignancy patients with inoperable bowel obstruction (IBO) receiving HPN. As described in Chapter 3, IBO was identified as the most logical and judicious indication for palliative malignancy HPN, but the results are also likely to be relevant to the majority of palliative malignant patients with and without IBO.

7.2 Methods

To evaluate the health economics of HPN for patients with malignant IBO in the palliative phase of malignancy, a base-case cost calculation and incremental cost effectiveness ratio (ICER) analysis was undertaken. The sensitivity analysis was deterministic, hence encompassing the best, worst and the most likely costs as represented by the lowest, highest and base-case analysis costs.

7.2.1 Resource use

Rates of resource use are summarised in Table 16 on the basis of the following considerations:

HPN - It was assumed that HPN was used seven days per week, consistent with practice in many centres.

Hospital admissions - Pironi et al (74), reported that out of 29 patients, 18 were admitted on 38 occasions (mean 1.3 per patient in study); and King et al (55) reported a median admission rate of 1 per patient and mean of 2. Given the limited data available, the admission rate for the base-case analysis was conservatively set at 1 per patient, but in the sensitivity analysis it was varied from 0.5 to 2 admissions per patient.

Palliative chemotherapy - Three studies included in the systematic literature review in Chapter 3 reported on rates of chemotherapy for palliative malignancy IBO patients receiving HPN. In one of these studies 64% of patients received chemotherapy (101), and from the data provided it was calculated that the number of cycles per patient was ≥1.3. In the second study (107), of only 9 patients, 5 (56%) were receiving chemotherapy at the time PN was started, but the number of cycles of chemotherapy per patients was not reported. In the final study (70) only 39% of patients received chemotherapy but the study did not report the number of cycles per patient. In the base-case analysis we conservatively assumed that there was 1 cycle per patient and in the sensitivity analysis this was varied from 0.5 to 2.0 cycles per patient.

Outpatient visits - The rate of hospital outpatient visits was set at 1 per month (0-3 per month in the sensitivity analysis), according to expert opinion and accounting for a small minority of the costs, see below.

Community palliative home care visits - The rate of home care visits by palliative care nurse was set at 1 per week for one hour per visit (0-4 visits per week in the sensitivity analysis), based on expert opinion and accounting for a small minority of the costs, see below.

7.2.2 Unit costs

Unit costs for the above resources are summarised in Table 16 (page 110) on the basis of the following considerations:

HPN - The base-case cost per day of HPN was set at £150 (inclusive of nursing care, parenteral nutrition, supplemental fluids, micronutrient additives, intravenous sets, infusion pumps, catheter dressing and other ancillaries). The actual daily costs of HPN to the National Health Service in the UK by commercial companies are confidential. The daily cost of HPN used in this calculation were based on a combination of local contract prices, confidential information from companies providing HPN services in England, expert opinion from the British Artificial Nutrition Survey (BANS) members and personal communications with experts from other countries. To account for the uncertainties and variable local costs, this was subjected to a sensitivity analysis of ±33%.

Hospital admissions - The cost of hospital admission was set at £2014. This was based on information from 'Payment by Results' regarding the mean cost of a hospital admission for adults for the year 2011/12, the data were provided by the Health and Social Care Information Centre, on special request by Professor Elia (personal communication). The costs were inflated to 2013 prices at a rate of 2.9% per year based on National Institute of Statistics data (130). This conservative estimate of costs was varied by ±50% in the sensitivity analysis.

Palliative chemotherapy - Palliative chemotherapy is highly dependent on the administration route, administration setting, cost of drugs and equipment required. Hence the cost of a single

cycle of chemotherapy was set as £1579, equivalent to two day-case admissions (again using 'Payment by Results' data provided by the health and Social Care Information Centre). The base-case cost was subjected to a sensitivity analysis of ±50%.

Outpatient visits and community palliative home care visits - Costs were based on Payment by Results, which were inflated to 2013 prices and Curtis (131). Both were minor costs and not subjected to a sensitivity analysis.

In the non-treatment group the absolute costs for hospital, hospices or care homes were assumed to be equal to the cost of the training period for HPN in the treatment group in the hospital setting. Therefore, they were offset in the cost increment calculations.

7.2.3 Quality adjusted life years (QALYs)

QALYs were established from survival length and utility scores (i.e. QoL). The mean survival length for the base-case was calculated by using the meta-analyses data in Chapter 4. Mean survival time for the base-case in patients receiving HPN was estimated to be 116 days, in the sensitivity analysis this was varied by ±50. The base-case survival time in the control group was assumed to be 14 days (given the very poor outcome expected in this group of patients), but in the sensitivity analysis it was varied by ±100%.

Apart from the limited data on QoL summarised in Chapter 3, additional information was also taken into account to establish values that could be used in the base-case utility score and sensitivity analyses. For example, in a study of terminal phase malignancy in which the median survival was 13 days (without PN), quality of life, assessed with the visual analogue scale of EuroQoL, was calculated to be 37% (scale 0-100%) (132). Another study involving a subgroup of patients with terminal malignancy who survived for up to 3 months, quality of life was found to be about 47% using the EuroQoL visual analogue scale, and about 35-65% (depending on the domain of quality of life being examined) using the EORTC QLQ-C30 (133). Due to the lack of quantitative QoL data in the palliative HPN patient group for the purpose of these calculations a utility value of

0.5 (scale 0-1) was used in the base-case analysis, both for the HPN and control groups. In the sensitivity analyses the QoL for both groups were varied between 0.3 and 0.7 to encompass uncertainty.

Table 16 Cost and sensitivity analysis for base-case economic analysis

Type of resource	Unit cost in base-case	Number of units in base-case	Total in base-case	Sensitivity analysis		Source of unit costs
				Cost of resource	Frequency of resource use	
Parenteral nutrition	£150/day	1 per day for 116 days	£17,400	±33%	-	Typical cost from expert opinion
Hospital admission	£2014	1 per patient	£2,014	±50%	0.5-2.0 per patient	Health and Social care Information Centre*
Cycle of chemotherapy	£1579	1 per patient	£1,579	±50%	0.5-2.0 per patient	Health and Social care Information Centre*
Outpatient attendance	£133	1 per month	£133	-	0-3 per month	Health and Social care Information Centre*
Home visit by community palliative nurse specialist (1h per visit)	£42	1 visit per week	£42/week × weeks survived	-	0-4 per month	Curtis (131)

* Data provided by the Health and Social Care Information Centre

7.2.4 Calculating incremental cost effectiveness ratio

The incremental cost effectiveness ratio (ICER) was calculated as the ratio (Figure 15) of incremental cost to incremental QALY gained (i.e. extra cost/QALY gained).

$$\text{ICER} = \frac{\text{Cost of using treatment} - \text{cost of not using treatment}}{\text{QOL for patients using treatment} - \text{QOL for patients not using treatment}}$$

Figure 15 Equation for calculation of Incremental Cost Effectiveness Ratio (ICER)

7.3 Results

7.3.1 Base-case cost analysis

Using the information provided in Table 16, the following results were obtained for the base-case analysis. In the treatment and non-treatment groups the total number of QALYs gained was 0.1353 and 0.0192 respectively, hence the incremental QALY was 0.1161. In the treatment group the base-case incremental cost was calculated as £22,197. In the non-treatment group, the absolute costs for hospital, hospices or care homes were assumed to be equal to the cost of the period required to commence HPN in the treatment group in the hospital setting, hence these costs were not included in the calculations for either group, as they would make no difference to the subsequent calculations of incremental costs (difference in costs between treated and untreated groups).

7.3.2 Incremental cost effectiveness ratio and sensitivity analysis

The ICER for the palliative malignancy HPN patient group, at base-case costs and utility, was £176,587/QALY.

Figure 16 demonstrates the effect of one-way sensitivity analyses on the ICER, for survival length, utility (i.e. QoL), costs and resource use when the variations in each are made according to the assumptions set out in methods section above.

Variations in the assumptions of utility in the treatment group was found to have the most substantial effect on the ICER (-30% to +75%), with three further variables causing a substantial effect on the ICER; cost of parenteral nutrition (±26%) survival length of the treatment group (-24% to +10%) and survival length of the non-treatment group (-20% to +7%).

Multi-variant sensitivity analysis can be carried out for combinations of the four most cost influential factors. When improved utility of the treated patient is combined with reduced cost of HPN (i.e. less than 7 nights or use of parenteral fluids rather than PN or home nursing not required), then the ICER can reduce to £77,698/QALY and conversely increase to £354,940/QALY

if increased cost sensitivities are considered. With the addition of sensitivity analysis of survival length for the treated patient the ICER will favourably reduce to £35,317/QALY or unfavourably to £372,599/QALY. The further addition of sensitivity analysis for survival length in non-treatment patient would result in a cost neutral ICER (£0/QALY) to £384,960/QALY.

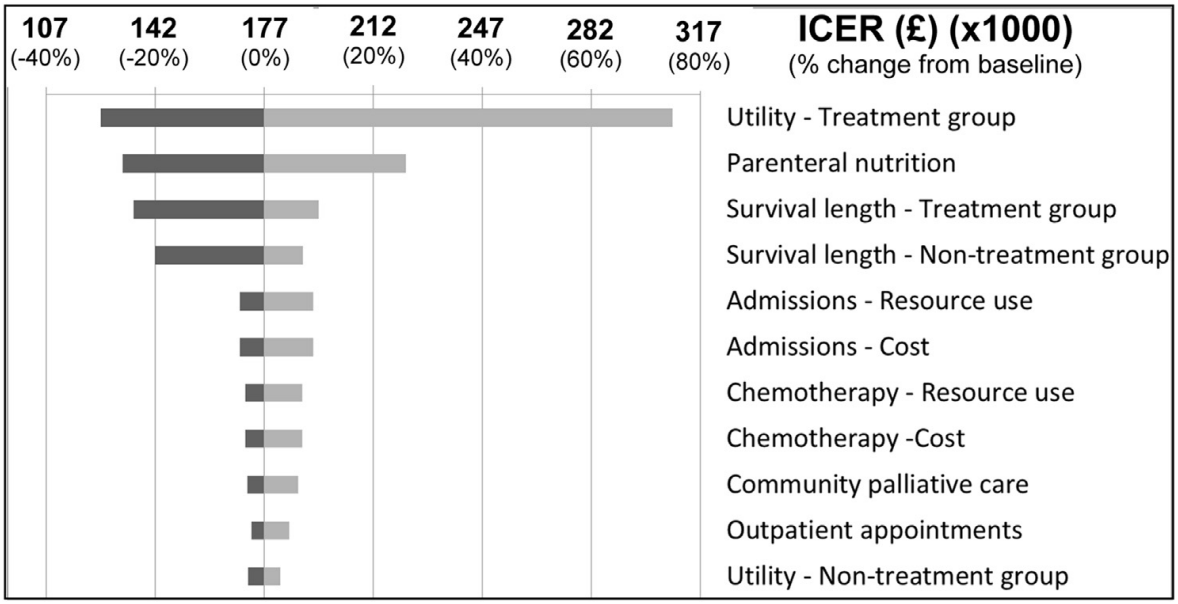

Figure 16 Tornado graph demonstrating the effect of one-way sensitivity analysis on incremental cost effectiveness ratio (see Table 16 for variation in assumptions)

7.4 Discussion

In the first health economic assessment of HPN treatment for palliative malignancy the treatments and associated costs are variable and complex, however the model shows the ICER for this therapy is high at £176,587/QALY at base-case analysis.

Sensitivity analysis was carried out due to the uncertainty of a number of assumptions, namely QoL, which remains poorly understood. This assessment shows that in this clinical situation QoL has the greatest single effect on the cost effectiveness.

Multi-variant analysis of the three costliest factors affecting the treatment group, in combination, can dramatically reduce the ICER to £35,317/QALY at the upper limits of favourable variation, i.e. treatment patient with double the mean base-case survival length (i.e. 232 days, 7.6 months), increased QoL to 0.75 (range 0-1) and reduced HPN costs by 33% from base-case costs.

In keeping with the first hypothesis for this chapter, it should be noted that regardless of the cost effectiveness, the actual cost to the economy is high at approximately £7,280 per month (£87,320 per year). This is only effected by the length of patient survival.

