Supportive care in the management of Neuroendocrine Neoplasms

Introduction

Improvements in the treatment of neuroendocrine tumours have led to corresponding increases in the number of patients living longer.

Unfortunately, there remain reports of significant delays in diagnosis, with the disease still frequently having progressed to metastatic stages before the diagnosis is made. This has resulted in increasing numbers of patients, many living with metastatic disease and ongoing symptoms which impacts the quality of life, financial stability and psychosocial wellbeing of patients and their families.

This section is in three chapters, focusing specifically on three key areas of supportive care:

Chapter 12: Diet and nutrition

Chapter 13: Psychosocial care

Chapter 14: Exercise and NENs

Chapter 12: Diet and Nutrition

Authors: Erin Laing, Caley Schnaid

Practice Points

- All patients with cancer (including NENs) should be screened for malnutrition and sarcopenia in all health settings at diagnosis and as the clinical situation changes throughout treatment and recovery.
- All patients with cancer (including NENs) identified as being 'at risk' of malnutrition following screening, or with a cancer diagnosis or treatment plan known to lead to a high risk of malnutrition, should have a comprehensive nutrition assessment using a tool validated in an oncology population.
- Patients presenting with unplanned weight loss or 'at risk' of malnutrition should immediately be referred to an accredited practicing dietitian (APD).
- A dietitian (APD) should be available for referral in all centres managing NENs
- Prophylactic niacin supplementation (40-80mg/day) may be considered in patients with carcinoid syndrome.
- Niacin supplementation of at least 100mg/day is warranted in patients with diagnosed niacin deficiency or overt signs of Pellagra (clinical niacin deficiency).
- Pancreatic enzyme replacement therapy (PERT) is the optimal management of pancreatic exocrine insufficiency (PEI) and subsequent fat malabsorption and fat-soluble vitamin deficiency. Consider referral to an APD to assist with PERT and dietary management.
- Patients experiencing NEN-related symptoms such as diarrhoea, bloating, flushing, and abdominal pain, should consult an accredited practicing dietitian (APD) before making any dietary change.

Introduction

Nutrition and nutritional status have been identified as important considerations for patients with cancer (Jann Arends et al., 2017). Patients with cancer are at increased risk of malnutrition and loss of muscle mass due to derangement in metabolism, altered food intake and reduced physical activity related to the presence of cancer and its treatment (J. Arends et al., 2017; Jann Arends et al., 2017). Malnutrition in patients with cancer has been demonstrated to impact negatively on patient outcomes, including increased morbidity, poorer quality of life and reduced ability to cope with cancer treatment (Nitenberg and Raynard, 2000; Arends et al., 2006). Malnutrition and other nutritional complications, such as vitamin deficiency, have been shown to be present among patients with neuroendocrine neoplasms (NENs) (Bouma et al., 2016; Maasberg et al., 2017; Massironi et al., 2017; Clement et al., 2019; Laing E, Kiss N et al., 2020). Neuroendocrine neoplasms have the potential to impact nutrition and dietary intake due to the physical tumour presence (e.g. gastrointestinal obstruction, pain, loss of appetite, nutrient malabsorption), their functional status and hormonal hypersecretory syndromes (e.g. carcinoid syndrome,

diarrhoea), and treatment (e.g. gastrointestinal resection, somatostatin analogue therapy) (Laing E, Kiss N et al., 2020). Symptoms of NENs and their hormonal hypersecretory syndromes (including diarrhoea, fatigue, flushing and abdominal discomfort) may indicate or lead to altered nutrient absorption and reduced oral intake (Laing E, Kiss N et al., 2020).

Malnutrition occurs in up to 25% of NEN patients, and up to 38% may be at risk of malnutrition (Qureshi et al., 2016; Maasberg et al., 2017; Borre et al., 2018). Review articles have suggested that nutrition is an important aspect of supportive care for patients with NENs and should be considered during the assessment and management process (Altieri et al., 2018; Clement et al., 2019; Laing E, Kiss N et al., 2020).

