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The clinical and cost-effectiveness of supplemental parenteral nutrition in oncology

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ABSTRACT

Background Clinical guidelines recommend that parenteral nutrition (PN) is added to enteral nutrition (EN; supplemental parenteral nutrition (SPN)) in order to meet energy and protein needs in patients with cancer when EN alone is insufficient. However, although cancer-related malnutrition is common, there is poor awareness of the value of nutritional care, resulting in SPN being chronically underused.

Methods We performed a targeted literature review and exploratory cost-utility analysis to gather evidence on the clinical effectiveness of SPN, and to estimate the potential cost-effectiveness of SPN versus EN alone in an example cancer setting.

Results The literature review identified studies linking SPN with malnutrition markers, and studies linking malnutrition markers with clinical outcomes. SPN was linked to improvements in body mass index (BMI), fat-free mass, phase angle (PhA) and prealbumin. Of these markers, BMI and PhA were strong predictors of survival. By combining published data, we generated indirect estimates of the overall survival HR associated with SPN; these ranged from 0.80 to 0.99 (mode 0.87). In patients with Stage IV inoperable pancreatic cancer, the incremental cost-effectiveness ratio versus EN alone was estimated to be £41 350 or £91 501 depending on whether nursing and home delivery costs for EN and SPN were combined or provided separately.

Conclusion Despite a lack of direct evidence, the results of the literature review demonstrate that SPN may provide important clinical and quality of life benefits to patients with cancer. The potential for any improvement in outcomes in the modelled patient population is very limited, so cost-effectiveness may be greater in patients with less severe disease and other types of cancer.

Key questions

What is already known about this subject?

► Supplemental parenteral nutrition (SPN) is used in malnourished patients with cancer when enteral or oral intake is insufficient. However, there is poor awareness of the value of nutritional care. Consequently, SPN is chronically underused, particularly in patients who can receive enteral nutrition (EN) but who remain malnourished.

What does this study add?

► This study gathered and assessed the available evidence linking the use of SPN to clinical outcomes in patients with cancer who are malnourished. From the evidence identified, we estimated the impact of SPN on overall survival and calculated the first estimate of the cost-effectiveness of SPN in an example cancer population.

How might this impact on clinical practice?

► Our study highlights a lack of direct evidence linking SPN to clinical outcomes, so further research is needed in this area. Parameters in the cost-effectiveness analysis were limited by data availability, so the analysis was restricted to a population with very poor prognosis. However, SPN could be cost-effective in patients with less severe disease or in different cancer settings. Additionally, where SPN is provided in the home setting, our findings show that improving efficiency of service delivery by combining nursing and delivery of SPN and EN could greatly improve cost-effectiveness.

INTRODUCTION

Malnutrition, presenting as weight loss mainly due to loss of muscle mass, is a common and serious comorbidity in cancer. It results in poorer clinical outcomes, increased healthcare costs and reduced patient quality of life.[1–3] Although often one of the first presenting symptoms, malnutrition can occur at any stage in the cancer journey.[4] Prevalence varies considerably by tumour type, from around 30% in patients with breast cancer or acute leukaemia to more than 85% in patients with pancreatic or gastric cancer.[5]

The causes of malnutrition in cancer are multifactorial; a combination of physical (diminished functional capacity) and psychological symptoms can inhibit food consumption and absorption.[6] Those at highest risk are patients with tumours of the digestive system, head and neck, and lungs, in whom malnourishment can be due to abnormalities in gastrointestinal function.[7] Nutritional status may also decline as a result of

treatment, including surgical procedures, chemotherapy, targeted therapies and radiotherapy.[7]

Loss of skeletal muscle impairs treatment effectiveness, increases morbidity and ultimately shortens survival; data from four landmark studies show that up to 23% of patients with advanced cancer die as a result of progressive malnutrition, rather than as a result of the tumour.[8–11] Malnutrition and weight loss also increase the risk for dose-limiting toxicity with chemotherapy, targeted therapy and immunotherapy, reducing patients' ability to tolerate and complete treatment.[12–14] Studies have also shown that cancer-related malnutrition is associated with more frequent and severe complications and significantly higher readmission rates.[15–18]