In the Richards and Irving (128) health economic analysis of benign HPN in the UK in 1996, the estimated absolute cost for the first year was £44,288, corresponding to £69,975 inflated to 2013 prices (assuming 2.9% inflation per year), equivalent to £192/day. This daily cost is lower, though comparable to the daily costs in the model of palliative HPN for the base-case patient at £240/day (to allow comparison in this calculation we have considered the cost of the commencing HPN as 2 weeks of in-patient admission, equivalent to £5,639). In the study of Richards and Irving (128) the ICER for the first year of treatment was estimated at £85,829/QALY, equivalent to £135,610/QALY inflated to 2013 prices. In keeping with the second hypothesis for this chapter, the ICER estimate for palliative HPN at base-case costs from the model is higher, though again comparable at £176,587/QALY. Although due to the significantly longer survivals in benign disease the concept of

'discounting' makes HPN more cost effective in the long term, which does not apply to palliative malignancy HPN patients.

In light of the economic analysis in this review, from a purely economic approach, in countries that use ICER thresholds, HPN for palliative malignant patients would need strong justification. However, these restrictions due to high costs are also applicable to the less controversial and accepted practice of HPN for benign disease. The multi-variant analysis also suggests that the selection of patients that are likely to survive longer, have better quality life, in combination with reduced PN costs (frequency, complexity, independent of nursing at home) would bring the ICER costs significantly lower, and close to the NICE ICER threshold.

The health economic method used in this review is the dominant method used currently in health economy, but this method may not be the most appropriate to appraise all treatments. Several experts have stated a preference for Willingness to Pay (WTP) in setting the thresholds (134). Research recently commissioned by the UK Department of Health (135) estimated the threshold of WTP to range as high as £70,000/QALY, depending on the approach used.

The current model is limited by a lack of detailed reporting re-admissions rates, complications and out-patient services required in this patient group, though this is accounted for in the sensitivity analysis. The actual costs levied to the NHS by private companies delivering HPN therapy is confidential and can vary geographically within and outside the UK, but the costs used in this model are based on a number of reliable sources as well as being subjected to sensitivity analysis. The calculations are further limited by a lack of quantitative QoL scores in either the treatment or the non-treatment group.

Despite the controversial health economic costs of this treatment there may be special circumstances for supporting the use of this expensive treatment to extend life, such as giving individuals valuable time to reach a short term goal (e.g. impending birth of child or other life events of equal magnitude), which could have long-lasting positive effects on the family and on

the image of a health system that has a compassionate attitude towards the care of the terminally ill patients.

Chapter 8 - Discussion, further work and conclusions

"One cannot think well, love well, sleep well… if one has not dined well" *Virginia Woolf*

As this quote suggests, the physical and psychological interdependency of food and health in the human conscience is complex and deeply ingrained. This leads to emotive circumstances for clinicians, patients and family members when facing incurable diseases that limit food intake. This in turn influences the controversy surrounding provision or refusal of artificial nutrition for patients with incurable malignancy. This controversy has been further fuelled by a lack of clarity on key issues such as survival time, quality of life, patient selection and health economics of HPN treatment for patients with incurable malignancy. The objectives of this thesis were therefore to provide clinically relevant information on these issues. This chapter summarises my findings in relation to key issues, draws conclusions and considers potential future work in this field.

8.1 Survival time

As demonstrated by the survey of attitudes in this thesis, uncertainty regarding the length of survival for incurable malignancy patients treated with HPN has been one of the major barriers for clinicians considering commencing this treatment in the UK. Several small retrospective trials had suggested short survival duration, but with large variability and wide confidence intervals contributing to the uncertainty. The systematic review and meta-analysis presented in this thesis amalgamated the available data to demonstrate that the mean survival for these patients is 3.8 months, median 2.7 months, with 45% and 22% alive at 3- and 6-months respectively. These results can give clinicians greater confidence when considering and discussing commencement of HPN for patients diagnosed with incurable malignancy.

Despite these results, uncertainties still remain regarding survival times in these circumstances. The systematic review highlighted four different definitions for the starting point of measuring survival time which, when overall survival is short, is paramount as any variability introduced by different definitions can have significant effect on the measured outcome. For example, the

chronologically earliest starting point defined the start of survival time as 'onset of gastrointestinal obstruction', while the latest was 'date of discharge home with PN'. The period between these points can vary from days to months depending on various patient and non-patient factors. For future work, I believe it would be most prudent to use the point at which patients are commenced on PN as the starting point for measuring survival time, regardless of time to or success in achieving discharge from hospital.

Notwithstanding the variability in definitions, the results of this survival duration meta-analysis are remarkably similar to those presented in a recent publication of a large multi-centred prospective case series of incurable malignancy patients treated with HPN (79). This case series reported a median survival length of 3 months in 414 patients, with 50% and 23% alive at 3- and 6-months. This therefore provides clinicians with further confidence in the use of these survival data, although this case series also does not clearly define the onset point for determining survival duration. However, from personal communication with the lead author, it is apparent that the date of discharge on HPN was often used as the start of survival time measurements, but this was not explicitly standardised amongst the 10 countries and 13 recruiting centres. With the significant variation in the logistical set up of HPN services across these countries, it is therefore likely that there was marked variation in the time spent in hospital on PN prior to discharge.

Furthermore, the use of hospital discharge date will also exclude patients who were commenced on PN for incurable malignancy, with the intention to discharge home, but who did not achieve discharge for medical or social reasons and hence introduces bias towards the fitter, longer surviving patients.

As discussed in Section 1.5, there is a lack of consensus on the effect of PN on tumour cell proliferation (58). There is a growing clinical evidence base that suggests PN increases survival duration in malnourished incurable cancer patients. Furthermore, the debate is not relevant when the patient has complete IF, as the inevitable dehydration and malnutrition caused by IF will

dramatically reduce survival duration, a supposition which is supported by the results presented in this thesis.

The UK has been relatively late in common use of HPN for incurable malignancy even for IBO and remains resistant to the use of supplementary HPN. This was confirmed by the survey of clinician attitudes presented in Chapter 6. For this reason, the selection of patients in the UK may differ from selection in other countries, leading to differences in survival duration for UK patients compared to those in Europe or the USA.

The case series of palliative HPN patients treated at University Hospital Southampton presented in this thesis suggests that this different patient selection may lead to a longer surviving cohort. This could be further explored by undertaking a wider multi-centre prospective UK-based case series. The possibility of undertaking such work was largely supported by respondents to the survey of clinician attitudes presented in this thesis.

The ESPEN 2009 guidelines (18) for incurable malignancy require the clinician to make a prediction of patient's survival time and supports the use of HPN treatment if that prediction is greater than 2-3 months. In light of the above survival data, these guidelines should be reviewed and updated, as despite the recommendations, approximately 50% of patients selected for this treatment do not survive beyond 3-months. Furthermore, the supplemental HPN part of the guidelines depended on the results of the study by Shang et al (80), which were later retracted as the study was not carried out according to the methods described in the article.

8.2 Patient selection

The use of matched patient-level data in the meta-analysis presented here has permitted identification of baseline patient factors that have prognostic qualities in relation to length of survival. The most important factors identified are baseline performance status, as measured by Karnofsky Performance Score (KPS), and the type of primary malignancy, whilst the use of palliative chemoradiotherapy did not appear to influence survival time. The ultimate goal of optimal patient selection is to improve patient outcomes by avoiding over- and under-utilisation of HPN, which can have a high burden for the patient.

The study of Bozzetti et al (2014) (79), also confirmed KPS as a prognostic tool, with additional use of Glasgow Predictive Score (GPS) (calculated on serum albumin and C-reactive protein). These two factors were used to classify patients into six sub-groups: favourable; intermediate and unfavourable, with significantly different proportions of patients alive at 3-months in each sub-group, varying from 33-78%.

This KPS/GPS model was tested in this thesis in the University Hospital Southampton case series. The case series was too small to validate this prognostic tool, but the results suggest that classifying patients according to these factors may be helpful in patient selection. Although the sensitively and specificity appears to be insufficient for use of the model as the sole patient selection tool.

The study of Bozzetti et al (2015) (136), added underlying malignancy type and presence of metastasis to the KPS/GPS model, with weighed scoring for each factor to produce a prognostic nomogram, which is also yet to be validated. With emerging evidence for prognostic indicators, guidelines would be more readily applicable if clinician prediction was complimented with quantifiable validated prognostic tools. Future work, such as a prospective UK based case series, would also be able to collect data on patient characteristics with the aim of validating prediction tools.

8.3 Quality of life

The results of the clinician attitude survey presented in this thesis show that a significant proportion of clinicians support the potential benefits to QoL as the main indication for HPN therapy for patients with incurable malignancy. QoL in patients with incurable malignancy treated with HPN is poorly understood, due to general lack of investigation in this patient group, variable tools for measurement, use of invalidated tools and multiple uncontrolled confounding factors.

In spite of these limitations, the existing data suggest that QoL is acceptable to the majority of patients, during a disease process that is known to be highly symptomatic and likely to decline, so even stabilisation of QoL should be considered a positive outcome, especially in patients with bowel obstruction.

Structured QoL interviews carried out by Orrevall et al (137) demonstrated that although HPN causes disruption to the social life of the patient and household, the salient feeling from patients and family members was positive towards the treatment. Patients and families felt there was security regarding nutrition intake. The feeling of security described in this study may have been confounded by the security afforded by the twice daily visit of highly trained PN nurses. This confounding factor will be hard to eliminate, as the vast majority of incurable malignancy patients treated with HPN receive home nursing due to the short survival length leading to insufficient time to learn the practical procedures required for independence.

The study by Bozzetti et al (2002) (102) described QoL of incurable HPN patient's as being improved in 50% and stabilised in 40% for the months preceding the final 2-months of life, when there was universal decline. The results of this study heavily influenced the ESPEN 2009 guidelines (18) recommending 2-3 month prognosis, to ensure patients had sufficient time to benefit from the treatment. As discussed in detail in Chapter 6, the presentation of the results in the graphical formats used in this article were difficult to interpret and the reported 2-months cut-off point was not as apparent as described by the authors. Encouragingly, however, further evidence to

corroborate initial improvement or stabilisation of QoL has also been reported by Culin et al in 2014 (138). This large study of 437 patients used the validated Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire. The study was only carried out over the first month of treatment, but reported 60% improvement and 15% stabilisation in QoL in that time.

There are confounding factors that will be difficult to control when assessing effect of HPN on QoL in the early stages of treatment. Multiple palliative interventions are often required in parallel to commencing PN for intestinal failure. These are often for significant symptoms of nausea, vomiting and pain, alleviated by medical treatments, gastric drainage or even surgical decompression. Hence, the degree of initial improvement in QoL, which may be assigned to HPN rather these therapies is unknown. Longer follow up in future studies would allow for reduced effect of confounding effects.

There are no studies of incurable malignancy HPN patients that compare the QoL reported directly by patients and that assigned by their clinician, but there are surrogate indications that clinicians both under- and over-estimate patients' QoL in individual cases. When the validated Rotterdam Symptom Check List was used in this patient population (102) baseline symptom burden was shown to be high (93% reporting significant symptoms), but when asked "How do you feel today?", 58% patients replied "well" or "very well". Clinicians' observation of these patients is likely to have under-estimated their QoL due to the symptomology, but not so by the patients themselves. In the study of Pironi et al (74), the nutrition support team retrospectively judged how well incurable malignancy patients treated with HPN accepted their treatment, using the classification: 'accepting well'; 'displaying annoyance' and 'scarcely tolerated'. Despite 10 out of 29 patients (34%) being classified in the latter two unfavourable groups, the authors conclusions were that HPN can be applied in this patient group 'without causing additional burden or distress'. This appears to be an overly optimistic interpretation of the results.

Further work is needed for a better understanding of QoL in the various stages of palliation for incurable malignancy patients treated with HPN. Additionally, the QoL of incurable malignancy

patients who have been offered HPN, but chose conservative palliative care, also need to be studies to allow comparison. These studies would need to be carried out prospectively using patient reported and validated tools at baseline and multiple intervals. Although it is unclear at this time which tool should be adopted, it is clear that efforts need to be made to capture QoL up to the last few weeks or days of life to guide future treatment.

8.4 Health economy

Reliable QoL data are also essential when calculating the health economic impact using models such as the Incremental Cost Effectiveness Ratio (ICER). This model was used in this thesis as it is the predominant method used in health economics currently and the ICER calculations presented in this thesis are the first detailed health economic assessment for HPN treatment in patients with incurable malignancy.

The results show that, at 2013 base-case prices, a mean survival of 3.8 months and mean QoL of 0.5 (range 0-1), the ICER for the treatment group was £176,587 per quality adjusted life year (QALY). This is comparable to the cost effectiveness of HPN treatment for benign disease calculated by Richards and Irvin (128), which was £135,610/QALY (when uplifted to 2013 prices by accounting for inflation rate). These costs are high, especially in the context that only 8% of treatments over £30,000/QALY appraised by NICE are approved for NHS use (126). To date HPN has not been appraised by NICE for either benign or malignant indications.