Assessing and managing nutritional status

The presence and risk of malnutrition among patients with NENs has been demonstrated in various studies (Qureshi et al., 2016; Maasberg et al., 2017; Borre et al., 2018; Laing E, Gough K et al., 2022). These studies focused on assessment of patients with gastroenteropancreatic (GEP) NENs and found that up to 29% were malnourished, and up to 38% were at risk of malnutrition (Qureshi et al., 2016; Maasberg et al., 2017; Borre et al., 2018; Laing E, Gough K et al. 2022). Malnutrition rates in patients with GEP NENs are comparable to the overall measured prevalence of cancer malnutrition in Australia – 26% (Marshall et al., 2019). It is strongly recommended that all patients with cancer are to be regularly assessed for malnutrition risk by evaluating nutritional intake, weight change and body mass index (BMI) (J. Arends et al., 2017; Jann Arends et al., 2017). Available validated nutrition screening tools are quick and useful to screen for malnutrition risk (e.g. Malnutrition Screening Tool (MST), Malnutrition Universal Screening Tool (MUST), Nutrition Risk Screening Tool (NRS-2002), Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) (Ferguson et al., 1999; Kondrup et al., 2003; Boléo-Tomé et al., 2012; Abbott et al., 2016; Jager-Wittenaar and Ottery, 2017). If risk of malnutrition is identified, further objective assessment of nutritional status is recommended using a validated tool for use in patients with cancer (PG-SGA) (Bauer, Capra and Ferguson, 2002; J. Arends et al., 2017).

Malnutrition screening practices of NEN clinicians are currently inconsistent (Laing E, Kiss N et al., 2022). Clinicians managing patients with NENs should consider screening for malnutrition at diagnosis and repeat screening at regular intervals throughout treatment or medical consultation. Screening is ideally performed using a validated malnutrition screening tool (MST, MUST, PG-SGA SF). If a screening tool is not available, general screening can be performed by asking the patient whether they have had change in their weight, food intake, and observe any signs of muscle mass loss (J. Arends et al., 2017; Jann Arends et al., 2017). If weight loss, reduced oral intake or malnutrition risk is identified then a referral to an accredited practicing dietitian (APD) would be warranted. All centres managing patients with NENs should have access to an APD, who can provide individualised assessment and management of malnutrition.

Sarcopenia

Sarcopenia, characterised by the loss of skeletal muscle mass and strength impacting on a person's function, is prevalent in patients with cancer and associated with poor outcomes including reduced survival and increased complications from cancer treatment (Kiss, N. et al., 2020). Sarcopenia and myosteatosis have been identified as prevalent in patients with NENs who have undergone treatment with peptide receptor radionucleotide therapy (PRRT) (Chan, D. et al., 2021). There is strong evidence from national and international guidelines that identification and treatment of cancer-related malnutrition and sarcopenia is important at cancer diagnosis, during and after treatment (Kiss, N. et al, 2020). The COSA Position Statement on Cancer-Related Malnutrition and Sarcopenia (2020) provides evidence-based guidance on assessment and management of sarcopenia (Kiss, N. et al, 2020).

Assessing and managing vitamin deficiency

Niacin

There is evidence that niacin deficiency exists among patients with NENs, particularly those with a NEN causing serotonin hyper-secretion and carcinoid syndrome (Shah et al., 2005; Bouma et al., 2016). Further research is required to confirm the proportion of NEN patients suffering carcinoid syndrome who have niacin deficiency. Clinical features of Pellagra (severe niacin deficiency) may only occur in less than 20% of patients with carcinoid syndrome, but biochemical or sub-clinical deficiency may occur in up to 45% (Bax et al., 1996; Bell et al., 2005; Shah et al., 2005). The timing of deficiency onset is currently unclear. The current gold standard for niacin testing is a 24-hour urine test to measure excretion of N1-methyl nicotinamide and its derivative N1-methyl-2-pyridone-5-carboxyamide (NHMRC, 2006), however, availability of pathology analysis is limited in Australia. Oral niacin supplementation has been shown to be effective in treating niacin deficiency (Bouma et al., 2016). Patients with overt or suspected carcinoid syndrome and serotonin production, may benefit from daily niacin supplementation of 40-80mg (Clement et al., 2019; Laing E, Kiss N et al., 2020). If niacin deficiency is identified, an oral niacin supplement of 100mg or more per day would be warranted (Laing, Kiss, Michael and Krishnasamy, 2020). As niacin is a water-soluble vitamin, excess consumption is excreted and toxicity risk is low (NHMRC, 2006).