Poor nutritional status in oncology patients increases hospital length of stay, in-hospital complications and non-elective re-admissions, increasing healthcare costs and reducing patient well-being.[19–21] Increased toxicity with immune and targeted therapies due to malnutrition and weight loss are likely to add substantially to the high cost burden of these therapies.[12]

Malnutrition can be assessed using non-invasive measurements and laboratory markers. Calculation of body mass index (BMI) and fat-free mass index (FFMI) requires measurement of total mass and fat-free mass (FFM), respectively, and height.[22] Another non-invasive indicator is phase angle (PhA), which measures resistance and reactance of body tissues using bioelectrical impedance analysis (BIA), providing information on the status of cell membranes.[23] A common laboratory indicator is prealbumin (PAB), a liver protein and marker of protein synthesis.[24]

European Society for Clinician Nutrition and Metabolism guidelines recommend regular screening for the risk or the presence of malnutrition in patients with cancer. Patients' energy and substrate requirements should be met by offering nutritional interventions in a stepwise manner. Nutritional interventions, namely oral nutritional supplements (ONS), enteral nutrition (EN; via enteral tubes) and parenteral nutrition (PN), should aim to maintain or improve food intake and mitigate metabolic derangements, maintain skeletal muscle mass and physical performance, reduce the risk of reductions, interruptions or dose modifications of scheduled anticancer treatments, and improve quality of life. Timely initiation is key, as any delays might compromise the potential benefits of both nutritional and anticancer therapies.[25]

PN may be used to augment enteral or oral intake in certain patients—this is known as supplemental parenteral nutrition (SPN). When EN alone fails to meet nutritional targets due to the gastrointestinal tract being unable to tolerate or absorb enough EN, clinical guidelines recommend the use of SPN to meet energy and protein requirements. Furthermore, supplemental EN, or SPN (if supplemental EN is not sufficient or possible), is recommended in patients undergoing curative cancer treatment and in whom oral food intake is inadequate despite counselling and ONS.[6]

Despite the high prevalence of cancer-related malnutrition, good nutritional practices are not routinely implemented due to poor awareness of the value of nutritional care.[26] In particular, although PN is widely used where it is strictly indicated (ie, in patients for whom enteral feeding is not possible), SPN is chronically underused in populations who are able to receive EN but who remain malnourished.[27] Where nutritional interventions are used delivery is often delayed, resulting in poorer outcomes.[25]

Our primary objective was to identify existing clinical and quality of life evidence associated with SPN. A secondary objective was to use the evidence identified to inform an exploratory analysis of the cost-effectiveness of SPN in an example setting. Cost-effectiveness analyses are commonly performed for healthcare interventions such as drugs and medical devices to ensure the best use of healthcare system budgets.

METHODS

Targeted literature review

A targeted literature review (TLR) was performed to identify direct evidence associated with SPN in oncology. However, as no direct evidence on the effect of SPN was identified in this TLR (TLR1) a second review (TLR2) was performed to identify indirect evidence. There is evidence to suggest that PN influences specific malnutrition markers, such as BMI and PhA, and that those markers influence clinical outcomes, such as overall survival (OS).[28–31] The objective of TLR2 was therefore to identify evidence on the impact of SPN or PN alone on malnutrition markers, and evidence linking these malnutrition markers to clinical outcomes.

Details of eligibility criteria, data sources and the data collection process are provided in the online supplementary file.

Cost-effectiveness model

Overview

An exploratory cost-utility analysis was performed, using evidence identified in TLR2 to inform indirect estimates of the effect of SPN on survival. The modelled intervention, comparator and population align with the main source of evidence identified in the TLR (Pelzer *et al*[32]; see the Results section). The analysis estimates costs and outcomes associated with home-based SPN (PN+EN) versus EN alone in patients with Stage IV inoperable pancreatic cancer, over a lifetime time horizon. However, prognosis is extremely poor in the modelled patient population, so the potential for quality-adjusted life year gain is limited.