Sensitivity analysis was carried out to account for the variability of this patient group, as well as the variable costs that may be encountered. In the sensitivity analysis the factor with the greatest influence on the cost effectiveness was QoL. By varying the range of QoL in the sensitivity analysis from 0.3 to 0.7 the ICER varies dramatically from -30% to +70%. The other two factors that had the greatest influence on cost effectiveness were 'cost of PN' and 'survival length of treatment group'. These factors can be influenced through optimal selection of patients, using the lowest effective frequency of PN nights, encouraging family members to learn the connection/disconnection, and considering intravenous fluid as an alternative for some or all treatment nights. These factors in combination can have profound effects on the cost effectiveness. At the favourable extremes; QoL (0.7), PN costs (-33%) and treatment group survival length (+50%), the cost effectiveness drops to £35,317/QALY.

Although ICER is the most prevalent method of assessing cost effectiveness, it has limitations when applied to end of life treatments, i.e. it will inevitably lead to high values due to the patient's short survival and large influence of poor QoL in palliative disorders. Hence, when assessing treatments regarding end of life, an alternative method of assessing cost effectiveness is required, or modifications need to be made to the ICER model, or the threshold for accepting treatments would need to be reviewed.

The Department of Health carried out a public engagement study in 2003 to gauge Willingness to Pay (WTP) for end of life treatments (134). The threshold suggested by this study was up to £70,000/QALY. If this WTP threshold was used the ICER for a significant proportion of incurable malignancy patients treated with HPN would fall below this.

It should be noted that regardless of the cost effectiveness, the real-term cost to the health economy is high at £7,280 per month (£87,320 per year), at base-case estimates. The two factors that influence real-term costs are 'cost of PN' and 'length of patient survival'. The peripheral costs such as out-patient visits, palliative chemoradiotherapy and community palliative care support make up a smaller proportion of the costs in comparison.

The high real-term cost of HPN for this patient group, within the context of a finite health economy, will become more pronounced as prevalence continues to increase. This increasing prevalence has been demonstrated by data collected for the British Artificial Nutrition Survey (BANS) (49). Both the percentage and number of new registrations with malignancy as the underlying diagnosis has risen from 12% (13 patients) in 2005 to 27% (115 patients) in 2015, i.e. now accounting for approximately one in 4 new registrations reported to BANS (personal communication). This increase is partially accounted for by improved reporting rates in the UK, but the rise in malignancy cases is disproportionately higher than other conditions reported to BANS and hence in keeping with other data sources showing true increasing prevalence of palliative HPN.

In 2013 there were 41,000 GI and 16,000 gynaecological cancers in the UK (53), with 12,800 deaths caused in the same year by colorectal and ovarian cancers alone (53). 10 - 28% of all gastrointestinal and 5 - 50% ovarian malignancies lead to bowel obstruction. Hence, if only the most severe cases leading to death are considered, a conservative estimate would suggest 1,040 – 4,600 cases of bowel obstruction per year. Some of these would be amenable to resolution conservatively or through surgical intervention, but with high recurrence rates the number of cases of malignant bowel obstruction in just these two cancers are high. Although the proportion of patients who would be suitable for HPN treatment is unknown, it is likely, when considering all malignancies, that this number would be much higher than current prevalence rates.

As HPN is increasingly recognised as an accessible and acceptable treatment for incurable malignancy patients with intestinal failure, the prevalence is likely to continue to rise. The national HPN framework was commissioned by the Department of Health to improve standards and access to HPN services (in England). Since it was first launched in 2013, the number of patients on HPN has risen dramatically. From 2011 to 2015 in England the prevalence of HPN has risen from 631 to 1323 (49), and as such the community services have been stretched. The initial improvement in the swift discharge of all HPN patients, including those with palliative cancer, is again at risk, with further impacts likely due to the increasing prevalence of palliative cancer patients.

8.5 Supplemental HPN in combined therapies for cancer cachexia

A further potential source of increased prevalence is supplemental HPN for incurable malignancy patients without intestinal failure. Data suggest that supplemental HPN makes up one-third of the palliative HPN therapy in Europe and North America already (79). The survey of UK clinician attitude in this thesis revealed that the only 13% supported use of supplemental HPN for incurable malignancy patient group despite the emerging evidence that survival, nutrition markers and QoL may be improved for incurable malignancy patients by the use of supplemental HPN, especially in combination with therapies aimed at reversing early cancer cachexia.

If future trials show significant benefits of combined PN and anti-cachexia treatments in patients without IF, the number of incurable malignancy patients with indication for HPN will increase dramatically. This will pose a challenge regarding the health economic implications.

8.6 Strengths and limitations

The systematic review in this thesis was comprehensive, using wide searching terms to capture studies with published data on the length of survival and QoL for this patient cohort. While the systematic review was limited by the lack of high quality studies in this field, it did yield data that could be extracted at the patient-level to allow meta-analyses.

One of the strengths of the meta-analyses was the validation method used to ensure that the data extracted from Kaplan-Meier graphs and scatter plot were accurate. This was done by comparing averages from the authors' publications with those from the extracted data.

A further strength of the systematic review, as well as the thesis as a whole, was the assistance that was received from leading authors in this field who kindly responded to correspondence, which allowed analysis of their published data in more detail. In some circumstances, without their guidance, the patient-level data extraction would not have been possible.

The systematic review and the meta-analyses were limited by the inability to reliably identify all HPN treated incurable malignancy patients. This was due to the variable use and definitions of the terms 'palliative', 'incurable' and 'terminal' malignancy, as well as mixed reporting of malignant and benign HPN patient outcomes. Hence, the population for the review was defined as those with inoperable bowel obstruction and malignant disease without further curative treatment. Defining this group had the advantage of reliable clinical and radiological evidence for the diagnosis, which would be consistent across the time span and countries of the search. Additionally, this sub-group represented the largest proportion of the patients with incurable malignancy treated with HPN.

Despite the limitations, the results of the meta-analyses based on the systematic review data extraction were remarkably similar to those of a prospective international case series published after the systematic review was completed (79). This case series of incurable malignancy patients treated with HPN was made up of approximately two-thirds of IBO patients. The survival lengths presented in this case series were near identical to the meta-analysis and in combination these data can be used for greater confidence in clinical practice. The results of the systematic review and meta-analyses have been published in a peer review journal (139).

The thesis was further strengthened by the generation of novel data. The University Hospital Southampton case series is the first case series of HPN treated incurable malignancy patients from any UK centre. This data also allowed the application of prognostic tools that may become standard practice in aiding optimal patient selection in the future. The limitation of the study was

the small patient numbers that was insufficient to validate the prognostic tools in this patient group.

The survey of IF clinicians was the first of its kind and has given a unique insight into the attitudes towards HPN for incurable malignancy in the UK, where the use of this treatment is less frequent than other countries with similar health economies. The survey was limited by the methodology as the proportion of participants who responded was unknown. This survey would have been further strengthened by increasing the clinician participation to include specialities such as oncology, elderly care and palliative medicine, as well as inviting clinicians from other countries to participate to allow comparison of attitudes.

The strength of the health economic assessment undertaken in this thesis is that it is the first published for HPN use in the incurable stage of malignant disease (139). The strengths of this assessment were the detailed costing attained from multiple sources and the use of expert knowledge in home company HPN costs, which are commercially sensitive and not publically available. The limitations of the assessment were the variability in costs that may apply depending on utilisation of services by HPN patients including out patients, palliative care and chemoradiotherapy. To account for this, where there where uncertainties, a sensitively assessment was carried out.

The strengths of this thesis are in the combination of the use of previously published data manipulated to be used in novel ways, the generation of novel new data and the addition of clinically and economically relevant information to the field of HPN therapy for patients with incurable malignancy and IF.

8.7 Conclusions and Future Directions of Research

This thesis has presented the results of the first systematic review and meta-analysis of survival duration in HPN treated patients with palliative incurable malignancy. The results of this meta-analysis have demonstrated that survival is short but variable, with a median of 2.7 months. The systematic review also identified patient baseline factors that have predictive qualities for survival time, hence supplying clinically relevant data for clinicians to optimise patient selection, while supplying information for patients regarding likely survival duration.

This thesis also presented survival results of the first UK-based case series of palliative malignancy HPN patients. This case series was used to examine an established generic prognostic tool for survival time prediction in the palliative malignancy cohort, as well as the recently developed prognostic tool for this patient group, showing superiority for the later. These results show, that with refinement and validation, such tools may have a role in aiding patient selection in the future.

The clinician's attitude survey results, presented in this thesis, demonstrated the importance clinicians place on the effect on QoL when commencing patients on HPN therapy in the incurable phase of malignancy. Future work would refine the survey and distribute internationally via nutrition societies such as ESPEN, ASPEN and AuSPEN.

Interpretation of the current published data shows a potential stabilisation or improvement in the initial quality of life when HPN is used. However, this thesis also identified the lack of robust data on QoL in this patient group. Future work should concentrate on using or developing a standardised QoL questionnaire for this patient group to be used prospectively.

Additionally, the results of the first health economic assessment of HPN in the palliative phase of malignancy are presented in this thesis, demonstrating high costs for this treatment. The cost effectiveness calculations carried out in this thesis allow comparison with other therapies. The data show that optimal patient selection can significantly increase the cost effectiveness of this

treatment. This health economic assessment could be used by health authorities when planning HPN services. Additionally, this information can also be used by clinicians in their decision making process, especially as uncertainties on the costs of this treatment were identified in the clinician's attitude survey as posing a barrier to treatment.

This thesis has met its aims and objectives in providing reliable clinical and economic data on the use of HPN in the palliative phase of incurable malignancy. The data can inform clinician's decisions regarding patient selection and can also provide patients with information to help them make an informed decision on this high burden therapy. This will ultimately lead to improved outcomes for patients through optimal end of life care.

Appendix A - Survey of attitudes

Use of home parenteral nutrition in patients with palliative malignancy

Dear Colleague,

Thank you taking the time to complete this questionnaire concerning home parenteral nutrition (HPN) for patients with palliative malignancy. The entire questionnaire should take less than 10 minutes to complete.

For the purpose of this survey a malignant condition is considered 'palliative' if the disease is beyond cure from surgical, chemotherapy or radiotherapy treatments. A patient should be considered as a 'Home' PN patient if the intention at time of commencing PN was to discharge the patient to a home environment, regardless of the eventual destination.

The reported rate of HPN use for palliative malignancy in the UK is 5% according to the British Artificial Nutrition Society (BANS) report. This survey aims to confirm this estimate and to address the underlying beliefs and attitudes towards this treatment with in the UK.

Please follow the below link to complete the questionnaire:

https://www.surveymonkey.com/s/palliativeHPN

Thank you again in advance,

Dr Mani Naghibi

Clinical Research Fellow in Nutrition and Intestinal Failure

University Hospital Southampton

Appendix A

Section 1: This short section aims to collect basic information about your home PN (HPN) practice for all indications.

Demographics

1) City/town of practice
2) Your occupation:
   - Gastroenterologist (Medical)
   - Surgical (Colorectal/Upper GI)
   - Anaesthetist
   - Chemical pathologist
   - Dietician
   - Pharmacist
   - Nurse
   - Other (details……)

Home parenteral nutrition practice (for all indications)

3) For your HPN service, are you personally responsible for the decisions regarding commencing home PN?
   - Yes (go to question 5)
   - No (go to question 4)

4) If not, who in your hospital/institution is responsible for the decision to commence home PN?
   - Gastroenterologist
   - Surgical (Colorectal/Upper GI)
   - Anaesthetist
   - Chemical pathologist
   - Dietician
   - Pharmacist
   - Nurse
   - Other (details……)

5) How many years of experience with HPN services do you have?
   - 0-3
   - 4-9
   - 10-14
   - >15

6) Type of hospital/organisation for your PN services:
   - National IF centre
   - Regional IF centre
   - District General Hospital

7) Approximately how many HPN patients (<u>of all indication</u>) have there been in your service in the last 5 years?

8) Approximately how many of the HPN patients in your service have been for palliative malignancy?

Appendix A

Section 2: Clinician practice and attitudes

This section is related to your PN practice/experience in the context of patients with palliative malignancy (with or without palliative adjuvant chemotherapy or radiotherapy), referred to from here on as 'palliative'.

Please indicate your level of agreement with the following statement regarding home PN in patients with palliative malignancy:	Strongly agree	Agree	Neither	Disagree	Strongly disagree	NA
Home PN indications:						
I would support the use of HPN only if I considered the treatment as life prolonging						
I would support the use of HPN to improving QoL/performance status with/without potential to prolong life						
I would generally only support the use of HPN if oral/enteral route feeding has failed due to intestinal failure						
I support the use of "supplemental" home PN for patients with viable oral/enteral route						
- In "supplemental" home PN, weight loss is a common indication						
- In "supplemental" home PN, dehydration is a common indication						
- In "supplemental" home PN, nausea is a common indication						
- In "supplemental" home PN, loss of appetite is a common indication						
- In "supplemental" home PN, patient preference is a common indication						
- In "supplemental" home PN, patient's family's preference is a common indication						
I am increasingly using HPN in palliative malignancy						
I am aware of the ESPEN 2009 guideline indications for PN in palliative malignancy patients						

Please indicate your level of agreement with the following statement regarding home PN in patients with palliative malignancy:	Strongly agree	Agree	Neither	Disagree	Strongly disagree	NA
Home PN outcomes:						
I believe HPN would improve the weight loss associated with palliative malignancy						
I believe HPN would improve fatigue associated with malignancy						
I believe HPN adversely affects tumour growth						
I believe HPN positively affects tolerance of palliative chemotherapy or radiotherapy						
I believe I am able to predict the length of survival for palliative patients below/above 2-3 months						
I believe I am able to predict the effect of HPN on patient's quality of life with reasonable accuracy						
I believe I can predict the effect of HPN on patient's performance status with reasonable accuracy						
I believe the risk of complications of HPN are too high for palliative patients						
I believe the equipment burden of HPN is too high for palliative patients						
I believe HPN is too expensive for use in this context						
I believe HPN can reduce the time palliative patients have for social interactions						
I believe HPN alleviates the pressure on patients from relatives to maintaining oral/enteral feeding						
When I have used HPN for palliative malignancy, I believe this improved QoL/performance status more often than caused a reduction						
When I have used HPN for palliative						

malignancy, I believe this significantly prolonged life more often than caused a reduction/had no effect						

Parenteral nutrition practice for patients with palliative malignancy

9) What are the biggest barriers to home PN in patients with palliative malignancy (please choose 3 from the below list):
   - Cost
   - Lack of community support
   - Risks > benefits
   - Burden of equipment
   - Criticism by colleagues
   - Relatives/family
   - Lack of clearly defined indications
   - Other (details……..)

Thank you for completing this survey, please leave any further comments:

……..

Appendix B - Peer reviewed publications from thesis

Naghibi M, Smith TR, Elia M. A systematic review with meta-analysis of survival, quality of life and cost-effectiveness of home parenteral nutrition in patients with inoperable malignant bowel obstruction. Clin Nutr. 2015;34(5):825-37.

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Meta-analyses

A systematic review with meta-analysis of survival, quality of life and cost-effectiveness of home parenteral nutrition in patients with inoperable malignant bowel obstruction☆

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SUMMARY

Background and aims: Inoperable bowel obstruction is the most common and judicious indication for long term parenteral nutrition in patients with palliative malignancy. Considerable uncertainty exists about the survival length, quality of life (QOL) and associated health economics of home parenteral nutrition (HPN) for this patient group.
Methods: A systematic review was carried out for survival length and QOL of adult patients treated with HPN due to malignancy causing inoperable bowel obstruction in the palliative phase. Whenever possible, individual patient data were extracted to allow meta-analyses. Health economic evaluation was undertaken to calculate cost and incremental cost effectiveness ratio (ICER).
Results: Twelve studies involving 437 patients, met the inclusion criteria. Meta-analyses of extracted survival length data, representing the largest published cohort of HPN patients with palliative malignancy and inoperable bowel obstruction ($n = 244$ patients), revealed a mean survival of 116 days, median 83 days, with 45% and 24% still alive at 3 and 6 months, and only 2% survival at one year. Limited evidence suggests QOL deteriorated before death in a highly symptomatic group. The ICER is £176,587 per quality adjusted life year.
Conclusions: This is the first health economic evaluation and systematic review of survival and QOL for patients with inoperable bowel obstruction receiving HPN during the palliative phase of malignancy. Meta-analyses reveal a short survival and health economic analysis demonstrates high associated costs. This information can be used by clinicians to inform and guide selection of patients in this cohort for HPN treatment.

1. Introduction

Bowel obstruction (BO) is a recognised complication of advanced malignancy and contributes to malnutrition with adverse effects on survival length and quality of life. At first presentation of BO secondary to malignancy surgical resolution can be achieved in the majority of cases [1], but recurrent BO can render repeat surgery unsuccessful, hence termed inoperable bowel obstruction (IBO). If not already so, the focus of treatment for the patient becomes palliation at this stage. Survival of palliative patients with malignant IBO is likely to be limited (<2 weeks to 2 months) without parenteral support [2] depending on grade of obstruction and pre-morbid state.

In several countries there has been a trend towards increasing use of home parenteral nutrition (HPN) in palliative malignancy, with and without BO [3–6], but considerable uncertainty exists about indications. Advocates argue that HPN extends survival and facilitates palliative chemoradiotherapy; but others argue that the treatment is expensive, with a high burden to patients and family members during limited remaining life span.

Uncertainty regarding the prevalence of palliative malignancy patients receiving HPN, with or without IBO, is due to mixed reporting of different patient groups. There are three distinct malignancy patient groups receiving PN for different reasons: short-term support during radical therapy; HPN for 'cured' malignancy with subsequent intestinal failure caused by therapies; and short or long-term PN during the palliative phase. Table 1, summarises the

☆ Conferences: British Society of Gastroenterology, Manchester, UK, June 2014.
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0261-5614/

Appendix B

prevalence rates of PN use in malignancy patients, though this data is difficult to evaluate, partly because not all studies distinguish between the three patient groups mentioned above, and partly because the prevalence rates are expressed in different ways (variable period prevalence or point prevalence).

Despite these limitations, it is clear that the practice of HPN for palliative malignancy is widespread. The lowest reported rates appear to be in the UK [6, 7] and highest in Italy and USA, with strong increasing trends worldwide [1,3,5–9].

National and international guidelines [10–12] for clinical practice have been useful but these have not been informed by a systematic evidence-based approach. In addition, none of the previous reviews of palliative HPN have extracted individual patient data to establish a more powerful database, allowing meta-analysis and providing additional insights into survival length. A further difficulty is that recent reviews [10,13] which have generally supported the use of HPN in palliative malignancy, have been unduly influenced by two favourable palliative HPN clinical trials [14,15], which have subsequently been retracted because they were not conducted in the manner described.

Economic considerations could also influence decisions about the use of HPN in this patient group, and although information is available regarding the health economics of HPN for benign disease [16,17] data are lacking for palliative malignancy.

The aim of this systematic review is to establish an evidence base, of clinically relevant outcomes (survival time, QOL and cost-effectiveness) in the palliative malignant IBO patient group to help inform and guide clinical practice for HPN therapy.

2. Methods

2.1. Eligibility criteria

This systematic review was performed according to the Cochrane Handbook for systematic reviews [21], and the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) statement. [22]

In order to identify relevant trials, a broad search strategy was implemented using pre-determined inclusion and exclusion criteria (Table 2). Included participants were adults, ≥18 years old, with a confirmed diagnosis of active malignancy during the palliative phase of disease (no further curative treatment available).

Studies were excluded if they did not provide data in which at least 80% of patients had a diagnosis of malignant IBO. A distinction was not made between patients where the mechanical cause of IBO was directly due to the malignant tumour, its metastasis or a benign process (e.g. adhesions) in the context of palliative malignancy.

HPN was defined as initiation of PN with intention to discharge to a home environment, even if home discharge with PN was not ultimately achieved.

IBO caused by malignancies such as pseudomyxoma peritonei and desmoid tumours were excluded because these tumours behave very differently (more favourable long-term outcome) than other types of malignancies causing gastrointestinal obstruction. Duplicate studies of the same patients were excluded.

Table 2
Inclusion and exclusion criteria for identifying relevant studies via search strategy.

Inclusion criteria	Exclusion criteria
≥18 years old	<80% inoperable bowel obstruction as the indication for HPN in malignant patient group
Confirmed diagnosis of malignancy in the palliative phase of disease with inoperable bowel obstruction treated with PN	Bowel obstruction caused by pseudomyxoma peritonei and desmoid tumours
Intention at time of commencing PN was to discharge to a home environment, regardless of eventual outcome	Lack of survival or QOL data
± Palliative chemoradiotherapy	Data from letters or abstracts, case reports or case series ≤ 3
English language	
≥ Year 1970	

Table 1
Prevalence of malignant conditions as indication for home parenteral nutrition.

Study	Country	Terminology of cancer indication	Total HPN patients	Number of HPN patients with cancer as indication	Proportion of HPN with cancer as indication	Period or point prevalence (years)	Data source
Vafa et al., 2010 [18]	Belgium	Advanced cancer	125	60	48%	*Period* prevalence (1987–2007)	Single academic centre database
Soo and Gramlich, 2008 [8]	Canada	Advanced cancer	158	38	48%	*Period* prevalence (Jan–Dec 2006)	North Alberta Home Total Parenteral Nutrition program database
Cazzaglio et al., 1997 [4]	Italy	Terminal malignancy	125	75 ('Majority considered terminal')	60%	*Period* prevalence (1983–1990)	Italian Home Parenteral Nutrition registry
Wanden Berghe et al., 2011 [5]	Spain	Palliative cancer	148	29	20%	*Period* prevalence (Dec 2009–Dec 2010)	Nutricion Artificial Domiciliaria y Ambulatoria (NADYA) database
Gillanders et al., 2011 [9]	Australia and New Zealand	Cancer	124	19	15%	*Period* prevalence (July 2010–July 2011)	Australian Society of Parenteral and Enteral Nutrition (AuSPEN) database
Jirka et al., 2011 [19]	Czech Republic	Cancer	138	51	37%	*Period* prevalence (2010)	National Home Parenteral Nutrition registry *(Poster abstract)*
Takagi et al., 1995 [20]	Japan	Malignant	231	93	40%	*Period* prevalence up to 1990 (start not reported)	National survey
Baxter et al., 2003 [7]	Scotland	Malignancy	72	7	10%	*Period* prevalence (Aug 2001–Aug 2001)	Managed Clinical Network Database
Smith et al., 2011 [6]	UK	Cancer	523	42	8%	*Point* prevalence 31/12/2010 (Percentage of new registrations during 2010–14%)	British Artificial Nutrition Survey (BANS) database
Howard et al., 1995 [3]	USA	Neoplasm	4520	2122	49%	Period prevalence (1985–1992)	North American Home Parenteral Nutrition database

The outcome measures were survival length, QOL and any cost or cost-effectiveness outcome measures.

2.2. Search strategy

The search strategy was undertaken using MEDLINE, EMBASE, CINAHL and Web of Knowledge, between 1st – 3rd April 2013. The search was limited to the English language and publications from 1970 onwards, because the first case reports of HPN were published in 1970 [23]. The following broad search terms were used to identify relevant papers: *cancer*, malig*, parenteral* and *nutrition*. A manual search of references of key articles was also carried out.

The first pass of studies was carried out by reviewing title or abstract. If a decision could not be reached as to the suitability of work, the full article was retrieved for more detailed assessment. The second pass involved reviewing full articles for their suitability.

Apart from the initial literature searches on the four databases indicated above, which did not exclude potential studies with economic outcomes, independent literature searches were carried out using the Cost-Effectiveness Analysis (CEA) Registry (Boston, USA) (using the term *parenteral*) and Health Economic Evaluation Database (HEED) (using the search terms *parenteral, nutrition* and *malignancy*) were undertaken.

2.3. Quality assessment

The quality and risk of bias assessment of included articles were carried out using the Critical Appraisal Skills Programme (CASP) [24] independently by two authors (MN and ME) and discrepancies were resolved through discussion. The questionnaire was adapted to the topic under consideration.

2.4. Data extraction

2.4.1. Survival length data

Both study level and patient level data extraction were carried out. Study level data were based on average survival length, age, gender and a summary of the type of malignancy and palliative chemoradiotherapy.

Patient level data were based on the survival of individual patients, which were either individually reported as raw data ($n = 3$ studies) [25–27] or extracted from Kaplan Meier plots ($n = 4$ studies) [28–31] and/or scatter plots [8]. In brief the graphs were enlarged and survival times of individual subjects were established by identifying the survival of individual patient data on the graphs. The methodology for validation is described below in Section 2.6.