The model takes the form of a partitioned survival model, with health states for progression-free disease, progressed disease and death. Partitioned survival models are commonly used in late-stage oncology modelling, and have been used in pancreatic cancer previously.[33]

The model adopts the perspective of the UK National Health Service and personal social services, and costs and outcomes are discounted at an annual rate of 3.5%, in line with current National Institute for Health and Care Excellence (NICE) guidance.[34] A cycle length of 1 week is used, with half-cycle correction implemented using the life-table method.

Clinical data

Data for the baseline survival curves for OS, progression-free survival (PFS) and time on treatment (ToT) were taken from the most recent NICE appraisal in the population of interest, with survival curves for gemcitabine plus nab-paclitaxel (considered to be standard of care) used in the base-case.[33] The generalised gamma distribution was found to be the best-fitting for each of OS, PFS and ToT in the NICE appraisal, and so it was used as the base-case distribution for each of the three curves.

The literature review only identified evidence for the OS HR associated with SPN (see the Results section). Estimates ranged between 0.80 and 0.99, therefore 0.87 was used in the base-case as it was the modal estimate and represented a reasonable mid-point. In the absence of other data, it was assumed that the HRs for PFS and ToT are the same as that for OS.

Utility data

The pre-progression utility value (0.52) was taken from the literature and the post-progression value (0.45) was calculated by subtracting a utility decrement (0.07) identified in the NICE appraisal.[33 35] A utility increment (0.29) for patients receiving SPN was also included to account for the potential quality of life benefit of no longer being malnourished. In Pelzer *et al*, 87.5% of patients were weight-gaining or weight-stable after receiving SPN.[32] This was multiplied by the utility increment for being