2.4.2. Quality of life

Reported measures of QOL were extracted and evaluated, taking particular account of QOL measures based on validated tools, collected directly and prospectively from patients, and where baseline measurements were available so that changes over time could be assessed.

2.5. Survival length data

A narrative description of study level survival length have been presented and supplemented whenever possible with meta-analyses of patient level data. To do this survival data from each study were extracted at monthly intervals and amalgamated using a series of random effects meta-analyses to give mean mortality proportion at each monthly point with 95% confidence intervals.

2.6. Validation of extracted survival length data

Where patient level survival length data were extracted from Kaplan–Meier or scatter plot graphs this was validated by establishing concurrent validity between the average values supplied by the author (mean and/or median where available) and those calculated from the extracted data (Section 3.5.2).

2.7. Health economic analysis

To evaluate the health economics of HPN for patients with malignant IBO in the palliative phase of illness a base-case cost calculation and incremental cost effectiveness ratio (ICER) analysis was undertaken. The sensitivity analysis was deterministic, hence encompassing the best, worse and the most likely costs as represented by the least, highest and base-case analysis costs.

2.7.1. Resource use

Rates of resource use are summarised in Table 3 on the basis of the following considerations.

HPN: It was assumed that HPN was used seven days per week, consistent with practice in many centres.

Hospital admission: Pironi et al. (1997) [32], reported that out of 29 patients, 18 were admitted on 38 occasions (mean 1.3 per patient in study); and King et al., 1993 [1] (not included in the review because only 72% of patients had IBO, falling short of the inclusion requirement of at least 80%) reported a median admission rate of 1 per patient (mean of 2). Given the limited data available, the admission rate for the base-case analysis was conservatively set at 1 per patient, but in the sensitivity analysis it was varied from 0.5 to 2 admissions per patient.

Palliative chemotherapy: Three studies included in this systematic review reported on rates of chemotherapy for palliative malignancy IBO patients receiving HPN. In one of these studies 64% of patients received chemotherapy [30], and from the data provided it was calculated that the number of cycles per patient was $\geq$1.3. In the second study [27], of only 9 patients, 5 (56%) were receiving chemotherapy at the time PN was started, but the number of cycles of chemotherapy per patients was not reported. In the final study [8] only 39% of patients received chemotherapy but the study did not report the number of cycles per patient. The base-case analysis assumed that there was 1 cycle per patient and in the sensitivity analysis this was varied from 0.5 to 2.0 cycles per patient.

Outpatient visits: The rate of hospital outpatient visits was set at 1 per month (0-3 per month in the sensitivity analysis) according to expert opinion.

Community palliative home care visits: The rate of home care visits by palliative care nurse was set at 1 per week for one hour per visit (0–4 visits per week in the sensitivity analysis) also based on expert opinion.

The last two items which were based on expert opinion accounted for a minor proportion of the costs (see below).

2.7.2. Unit costs

Unit costs for the above resources are summarised in Table 3 on the basis of the following considerations.

HPN: The base-case cost per day of HPN was set at £150 (inclusive of nursing care, parenteral nutrition, supplemental fluids, micronutrient additives, intravenous sets, infusion pumps, catheter dressing and other ancillaries). The actual daily costs of HPN to the National Health Service in the UK by commercial companies are confidential. The daily cost of HPN was based on a combination of local contract prices, confidential information from companies providing HPN services in England, expert opinion from the British Artificial Nutrition Survey (BANS) and personal communications

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Table 3
Cost and sensitivity analysis for base-case economic analysis.

Type of resource	Unit cost in base-case	Number of units in base-case	Total in base-case	Sensitivity analysis		Source of unit costs
				Cost of resource	Frequency of resource use	
Parenteral nutrition	£150/day	1 per day for 116 days	£17,400	±33%	–	Typical cost from expert opinion
Hospital admission	£2014	1 per patient	£2014	±50%	0.5–2.0 per patient	Health and Social care Information Centre*
Cycle of chemotherapy	£1579	1 per patient	£1,579	±50%	0.5–2.0 per patient	Health and Social care Information Centre*
Outpatient attendance	£133	1 per month	£133	–	0–3 per month	Health and Social care Information Centre*
Home visit by community palliative nurse specialist (1 h per visit)	£42	1 visit per week	£42/week × weeks survived	–	0–4 per month	Curtis (2013) [34]

*Data provided by the Health and Social Care Information Centre, sent to ME on special request.

with experts other countries. To account for the uncertainties and variable local costs, this was subjected to a sensitivity analysis of ±33%.

Hospital admission: The cost of hospital admission was set at £2014. This was based on information from 'Payment by Results' regarding the mean cost of a hospital admission for adults for the year 2011/12, the data were provided by the Health and Social Care Information Centre, on special request by one of the authors. The costs were inflated to 2013 prices at a rate of 2.9% per year based on National Institute of Statistics data [33]. In the sensitivity analysis the cost was varied by ±50%.

Palliative chemotherapy: Palliative chemotherapy is highly dependent on the administration route, administration setting, cost of drugs and equipment required. Hence the cost of a single cycle of chemotherapy was set as £1579, equivalent to two day-case admissions (again using 'Payment by Results' data provided by the health and Social Care Information Centre). The base-case cost was subjected to a sensitivity analysis of ±50%.

Outpatient visits and community palliative home care visits: Costs were based on Payment by Results, which were inflated to 2013 prices and Curtis (2013) [34]. Both were minor costs and not subjected to a sensitivity analysis.

In the non-treatment group the absolute costs for hospital, hospices or care homes were assumed to be equal to the cost of the training period for HPN in the treatment group in the hospital setting. Therefore, they were offset in the cost increment calculations.

2.7.3. Quality adjusted life years (QALYs)

QALYs were established from survival length and utility scores (i.e. QOL). The mean survival length for the base-case was calculated by using the meta-analyses data in Fig. 3. This involved extrapolation of the last point in the graph (6 months) to death of all patients, and using the total areas under the curve to calculated mean survival.

Using this method mean survival time for the base-case in patients receiving HPN was estimated to be 116 days, in the sensitivity analysis this was varied by ±50. The base-case survival time in the control group was assumed to be 14 days (given the very poor outcome expected in this group of patients), but in the sensitivity analysis it was varied by ±100%.

Apart from the limited data on QOL summarised in this systematic review (Section 3.7), additional information was also taken into account to establish values that could be used in the base-case QOL and sensitivity analyses. For example, in a study of terminal phase malignancy in which the median survival was 13 days (without PN), quality of life, assessed with the visual analogue scale of EuroQol, was calculated to be 37% (scale 0–100%) from the grouped results presented in the paper [35]. Another study involving a subgroup of patients with terminal malignancy who survived for up to 3 months, quality of life was found to be about 47% using the EuroQol visual analogue scale, and about 35–65% (depending on the domain of quality of life being examined) using the EORTC QLQ-C30 [36]. On the basis of the above information a utility value of 0.5 (scale 0–1) was used in the base-case analysis, both for the HPN and control groups. In the sensitivity analyses the QOL for both groups were varied between 0.3 and 0.7 to encompass uncertainty.

2.7.4. Calculating incremental cost effectiveness ratio

The incremental cost effectiveness ratio (ICER) was calculated as the ratio of incremental cost to incremental QALY gained (i.e. extra cost/QALY gained).

2.8. Statistics

Differences in survival between studies at given points in time were assessed using the Chi squared test and over the entire period of study using the log rank test obtained from the Kaplan Meier analysis.

Random effects meta-analyses were undertaken using Comprehensive Meta-analysis (CMA version 2, Biostat Inc, NJ, USA) after considering the clinical and statistical heterogeneity of the studies. When a meta-analysis was not possible simple descriptive statistics were provided with or without a narrative description. SPSS (version 21, Chicago, USA) was used for descriptive statistics and Chi Squared tests and GraphPad Prism (version 6, California, USA) for Kaplan Meier and log-rank tests of significance. A p-value <0.05 (two tailed) was considered to be significant.

3. Results

3.1. Quality assessment of included papers

Table 4 summarises the assessment of the quality of the studies using the Critical Appraisal Skills Programme (CASP) checklist [24]. Whilst many of the general criteria were met, some of the adapted criteria (see footnotes to table) were not, suggesting a potential risk of bias.

3.2. Studies meeting inclusion criteria

The broad search strategy identified 13,440 references, which reduced to 8262 studies once duplicates were removed. No additional relevant references were identified from the health economic registries CEA registry and HEED. After applying the inclusion and exclusion criteria, the number of studies was reduced to 12 (see Fig. 1 for details).

Two studies published in 1995 by Mercadante [26,37] were considered to contain relevant data but with probable duplication of some survival data. One of these studies [26] reported the

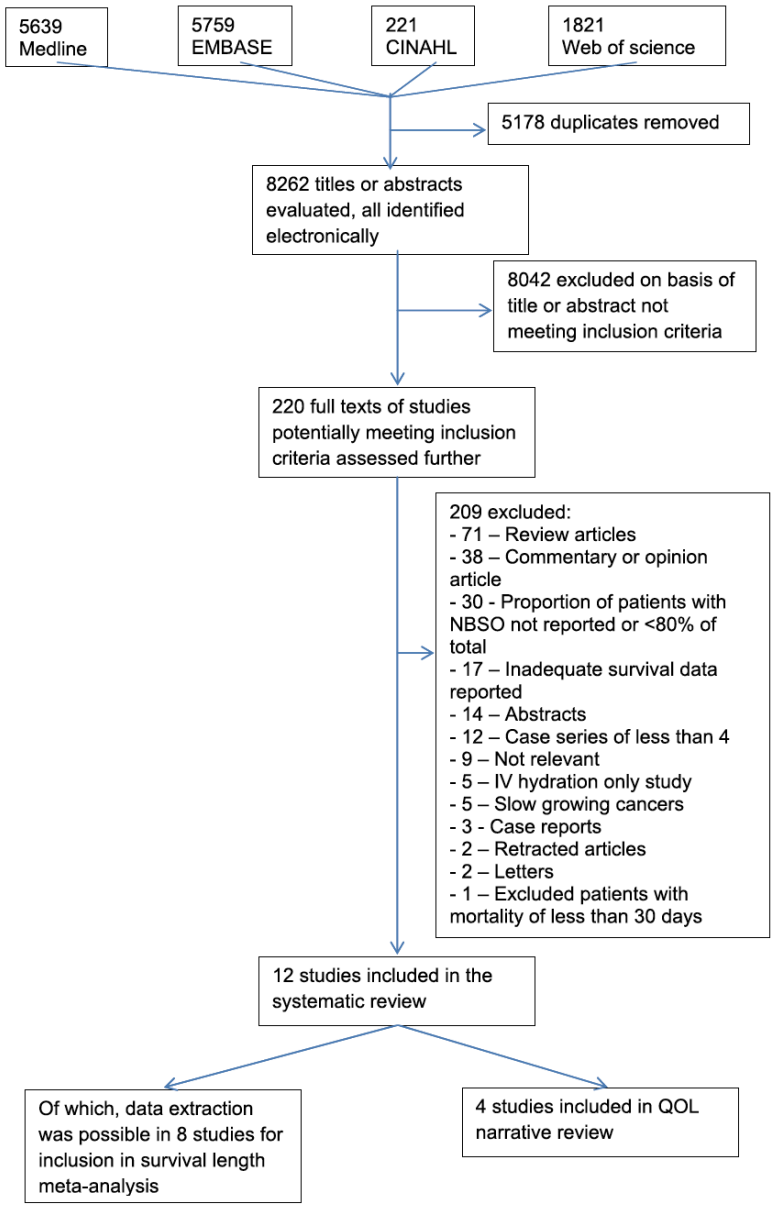

Fig. 1. Flow diagram of study selection process.

survival length of 13 patients, with raw data provided for each patient's survival length, without QOL data. The other study [37] reported QOL data and only mean survival length on 25 patients, without extractable information on the survival length of individual patients. Neither study reported the source of patients in detail, but it is reasonable to assume that the survival length data for some of the patients in these studies have been reported twice given the near identical time period of the study and comparable survival length data. Therefore the study with raw survival length data [26] was utilised for the patient level analysis of survival length and the study level data of QOL data [37] was utilised for the narrative description of QOL.

No studies with cost-effectiveness analyses were identified, although one study [32] undertook a very brief cost analysis, though this was judged not to be relevant to the health economic model in this review.

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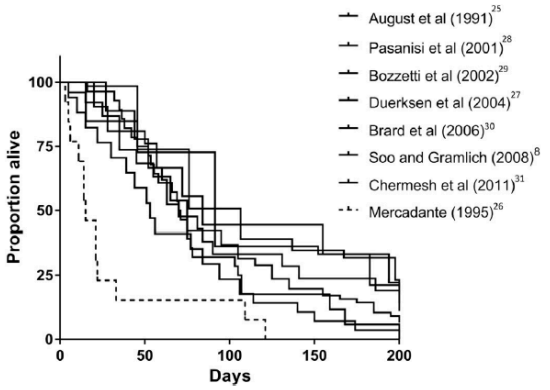

Fig. 2. Kaplan Meier survival curves using patient level data from the 8 included studies, demonstrating the difference between the broadly similar survival for seven studies in the first 100 days and the shorter survivals in Mercadante (1995).[26].

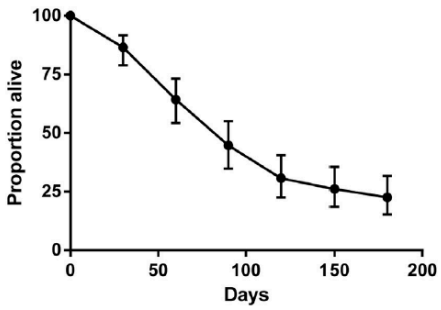

Fig. 3. Proportion of patients alive at monthly intervals during the first six months. Each point shows the mean and 95% confidence interval at each month, established using a random effects meta-analysis of extracted survival data from the included studies (7 studies [8,25,27–31], 244 subjects).

3.3. Study outcomes

The primary outcome of all 12 studies was survival length (n = 437), while four studies also reported QOL [25,29,32,37] (n = 140 patients). Secondary outcome measures included identification of factors for predicting survival time [8,28,30,32], and hospital re-admission rates [27,31,32].

3.4. Patient characteristics

The mean age of patients was reported in 9 studies [8,26–28,30,31,37–39], with a range of 45–61 years. Two studies reported the median age [25,29], (54 and 58 years) and another [32] did not report either mean or median age. The age of individual patients ranged from 33 to 82 years (Table 5).

Eleven studies [8,25–31,37–39] reported the gender distribution of the patients, with an overall predominance of females (64%). The underlying primary malignancy was gynaecological in 25% of patients (accounting for the female predominance), gastrointestinal tract in 53% and other sites in 22%. IBO was reported in 100% of patients in 9 studies [25–28,30,32,37–39] and a range of 82–87% in the other three studies [8,29,31], equating IBO in 96% of patients included (Table 5).

3.5. HPN complications, palliative chemoradiotherapy and admission rates

Within the 12 included studies sufficient data were reported by five studies [8,27,30–32] to allow calculation of central venous catheter sepsis rates, which ranged from 0.40 to 2.89 per 1000 days. Only one study [31] compared the rates of patients receiving HPN for malignancy to those for benign disease, reporting higher rates in those with malignancy (0.19 vs 1.92 per 1000 days, $p < 0.001$).

Thrombotic complications were reported by two studies [27,38], with a wide discrepancy between them: one reporting a rate of 0.19 per 1000 days [38] and the other 4.34 per 1000 days (although 5 out of the total of 6 thrombotic episodes were in the same patient) [27]. Metabolic complications were reported by three studies [8,31,32] ranging from 0.32 to 1.37 per 1000 days.

Four studies reported the proportion of patients to undergo palliative chemotherapy, varying from 39 to 100% [8,27,30,38]. Two of these studies indicated that each patients received a median of

Table 4
Quality and risk of bias assessment using the Critical Appraisal Skills Program [24].

Study	Q1	Q2	Q3	Q4 – For survival outcomes	Q4 – For QOL outcomes	Q5	Q6	Q9	Q10	Q11
August et al, 1991 [25]	Y	Y	Y	Y	N	N (c, d)	Y	Y	Y	Y
Mercadante, 1995 [37]*	Y	Y	Y	NA	N	N (c, d)	Y	Y	N†	N¥
Mercadante, 1995 [26]*	Y	N**	Y	Y	NA	N (c, d)	Y	Y	N†	N¥
Pironi et al, 1997 [32]	Y	N**	Y	Y	N	N (d)	Y	Y	Y	Y
Abu-Rustum et al, 1997 [38]	N¥	N**	Y	Y	NA	N (c)	Y	Y	Y	Y
Pasanisi et al, 2001 [28]	Y	Y	Y	Y	NA	N (c, d)	Y	Y	Y	Y
Bozzetti et al, 2002 [29]	Y	N**	Y	Y	Y	Y	Y	Y	Y	Y
Duerksen et al, 2004 [27]	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y
Brard et al, 2006 [30]	Y	Y	Y	Y	NA	N (c)	Y	Y	Y	Y
Fan, 2007 [39]	Y	N**	Y	Y	NA	N (d)	Y	Y	Y	Y
Soo and Gramlich, 2008 [8]	Y	Y	Y	Y	NA	N (c)	Y	Y	Y	Y
Chermesh et al, 2011 [31]	Y	Y	Y	Y	NA	N (c, d)	Y	Y	Y	Y

*Two Mercadante studies published in 1995, see results Section 3 for clarification. Q1 – Did study address a clearly focused issue (¥denotes no clear focus of study, but results relevant to this review), Q2 – Was cohort recruited in acceptable way (**denotes representativeness of population not state), Q3 – Was the exposure accurately measured to minimise bias? (exposure was taken to be HPN), Q4 – Was outcome accurately measured to minimise bias (NA – denotes not applicable were outcome not given), Q5 – Have the authors identified all important confounders (we prioritised 4 confounders as (a) age, (b) origin of malignancy (c) metastasis (d) chemoradiotherapy – the above lists the confounder not reported in study, Q6 – Was follow up of subjects complete, Q9 – Do you believe the results, Q10 – Can the results be applied to the local population (†Denotes results can not be applied locally – see results in Section 3 for clarification), Q11 – Do the results fit with other available evidence (¥Denotes results do not fit with other evidence – see Results in Section 3 for clarification). Q7, Q8 and Q12 were not scored because they are addressed in detail in the Results and Discussion.

two cycles of treatments [30,38], and one also reported that a mean of 1.6 cycles was provided [30].

The admission rate after discharge with HPN was reported in sufficient detail in one study only [32]. This study of 29 palliative HPN patients described 38 admissions for 18 (62%) patients, equivalent to 1.3 admissions per patient. Only 3 (8%) of these admissions were related to PN directly.

3.6. Survival length outcome analysis

3.6.1. Study level survival length data

Of the 12 included studies, none provided summary data at monthly intervals with measures of variability (standard deviation or standard error). It was possible to extract patient level data from eight studies [8,25–31] for use in meta-analyses.

Nine studies [8,25–32] reported both median and mean survival length, one [38] reported median length alone, and another [39] used the terms median and mean interchangeably. The range of median survivals was 15–140 days, excluding reference [39]. In all but one study [31] the mean was higher than the median. The range of survival in individual patients varied from 3 to 1004 days, but only nine (2%) patients survived longer than one year. The survival data are summarised in Table 5.

Amongst the 12 studies four different definitions of survival length were used, depending on the starting point: from diagnosis of 'terminal intestinal obstruction' [26,30,37], from insertion of venting gastrostomy [38], from the start of PN in hospital [27,29,39], and from the date of discharge from hospital [25]. Four studies did not define the start of the survival period [8,28,31,32]. In general HPN treatment was continued until death or a few days before death.

3.6.2. Validation of extracted patient level data for use in meta-analysis

It was possible to extract survival data for individual patients from eight studies that presented as raw data [25–27], Kaplan Meier curves [28–31] and a scatter plot [8]. To validate the extraction method the extracted data from graphs were averaged and compared with those averages reported by the authors. Table 6 shows these results and provides evidence for concurrent validity.

The extracted patient level data were used in two different ways: to undertake random effects meta-analyses, which assume that the patients originated from distinct populations, and to undertake subgroup analyses (according to specific characteristics such as type of malignancy or performance status), which assume that the patients originated from the same population.

3.6.3. Variability between studies

Before undertaking meta-analyses on survival length, the characteristics of survival pattern in each study were examined. Figure 2, which is based on individually extracted patient data, shows a broadly comparable survival pattern with an almost linear decline between 0 and 100 days with the exception of one study Mercadante (1995) [27] (represented by the dotted line).This study involved a particularly short survival time which can be explained by a low threshold for initiating HPN in patients with more severe or advanced disease. Meta-analyses were undertaken with and without this study.

3.6.4. Meta-analysis of patient level survival length data

Without the study of Mercadante (1995) [26], (7 studies [8,25,27–31], 244 patients, 92.6% with IBO) the median survival was found to be 83 days (95% CI 67–100 days) and the mean was 116 days. With the study of Mercadante (1995) [26] (8 studies [8,25–31], 257 patients, 93.0% with IBO) the meta-analysis showed a shorter median survival time of 77 days and the mean 112 days.

A series of meta-analyses of survival at monthly time points were carried out. The results (without the study of Mercadante (1995) [26]) are presented in Fig. 3 demonstrating the mortality to be 14%, 36%, 55%, 69%, 74% and 78% at 1, 2, 3, 4, 5, and 6 months respectively. Analysis of the extracted data shows a mortality of 98% at one year.

3.6.5. Analysis of survival length by patient characteristics

Survival length by type of malignancy, performance status and concomitant palliative chemoradiotherapy was examined using individually extracted data. Since these subject characteristics could only be extracted from some studies, the analyses below were based on a total of 130 patients or less.

3.6.5.1. Type of malignancy. Survival data for type of primary malignancy was available for 53 patients from 3 studies. Gastrointestinal malignancy patients ($n = 15$ from 2 studies [25,27]) were found to survive longer than those with gynaecological malignancy ($n = 38$ from 3 studies [25,27,30]) with a median survival 106 days vs. 57 days respectively ($p = 0.012$, log rank test) (Fig. 4(a)).

3.6.5.2. Performance status. Survival data and baseline performance status, assessed using the Karnofsky performance score (KPS) (range 0–100), was available for 81 patients, from two studies. Patients with a higher performance status, defined as KPS>50, ($n = 27$ from two studies [27,28]) were found to survive longer than those with a KPS<50 (54 patients from two studies [27,28]) with a median survival 183 days vs. 91 days respectively ($p = 0.01$, log rank test) (Fig. 4(b)).

Soo and Gramlich (2008) [8] did not report the survival length of individual patients in a way that could be matched with performance status, but a summary statement in the paper also indicated significantly higher survival in patients with KPS>50 compared to those with KPS≤50 (median survival 183 vs. 91 days; $p = 0.01$, the number of patients in each group was not reported).

3.6.5.3. Concomitant palliative chemoradiotherapy. Survival length and concomitant palliative chemoradiotherapy was established for 37 patients from two studies. There was no significant difference between the survival length of patients receiving palliative chemoradiotherapy ($n = 22$, from 2 studies [27,30]) and those not receiving it ($n = 15$, from 2 studies [27,30]) (median survival 75 vs. 52 days respectively; $p = 0.535$, log-rank test) (Fig. 4(c)).

3.7. Quality of life

Four studies involving a total of 140 patients examined QOL in patients treated with HPN within the palliative phase of malignant IBO. The results are summarised in Table 7 [25,29,32,37]. Since all four studies used different tools were used to assess QOL and results of each study are reported separately, it is not possible to subject them to a meta-analysis.

Only one study [29] reported QOL using a validated tool. Two studies [29,32] assessed QOL using information provided solely and directly by the patients, and the two others [25,37] used a mixture of information from patients, family members and clinician's opinion based on patient's notes. Two of the studies [29,32], both with baseline measurements, established a symptom based QOL score prospectively.

It is noteworthy that despite the high symptom burden of patients (with 96% of patients reporting symptoms 80% of the time) in the study of Bozzetti et al. [29] 58% of patients reported feeling "well" or "very well" at baseline. The results of this study, based on

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Table 5
Summary of study characteristics, patient demographics, survival length and of quality of life.