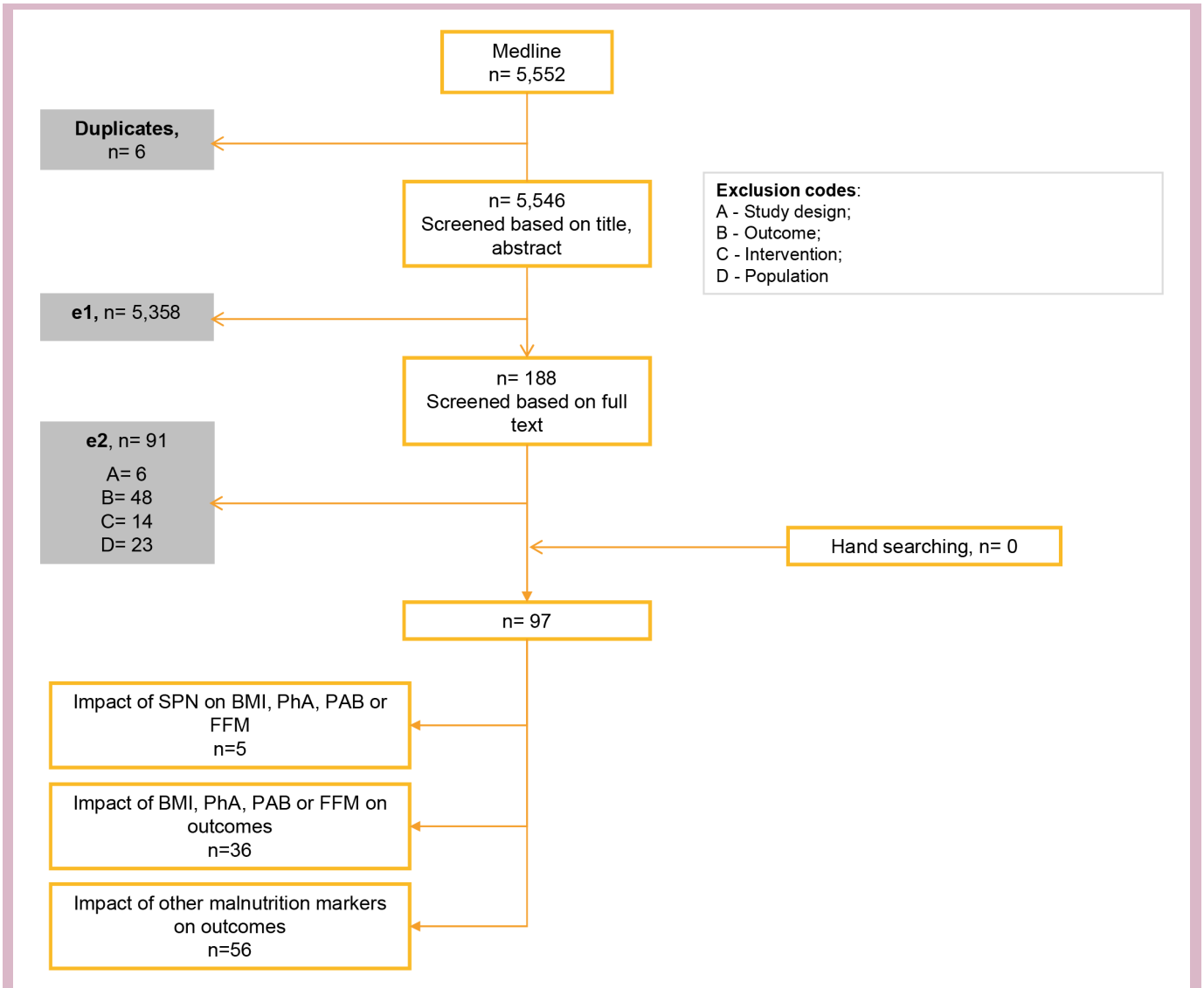

Figure 1 Flow of studies through TLR2. BMI, body mass index; FFM, fat-free mass; PAB, prealbumin; PhA, phase angle; SPN, supplemental parenteral nutrition; TLR, targeted literature review.

weight-stable compared with being weight-losing (0.33) in O'Gorman *et al*.[35]

Cost and resource use data

All costs were valued in 2019 UK pounds, and unless otherwise stated unit costs were taken from published national sources. Where necessary, costs were inflated using inflation indices issued by the Personal Social Services Research Unit.

Weekly clinical nutrition costs for EN and SPN were calculated based on daily calorie targets according to nutritional guidelines for patients with cancer, average patient weight, the energy (in kilocalories) per unit and the cost per unit, and the proportion of energy requirements assumed to be delivered by each of EN and SPN.[6 36] There was uncertainty around the feasibility of combining nursing and delivery for EN and SPN (ie, whether the same healthcare team could deliver both EN and SPN), so two base-cases were considered. In one these costs were included, and in the other they were removed.

The anti-cancer therapy costs applied in the model reflect the regimen chosen as the standard of care for advanced pancreatic cancer. Drug costs were based on average body surface area and were modelled as a cost applied at the beginning of every treatment cycle for progression-free patients until discontinuation. Medical resource use in each of the progression-free and progressed health states were informed by the costs presented in the NICE appraisal.[33] Total costs associated with hospitalisation and adverse events in patients with Stage IV pancreatic cancer were sourced from the literature. In the absence of other evidence, a hypothetical decrease of 20% was applied to hospitalisation and adverse event costs in the SPN+EN arm.

RESULTS

Targeted literature review

The first TLR identified no studies for inclusion (see online supplementary file for the flow of studies). In TLR2, the electronic database search identified 5552 citations, of which six were identified as duplicates and excluded. Following screening and hand searching, a total of 97 studies were identified for final inclusion. The overall flow of studies is illustrated in figure 1.

SPN studies

Five studies were included that evaluated the impact of SPN on malnutrition markers,[28 32 37–39] particularly PhA, PAB, BMI and FFM. Three studies assessed PN administered at home,[32 37 39] while two studies assessed PN administered in a hospital setting.[28 38] Three studies were single-arm trials,[28 32 37] one was a cross-over, controlled trial,[38] and one was a randomised controlled trial (RCT).[39] Three studies examined patients with multiple cancer types,[28 37 38] while one evaluated patients with incurable gastrointestinal cancer[39] and one evaluated patients with incurable pancreatic cancer.[32]

Pelzer *et al* conducted a Phase II, single-arm trial to examine the impact of SPN (as a supplement to EN) in the home setting on outpatients with stage IV inoperable pancreatic cancer and progressive cachexia (n=32). This study demonstrated the positive effect of SPN

Table 1 Calculation of indirect OS HRs

Study linking SPN and malnutrition marker and finding	Study linking malnutrition marker and OS HR and finding	Calculation	HR for SPN
Cotogni *et al*[37] % of patients with BMI ≤18.5 decreased from 33.8% to 30.7%	Deluche *et al*[54] BMI <18.5 kg/m^2 associated with an OS HR of 1.49	$\frac{(0.307\times1.49)+0.693}{(0.338\times1.49)+0.662}$	0.99
Pelzer *et al*[32] BMI was stabilised or increased in 87.5% of patients	Wallengren *et al*[40] Weight loss >5% has an OS HR of 1.3	$\frac{0.875}{1.3}+0.125$	0.80
Pelzer *et al*[32] PhA increased by 0.3°	Gupta *et al*[49] A 1° increase in PhA is associated with an OS HR of 0.64	$0.64^{0.3}$	0.87
	Gupta *et al*[55] A 1° increase in PhA is associated with an OS HR of 0.82	$0.82^{0.3}$	0.94
	Gupta *et al*[56] A 1° increase in PhA is associated with an OS HR of 0.79	$0.79^{0.3}$	0.93
	Lee *et al*[57] A 1° increase in PhA is associated with an OS HR of 0.64	$0.64^{0.3}$	0.87

BMI, body mass index; HR, hazard ratio; OS, overall survival; PhA, phase angle; SPN, supplemental parenteral nutrition.

Table 2 Model outcomes

Nursing and home delivery costs	Outcome	EN alone	EN+SPN	Incremental
Excluded	Total costs (£)	31 644	37 476	5832
	Total QALYs	0.45	0.59	0.14
	ICER (£/QALY)	–	–	41 350
Included	Total costs (£)	31 644	44 549	12 905
	Total QALYs	0.45	0.59	0.14
	ICER (£/QALY)	–	–	91 501

EN, enteral nutrition; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SPN, supplemental parenteral nutrition.

on the nutritional status (particularly BMI and PhA) of malnourished patients with advanced pancreatic cancer.[32]

Caccialanza *et al* conducted a bicentric single-arm clinical trial to evaluate the effects of early seven-day SPN (as a supplement to oral diet) on bioimpedance vector analysis (BIVA)–derived body composition, handgrip strength and PAB in hypophagic, hospitalised patients with cancer at nutritional risk, with contraindications for EN (n=131). This study provided evidence that strictly monitored early short-term SPN results in the improvement of BIVA-derived body composition, functional status and PAB in hypophagic hospitalised patients with cancer at nutritional risk, in the absence of any relevant clinical complication.[28]

Cotogni *et al* conducted a prospective, longitudinal, single-arm trial to investigate the impact of home SPN (as a supplement to oral diet) in malnourished patients with advanced cancer receiving chemotherapy. Malnutrition was assessed using BIA, clinical and laboratory measures (n=65). Overall, patients experienced significantly improved body weight and BMI with SPN. After 90 days, patients had significant improvements in nutritional status and some BIA measures.[37]

De Cicco *et al* conducted a prospective, cross-over, controlled trial to evaluate the effectiveness of PN in patients with various cancer types (n=43). The total amount of calculated nutritional intake was provided by PN for at least seven days (irrespective of oral intake) after which SPN (as a supplement to oral diet) was used based on achieved oral intake. In undernourished patients, PAB and retinol-binding protein increased (p<0.02) at the intracycle analysis in the chemotherapy+total PN course. On cross-over to chemotherapy alone the trend was reversed and PAB decreased (p<0.03).[38]