Study	Study characteristics					Patient demographics and conditions						Survival data (days)			QOL Data
	Period of study	Country	Singles/ multiple	Source of data for survival length	Definition of length of survival	No. treated with HPN with survival data	% patients with IBO	Age mean or median (range/SD)	% female	Underlying malignant condition (%)	Nutrition status/ weight (kg) at baseline	Palliative chemo-radiotherapy received during HPN	Mean	Median	Range	
August et al, 1991 [25]	1980–1989	USA	Single	Raw data for each patient	From discharge with HPN to death	17	100%	Median 58 (33–79)	82%	Gynaecological (59%) Gastro-intestinal tract (41%)	Not reported	Not stated	72	53	5–208	Yes
Mercadante[a] 1995 [37]	1990–1994	Italy	Multiple	Average reported only	From diagnosis of intestinal obstruction	25	100%	Mean 61 (35–65)	48%	Gastro-intestinal (52%) Gynaecological (28%) Other (20%)	Not reported	Not stated	19	Not stated	3–53	Yes
Mercadante[a] 1995 [26]	5 year period – dates not stated	Italy	Multiple	Raw data for each patient	From diagnosis of intestinal obstruction	13	100%	Mean 53 (32–71)	62%	Gynaecological (15%) Gastro-intestinal tract (62%) Other (20%)	Not reported	Not stated	30	15	3–121	No
Pironi et al, 1997 [32]	1990–1996	Italy	Multiple	Average reported only	Not defined	29	100%	Not stated	Not stated	Gastro-intestinal tract (62%) Head & neck (10%) Lung (3%) Genitourinary (14%) Other (10%)	"Protein-energie mal-nutrition in 82%"	Not stated	85	56	14–343	Yes
Abu-Rustum et al, 1997 [38]	1990–1995	USA	Single	Average reported only	From insertion of venting gastro-stomy to death	11	100%	Mean 55 (32–75)	100%	Gynaecological (100%)	Not reported	100%	Not stated	89	Not stated	No
Pasanisi et al, 2001 [28]	1995–1999	Italy	Multiple	Extracted from Kaplan Meier graph	Not defined	76	100%	Mean 57 (+/− 14 SD)	71%	Gynaecological (24%) Gastro-intestinal tract (58%) Other (18%)	Mean weight 54.2 (+/− 9 SD), Mean BMI 20.8 (+/− 3.7 SD)	Not stated	98	74	6–301	No
Bozzetti et al, 2002 [29]	3 year period – dates not stated	Italy	Multiple	Extracted from Kaplan Meier graph	From PN in hospital to death	48	84%	Median 54 (29–82)	59%	Gynaecological (19%) Gastro-intestinal tract (53%) Other (28%)	Median weight – 53 (35–78)	Not stated	156	91	30–426	Yes
Duerksen et al, 2004 [27]	1997–2002	Canada	Single	Raw data for each patient	From PN in hospital to death	9	100%	Mean 45 (35–57)	33%	Gastro-intestinal tract (89%) Other (11%)	Not reported	56%	166	84	27–433	No
Brard et al, 2006 [30]	1994–2002	USA	Single	Extracted from Kaplan Meier graph	From diagnosis of intestinal obstruction	28	100%	Mean age 54 (+/− 9.8 SD)	100%	Gynaecological (100%)	Not reported	64%	90	74	16–485	No
Fan, 2007 [39]	2000–2006	China	Single	Averages reported only	From PN in hospital to death	115	100%	Mean 51 (31–74)	54%	Gastro-intestinal tract (70%) Other (30%)	Mean 9 kg weight loss	Not stated	[b]	[b]	Not stated	No

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Soo and Gramlich, 2008 [8]	1999 –2006	USA	Multiple	Extracted from scatter graph	Not defined	38	87%	Mean 49 (+/− 14 SD)	71%	Gynaecological (37%) Gastro-intestinal tract (42%) Other (21%)	Not stated	39%	164	89	8–1004	No
Chermesh et al. 2011 [31]	2003 –2009	Israel	Single	Extracted from Kaplan Meier graph	Not defined	28	82%	Mean 60 (+/− 12.7 SD)	47%	Gynaecological (32%) Gastro-intestinal tract (43%) Other (25%)	BMI 20.4 (+/− 4.8 SD)	Not stated	130	140	20–783	No

IBO – inoperable bowel obstruction. BMI – body mass index, HPN – home parenteral nutrition, QOL – quality of life.
[a] Two Mercadante studies published in1995, see results Section 3 for clarification.
[b] In Fan (2007) (Reference39) survival length mean and median terminology is interchange and both reported as198 days without qualification.

the Rotterdam Symptom Check List (RSCL) (four domains and a totalled score), were presented graphically without raw or extractable data on individual patients. Examination of graphical results were difficult to interpret because median scores were obtained from a different number of patients, at various time points between 0 and 10 months before death. There was no obvious trend over time in median results for the 'psychological' and 'well-being' domains and there was substantial variability within all domains at the same time points. In addition, there was substantial variability in three individual domains ('physical', 'activity' and 'total QOL scores') at various time points during the last few months before death, with some of them showing better scores at 2–3 months than at 4 months before death, the worst being at 1 month before death. The study authors identified 2–3 months before death as the time point at which QOL deteriorates in HPN treated palliative malignancy patients, but from the graphical data presented the authors of this review can not identified a clear time point before death that marked deterioration in QOL. Nevertheless, the results for the 'activity' and 'physical' domains, as well as the 'total QOL score' suggested that the values at 6 months were comparable to baseline values, those at >6 months before death were better than the baseline values and those <6 months worse or comparable to baseline values.

The improvement in symptoms reported by Mercadante (1995) [37] after commencing PN therapy may have been confounded by variables that were introduced at the same time as starting PN, such as decompression of stomach with nasogastric tubes in 7/25 (28%) patients and administration of anti-secretory treatment to most patients.

3.8. Health economics

3.8.1. Base-case cost analysis

Using the information provided in Table 3, the following results were obtained for the base-case analysis. In the treatment and non-treatment groups the total number of QALYs gained was 0.1353 and 0.0192 respectively. In the treatment group the base-case incremental cost was calculated as £22,197. In the non-treatment group the absolute costs for hospital, hospices or care homes were assumed to be equal to the cost of the period required to commence HPN in the treatment group in the hospital setting, hence these costs were not included in the calculations for either group, as they would make no difference to the subsequent calculations of incremental costs (difference in costs between treated and untreated groups).

3.8.2. Incremental cost effectiveness ratio and sensitivity analysis

The ICER for the palliative malignancy HPN patient group, at base-case costs and utility, was £176,587/QALY. Figure 5 demonstrates the effect of one-way sensitivity analysis on ICER, as described in Section 2.7, for survival length, utility, costs and resource use. Variations in the assumptions of utility in the treatment group was found to have the most substantial effect on the ICER (−30% to +75%), with three further variables causing a substantial effect on the ICER; cost of parenteral nutrition (±26%) survival length of the treatment group (−24% to +10%) and survival length of the non-treatment group (−20% to +7%). Even so, in the one-way sensitivity analyses, the ICER in all cases remained above £123,000/extra QALY gained.

4. Discussions

This is the first systematic review examining survival length and QOL in patients treated with palliative HPN for inoperable bowel

Appendix B

Table 6
Validation of extracted data by comparison of study reported mean/median survival (days) to those acquired by data extraction.

Study	Source of data extraction	Author's mean	Data extraction mean	Author's median	Data extraction median
Pasanisi et al., 2001 [28]	Kaplan Meier graph	Not reported	–	74 days	75 days
Bozzetti et al., 2002 [29]	Kaplan Meier graph	Not reported	–	3.0 months	3.1 months
Brard et al., 2006 [30]	Kaplan Meier graph	Not reported	–	74 days	70.5 days
Soo and Gramlich, 2008 [8]	Scatter graph	164 days	158.6 days	89 days	89 days

obstruction caused by malignancy. It is also the first to examine the cost and cost-effectiveness of HPN in such patients.

International guidelines [10,11], made without formal systematic review or cost-effectiveness analysis, have generally supported the use of PN in patients with malignancy who have failed oral and enteral tube feeding and who have an expected survival longer than 2–3 months. The meta-analysis in this review reveals that only 45% of the patients treated with HPN for palliative malignant IBO survive to 3 months. The median and mean survival length for this group of patients was also found to be short, at 83 days and 116 days respectively (55% mortality at 3 months and 76% mortality at 6 months).

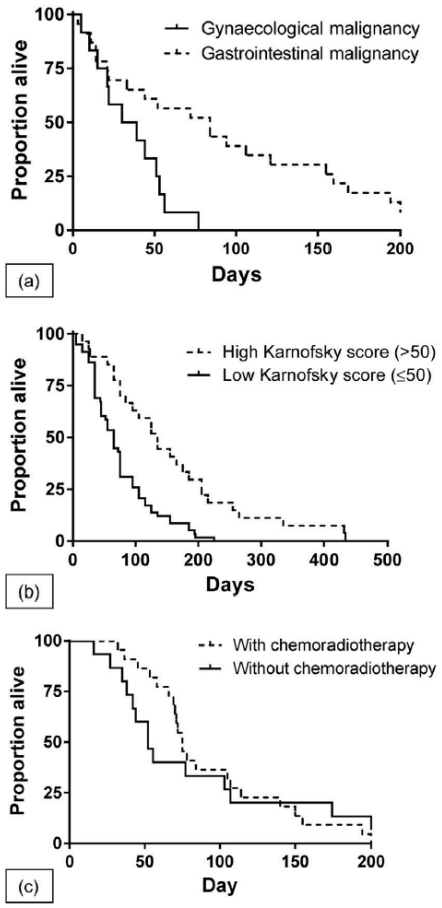

Fig. 4. (a), (b) and (c) – Kaplan Meier survival curves, based on extracted data, by patient characteristics demonstrating statistically significant difference in survival depending on (a) type of malignancy ($p = 0.012$) and (b) performance status (measured by Karnofsky performance score) ($p = 0.01$) and lack of a difference for patients who underwent (c) concurrent palliative chemoradiotherapy during parenteral nutrition treatment (not significant).

Since our literature search was undertaken for this review, a study involving a large prospective multinational case series of 414 patients (approximately 67% with IBO) treated with HPN during palliative malignancy has been published by Bozzetti et al. (2014) [2]. Despite the lower proportion of IBO patients in this study, the survival pattern observed corresponds closely to that of this review (median 91 days, 50% mortality 3 month and 77% mortality at 6 month).

The clinical challenge is to accurately identify those patients who are likely to survive for long enough to benefit from HPN treatment. The amalgamation of data in this review suggests the Karnofsky performance score and type of malignancy can statistically discriminate between longer and shorter survival, but there is substantial overlap between the categories (see Fig. 4 (a) and (b)), hence the clinical application of these two factors prospectively is limited without a wider assessment of each case.

The above mentioned case series by Bozzetti et al. (2014) [2] evaluated the potential predictive value of combining Glasgow Predictive Score (GPS) and Karnofsky performance score (KPS) to identify the probability of surviving up to 3 and 6 months. For example, 79% of patients with a combination of the more favourable GPS score (zero) and KPS (>50) were alive at 3 months, compared to 33% in those with a combination of the more unfavourable GPS score (two) and KPS (≤50) (similarly 40% vs. 5% at 6 months respectively). The use of these factors may help in patient selection prospectively for HPN treatment in palliative malignancy patients and requires further investigation.

We have not reviewed the evidence for the controversial topic of PN induced malignant tumour growth, which could limit survival length. This topic has recently been addressed by Bossola et al. (2011) [40], who reported conflicting and inconclusive evidence.

The second aim of this review was to gather information on QOL during HPN treatment. Unfortunately only a limited number of studies exist to address this issue in patients with malignant IBO and most of these studies used tools that were not validated.

The recommendation in the ESPEN (2009) [10] guideline that PN may be considered if the anticipated survival is longer than 2–3 months, is predominantly based on QOL data from the two studies: Bozzetti et al. (2002) [29] and Cazzaglio et al. (1997) [4]. In the study of Bozzetti et al. (2002) [29] HPN therapy was recommended for patients expected to survive at least three months because QOL parameters were considered by the authors of the paper to remain largely stable until 2–3 months before death. In the absence of raw data, it was difficult to draw definitive conclusions from the graphical data regarding the identification of a single time point before death at which QOL can be reliably identified to worsen. This difficulty arose because; no absolute values for QOL were presented, different numbers of patients were reported at various time points, with no information reported on trends in the same patients, and the variability observed between patients at each time point was large. In the study by Cozzaglio et al. (1997) [4], (excluded from this review because the proportion of IBO patients was <80%)

Table 7
Summary of quality of life study characteristics and results. RSCL – Rotterdam symptom check list.