Obling *et al* conducted a single centre, open-label, RCT to evaluate the effects of SPN (primarily as a supplement to ONS) in the home setting on FFM, muscle function, quality of life and OS among patients with incurable gastrointestinal cancer (n=47). Overall, this study showed that providing SPN may prevent loss of FFM, and even increase FFM in patients with incurable gastrointestinal cancer.[39]

Malnutrition marker studies

Thirty-six studies were included that evaluated the impact of malnutrition markers identified in the SPN studies on clinical outcomes. These markers were BMI (24 studies), PhA (13 studies), PAB (six studies) and FFM/FFMI (three studies). Most of these studies were retrospective analyses that included patients with cancer of varying types, including blood cancers, colorectal, kidney, breast and head and neck cancers.

Consistent trends were found across BMI studies by BMI category (although with varying cut-off points). Malnutrition or a very low BMI was associated with poor clinical outcomes, including reduced survival, lower quality of life (for both children and adults), longer length of stay, greater toxicities and higher rate of infection. For example, Wallengren *et al* found that a BMI <20 was associated with adverse quality of life and more symptoms (OR=2.9, p<0.05).[40] Luo *et al* showed that among patients with lung cancer, a low BMI (HR=2.14, 95% CI: 0.96 to 4.76, p=0.06) or higher BMI (HR=0.76, 95% CI: 0.42 to 1.35, p=0.35) were both predictors of survival.[41] No clinical benefits of a very low or very high BMI were identified. A normal BMI (nourished/well-nourished) was predictive of longer survival and complete response to therapy.

Clear trends were also observed across all studies which evaluated the association between PhA (although with varying cut-off points) and survival. Decreased PhA is a strong predictor of shortened survival and early mortality. Norman *et al* showed that compared with patients with a higher PhA, patients with a PhA in the bottom fifth percentile had more comorbidities (4.2±2.3 compared with 3.5±2.2, p<0.001) and consumed more drugs per day (7.7±3.8 compared with 5.4±3.6, p<0.0001).[42] PhA was a strong predictor of impaired functional status (coefficient=4.121; 95% CI: 2.126 to 6.115, p<0.0001). Gupta *et al* showed PhA to be significantly correlated with the physical and role function scales and fatigue and appetite loss symptom scales.[43] Each 1° increase in PhA was associated with an increase of 4.5 points and 8.4 points in the physical and role function scales, respectively. Similarly, each 1° increase in PhA was associated with a decrease of 5.9 points in the fatigue symptom scale.

Among studies that evaluated FFM/FFMI and clinical outcomes, one found that among outpatients with oesophageal cancer, FFMI was not significantly associated with treatment modifications (OR=1.130, 95% CI: 0.928 to 1.378, p=0.224).[44] Another found that among patients with metastatic renal cell cancer receiving sunitinib, those whose FFM was in the top quartile received a higher dose of sunitinib/kg FFM (1.105 mg/FFM) compared with those with FFM in the bottom three quartiles (1.099 mg/FFM).[45] A third study investigated the quality of life of children cancer patients who received curative treatment. Although FFM was mixed with indicators of BMI (as to categorise patients' nourishment status), undernourished or over nourished patients reported lower social, emotional and physical functioning compared with well-nourished patients.[46]

No clear trends were observed in the six studies that evaluated PAB and clinical outcomes. Two studies found no significant associations with PAB and clinical outcomes among patients with cancer, specifically quality of life and survival, while other studies did find associations.[43 47–51]

Combining indirect evidence to estimate clinical impact of SPN

For each study linking SPN to a malnutrition marker, we assessed each study linking that malnutrition marker to an outcome. In six instances it was possible to combine the results of two studies to generate estimates of the indirect OS HR associated with SPN; it was not possible to generate indirect estimates of any other outcomes. Most of the available indirect evidence makes use of the Pelzer *et al* paper.[32] Results and calculated indirect OS HRs are presented in table 1.

Cost-effectiveness model

Key model outcomes are presented in table 2. The exploratory cost-effectiveness analysis suggests an incremental cost-effectiveness ratio (ICER) between £41 350 and £91 501 (€48 247–€106 763) depending on whether nursing and homecare delivery for EN and SPN are provided together or separately. Note that the conversion to Euros is presented for reference only—the analysis was undertaken from a UK perspective and so the ICER is not expected to apply in different settings. Conversion was based on the December 2019 exchange rate at a rate of £1 to €1.1668.

The model predicts an increase of 0.1 life years, which represents an 11% increase in life expectancy in patients with late-stage metastatic pancreatic cancer.

DISCUSSION

The first TLR highlighted a lack of direct clinical evidence to support the use of SPN. However, the results of the second TLR highlighted the benefits of SPN on nutritional and functional status among advanced patients with cancer at risk of malnutrition. SPN was linked to improvements in BMI, FFM, PhA and PAB, and the prevention of further complications. Among the studies that evaluated those specific malnutrition markers and clinical outcomes among patients with cancer, both BMI and PhA were strong predictors of survival. A decreased PhA or a too low or too high BMI were consistently associated with shortened survival and lower quality of life. Similarly, too low or too high FFM was associated with low quality of life. The small number and heterogenous nature of the studies evaluating PAB made synthesising results difficult; no clear trends were determined.

The exploratory cost-utility analysis performed presents the first estimate of the potential cost-effectiveness of using SPN (specifically PN+EN) in an example cancer population. Results demonstrated that SPN has the potential to extend survival. Individuals with Stage IV inoperable pancreatic cancer have very severe disease with extremely poor prognosis, so the potential for improvements in outcomes is limited. It is therefore possible that clinical and cost-effectiveness outcomes will be improved in patients with less severe disease and longer survival.

Wherever possible, the approach and use of data aligned with the most recent NICE appraisal in Stage IV pancreatic cancer (TA476); the Evidence Review Group involved in the appraisal considered the assumptions to be broadly appropriate.[33]

Limited evidence is available on the relationship between SPN and malnutrition markers. Only five studies that evaluated SPN and markers were included in this review, three of which were single-arm trials. Most of the studies evaluating associations between malnutrition markers and clinical outcomes were retrospective observational studies, so true effect sizes may have been distorted by confounding factors (a bias known as confounding by indication).[52] For example, relationships between nutritional status and clinical outcomes may have been confounded by the presence of more severe disease among those with poorer nutritional status.

Using sources identified in the TLR we estimated the efficacy of SPN versus those receiving EN alone on OS. Estimates of the HR were similar (ranging from 0.80 to 0.99), however a key limitation of this approach is the assumption that the relationship between malnutrition markers and OS is causal. Additional limitations include those associated with combining studies with differences in patient populations and interventions. Furthermore, due to the low number of studies identified, five out of six estimates were based on the data provided in a single paper (Pelzer *et al*[32]), so the results are highly influenced by this single study. The selection of comparator (EN rather than ONS) was also driven by data availability; the cost-effectiveness of PN supplemental to ONS remains to be determined.

Our analysis considers the homecare setting. Home PN has a key role in the treatment pathway for patients with cancer, providing important nutritional, functional and clinical benefits, with a relatively low rate of catheter-related complications.[53] A key uncertainty in the model was whether delivery and nursing services for EN and SPN would be provided separately or together. Providing SPN in a home-based setting is expected to reduce hospital

costs, however the cost-effectiveness of SPN may be further improved if home care services are consolidated and optimised.

Overall, this study demonstrates that SPN is linked to improvements in BMI and PhA, and healthy BMI and PhA levels are potentially linked to improvements in survival and quality of life. Potential links may therefore exist between SPN and these outcomes among patients with cancer at risk of malnutrition.

Future studies should aim to substantiate these associations, with the aim to focus on patients with different types and stages of cancer. This will help to identify populations who may benefit most from SPN, and to determine how cost-effectiveness may differ in patients with cancer with less severe prognosis receiving earlier interventions with SPN.

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