Study	N	Source of data	Prospective/ retrospective	Baseline/ post-treatment/both	Type of assessment	Description of findings
Bozzetti et al., 2002 [29]	69	Patient	Prospective	Both	RSCL (includes symptoms, activity levels, psychosocial and overall well being)	96% of patients reported symptoms 80% of the time Transient benefit in physical symptoms, followed by decline 2–4 months before death 58% said they were "well" or "very well" (related to overall health), despite needing help with activities of daily living
Mercadante, 1995 [37]	25	Patients	Prospective	Both	Symptoms	Improved symptom control one week after starting PN, though confounded by other palliative treatments
August et al., 1991 [25]	17	Patient, family and Clinician review of medical notes	Prospective and Retrospective	Post-treatment	Effect of treatment	65% benefit from PN, 18% may have benefited and 18% did not benefit
Pironi et al., 1997 [32]	29	Clinician review of medical notes	Retrospective	Post-treatment	Effect of treatment	66% accepted PN well, 24% displayed annoyance at PN and 10% scarcely tolerated PN

improvements in QOL was reported in 68% of patients who survived >3 months, compared to only 9% < 3 months, although QOL was judged by the clinicians using unvalidated methodology.

In view of the limited data on QOL in patients with IBO during palliative HPN, it is helpful to consider data from two structured questionnaire studies by Orrevall et al., [41,42] even though these were carried out in a predominantly non-IBO palliative HPN patient group. These studies reported that the most salient effect of HPN treatment on patients and family was positive, due to the sense of relief and security that nutritional needs were being met by HPN. The negative effects were the restriction on family life and social contacts, however positive effects were generally said to outweigh the negative.

It is clear that further data on QOL are needed before more informed decisions about the value of HPN in the palliative IBO malignancy group of patients can be made, especially regarding the minimal length of survival needed before benefit is likely to be experienced.

The third aim of the review was to consider the cost and cost-effectiveness of this treatment. Our model was based on limited data on rates of re-admissions, complications and chemotherapy, while further informed by the survival length findings of the current review. Costs were based on those in the UK [33,34], with sensitivity analysis accounting for variability. The treatments and associated costs of palliative malignant IBO patients are complex, however our model is sufficiently robust to show the ICER for this therapy is high at £176,587/QALY at base-case analysis.

Richards and Irving (1996) [16] have carried out the only other detailed health economic analysis of HPN in the UK, but it was carried out in an exclusively benign patient group in the mid-1990s. Nevertheless, the estimated absolute costs for the first year were £44,288, corresponding to £69,975 at 2013 prices (assuming 2.9% inflation per year) [33], equivalent to £192/day. This is lower, though comparable to the daily costs in our model of palliative HPN for the base-case patient at £240/day (in this calculation we have considered the cost of the commencing HPN as 2 weeks of in-patient admission, equivalent to £5,639, based on information from 'Payment by Results'). In the study of Richards and Irving (1996) [16] the ICER for the first year of treatment was estimated at £85,829/QALY, equivalent to £135,610/QALY inflated to 2013 prices. The ICER estimate for palliative HPN from our model is higher, though comparable at £176,587/QALY. Although due to the significantly longer survivals in benign disease the concept of 'discounting' makes HPN more cost effective in the long term.

Many health systems use ICER thresholds to identify cost-effective treatments. In England a threshold in the range of £20,000 - £30,000/QALY has been used by the National Institute of Clinical Excellence (NICE), with treatments associated with ICERs over £30,000/QALY only having an 8% probability of approval (Written evidence to House of Commons Health Committee, 2012)

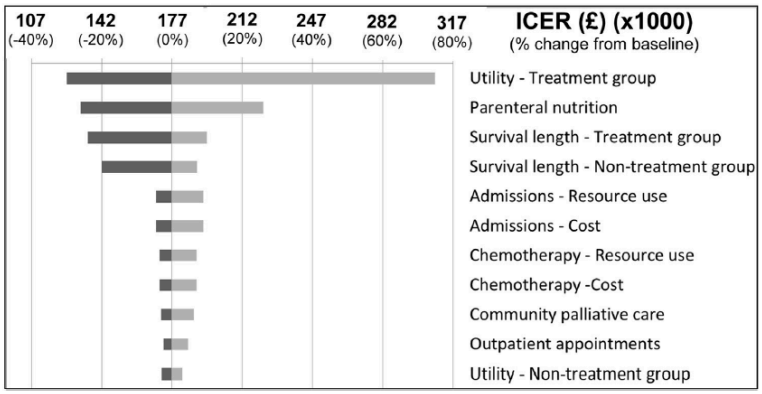

Fig. 5. Tornado graph demonstrating the effect of one-way sensativity analysis on incremental cost effectiveness ratio (ICER: extra cost/QALY gained) (see Table 3 for variation in assumptions).

Appendix B

[43]. In several other countries comparable thresholds have been used, although controversy exists about the exact values that should be used (for example, in the Netherlands a threshold of Euros 100,000/QALY has been proposed according to severity of disease). [44]

In light of the economic analysis in this review, from a purely economic approach, in countries that use ICER thresholds, HPN for palliative malignant IBO patients would need strong justification (in likelihood this would also apply to non-IBO indications for HPN in the palliative phase of malignancy). However these high costs are comparable to the less controversial and accepted practice of HPN for benign disease.

The health economic method used in this review is the dominant method used currently in health economy, but this method may not be the most appropriate to appraise all treatments. Several experts have stated a preference for Willingness To Pay (WTP) in setting the thresholds [45]. Research recently commissioned by UK Department of Health [46] estimated the threshold of WTP to range as high as £70,000/QALY.

NICE have also set out proposed criteria for 'end of life treatment'. These criteria are: small population group, use of a treatment that is likely to prolong life by ≥ 3 months, in patients with a life of expectancy of <24 months, and robust health economic assessment. Given these criteria are met by palliative HPN, the QOL score assigned can be uplifted to the level experienced by age matched healthy subjects (i.e. 0.8 based on the EuroQoL visual analogue score) [47]. However when the uplifted utility is applied to the palliative malignant HPN population in our model, the calculated ICER (£107,000/QALY gained) still remains higher than even the proposed new threshold for WTP.

The limiting factors in this review include the challenging definition of the palliative phase of a malignant condition, but IBO as the indication for palliative HPN is relatively easy to identify and can be considered the most judicious indication, with a high prevalence amongst palliative malignancy patients treated with HPN. However, even IBO can sometimes be variable and intermittent. The included studies also used a variable definition for the starting point for measuring survival length. Furthermore, despite extracting individual patient data from the papers for patient level analysis, the number of subjects is still limited. Additionally, the studies or components of studies were judged to be of variable quality and potentially subject to moderate risk of bias. The criteria for stopping HPN were not specifically investigated by any of the reviewed papers; this important topic remains to be addressed.

In summary, we recognise that decisions about starting HPN in patients with palliative malignancy are difficult and that such decisions vary according to country, clinician attitudes, and local economies. Circumstances arise for supporting the use of this treatment to extend life, such as giving individuals valuable time to reach a short term goal (e.g. impending birth of child or other life events of equal magnitude), which could have long-lasting positive effects on the family and on the image of a health system that has a compassionate attitude towards the care of the terminally ill patients.

This review summarises the available evidence and describes a model of cost-effectiveness that can be used to inform decisions about the use of HPN in patients with palliative malignant IBO. While no single recommendation will satisfy all situations, the paramount objective for clinicians considering HPN in the palliative phase of malignancy should be to identify patients who are most likely to benefit from this costly treatment. On current evidence this should take account, but not depend entirely on the patient's performance status at the time of starting HPN, while further evidence from prospective research is required to improve prediction of survival and QOL.

Clinicians should recognise that the majority of palliative malignancy patients do not meet the international guideline criteria for HPN therapy and in some who do meet the criteria, the high burden of this treatment may not always be beneficial.

Statement of authorship

All authors planned and discussed the results of this systematic review.

MN/ME: systematic search, study quality assessment, statistical analysis, health economic analysis.

All authors read and approved the final manuscript.

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Conflict of interest

None declared.

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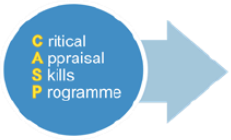
Appendix C - Critical Appraisal Skills Program tool



12 questions to help you make sense of cohort study

How to use this appraisal tool

Three broad issues need to be considered when appraising a cohort study:

Are the results of the study valid? (Section A)
What are the results? (Section B)
Will the results help locally? (Section C)

The 12 questions on the following pages are designed to help you think about these issues systematically. The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions.

There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

These checklists were designed to be used as educational pedagogic tools, as part of a workshop setting, therefore we do not suggest a scoring system. The core CASP checklists (randomised controlled trial & systematic review) were based on JAMA 'Users' guides to the medical literature 1994 (adapted from Guyatt GH, Sackett DL, and Cook DJ), and piloted with health care practitioners.

For each new checklist a group of experts were assembled to develop and pilot the checklist and the workshop format with which it would be used. Over the years overall adjustments have been made to the format, but a recent survey of checklist users reiterated that the basic format continues to be useful and appropriate.

Referencing: we recommend using the Harvard style citation, i.e.:

Critical Appraisal Skills Programme (2017). CASP (insert name of checklist i.e. Cohort Study) Checklist. [online] Available at: *URL*. Accessed: *Date Accessed.*

(A) Are the results of the study valid?

Screening Questions

1. Did the study address a clearly focused issue? ❒ Yes ❒ Can't tell ❒ No

HINT: A question can be 'focused' In terms of

- The population studied
- The risk factors studied
- The outcomes considered
- Is it clear whether the study tried to detect a beneficial or harmful effect?

2. Was the cohort recruited in an acceptable way? ❒ Yes ❒ Can't tell ❒ No

HINT: Look for selection bias which might compromise the generalisability of the findings:

- Was the cohort representative of a defined population?
- Was there something special about the cohort?
- Was everybody included who should have been included?

Is it worth continuing?

Detailed questions

3. Was the exposure accurately measured to minimise bias? ❒ Yes ❒ Can't tell ❒ No

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measurements truly reflect what you want them to (have they been validated)?
- Were all the subjects classified into exposure groups using the same procedure

4. Was the outcome accurately measured to ❒ Yes ❒ Can't tell ❒ No

minimise bias?

HINT: Look for measurement or classification bias:

- Did they use subjective or objective measurements?
- Do the measures truly reflect what you want them to (have they been validated)?
- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?
- Were the measurement methods similar in the different groups?
- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?

---

5. (a) Have the authors identified all important confounding factors? ❒ Yes ❒ Can't tell ❒ No

List the ones you think might be important, that the author missed.

(b) Have they taken account of the confounding factors in the design and/or analysis? ❒ Yes ❒ Can't tell ❒ No

HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors

---

6. (a) Was the follow up of subjects complete enough? ❒ Yes ❒ Can't tell ❒ No

(b) Was the follow up of subjects long enough? ❒ Yes ❒ Can't tell ❒ No

HINT: Consider

- The good or bad effects should have had long enough

to reveal themselves
- The persons that are lost to follow-up may have different outcomes than those available for assessment
- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?

(B) What are the results?

7. What are the results of this study?

HINT: Consider
- What are the bottom line results?
- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?
- How strong is the association between exposure and outcome (RR,)?
- What is the absolute risk reduction (ARR)?

8. How precise are the results?

HINT: Look for the range of the confidence intervals, if given.

9. Do you believe the results?

❒ Yes ❒ Can't tell ❒ No

HINT: Consider
- Big effect is hard to ignore!
- Can it be due to bias, chance or confounding?
- Are the design and methods of this study sufficiently flawed to make the results unreliable?
- Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)

(C) Will the results help locally?

10. Can the results be applied to the local population? ❒ Yes ❒ Can't tell ❒ No

HINT: Consider whether

- A cohort study was the appropriate method to answer this question
- The subjects covered in this study could be sufficiently different from your population to cause concern
- Your local setting is likely to differ much from that of the study
- You can quantify the local benefits and harms

---

11. Do the results of this study fit with other available evidence? ❒ Yes ❒ Can't tell ❒ No

---

12. What are the implications of this study for practice?

HINT: Consider

- One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making
- For certain questions observational studies provide the only evidence
- Recommendations from observational studies are always stronger when supported by other evidence

Glossary of Terms

Health economics – is the scientific economic approach to issues related to efficiency, effectiveness, value of healthcare

Incurable cancer – is the point at which the patient's malignant disease process is not amenable to treatments that can cure the disease or the patient's physiological health is not sufficient to undergo curative treatments

Palliative care – is the phase of therapy where the focus turns away from cure and the approach is to improve the quality of life of patients and their families, through the prevention of pain and support for psychosocial and spiritual needs

Parenteral Nutrition - is a treatment whereby macronutrients (amino acids, proteins, carbohydrates and fats), electrolytes, micronutrients (vitamins and trace elements) and hydration are supplied by means of a venous catheter device directly into the blood circulation

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