Fat-soluble vitamins

Fat-soluble vitamin deficiency can occur in patients with pancreatic exocrine insufficiency (PEI). PEI is characterised by a reduction in pancreatic enzyme function, leading to maldigestion of fats and in some cases subsequent steatorrhoea (Lindkvist, 2013). PEI is a known side-effect from pancreatic (Whipple procedure, pancreatectomy) and small bowel resections, and adverse event from somatostatin analogue (SSA) treatment (Creutzfeldt et al., 1987; Lembcke et al., 1987; Lamarca et al., 2018). Risk of fat-soluble vitamin deficiency in patients treated long-term with SSAs, has been demonstrated in some studies (Fiebrich et al., 2010; Lind, Wängberg and Ellegård, 2016; Massironi et al., 2017; Robbins et al., 2018). Between 31–68% of patients in these studies had vitamin D deficiency, and up to 80% of patients treated long-term (>18months) with SSA in one study (Fiebrich et al., 2010)

had deficiency of at least 1 fat-soluble vitamin. Pathology testing and analysis of vitamin D is readily available, however testing of other fat-soluble vitamins (A, E and K) is harder to access. Pancreatic enzyme replacement therapy (PERT) is the recommended treatment for PEI. Effective treatment with PERT should improve fat absorption and subsequently reduce risk of fat-soluble vitamin deficiency. If a patient is suspected to have PEI, particularly if symptoms of excessive diarrhoea or steatorrhoea (pale, oily, floating stool) are present, then treatment with PERT would be beneficial. Clinicians should consider appropriate dosage and timing of PERT according to each individual patient's requirements. Referral to an APD for assistance with PERT management is recommended, to enable tailored implementation, education and monitoring in collaboration with the medical team. Appropriate treatment with PERT in most cases should reduce the need for fat-soluble vitamin monitoring and supplementation. Due to evidence that PEI may occur in some patients on SSA treatment (Caplin et al., 2014; Lamarca et al., 2018), patients on SSA treatment for more than a year may benefit from screening of fat-soluble vitamin levels (Laing E, Kiss N et al., 2020). Further research is required to investigate the proportion of NEN patients with fat-soluble vitamin deficiency as a result of SSA treatment.

Dietary management and recommendations

Dietary change may be prevalent among patients diagnosed with a NEN. Up to 58% of NEN patients have reported making a change to their diet as a result of their NEN diagnosis (Singh et al., 2017; Laing E, Gough K et al., 2022). Some studies have indicated that NEN patients may initiate dietary restriction in response to disease-related symptoms that they experience, such as diarrhoea and bloating (Lind, Wängberg and Ellegård, 2016; Laing E, Gough K et al., 2022). However, the impact of NEN and treatment-related symptoms on dietary requirements is still relatively unknown. There are currently no NEN-specific dietary clinical practice guidelines available. Patients with NENs, particularly those who are asymptomatic or with mild symptoms, should follow a general healthy and balanced diet, and avoid unnecessary dietary restriction (Altieri et al., 2018; Clement et al., 2019; Laing E, Kiss N et al., 2020).

Diet for carcinoid syndrome

General dietary recommendations for patients suffering from carcinoid syndrome include reducing meal size, reducing fat and spice content of meals, and reducing alcohol intake. Foods and drinks containing high amounts of amines may induce or worsen symptoms related to carcinoid syndrome, although evidence for this association is mostly anecdotal. Foods and drinks moderate-to-high in amine content include: aged cheese, alcohol, smoked/salted fish and meat, yeast, fermented foods (tofu, sauerkraut), caffeine (in high volumes), chocolate, some nuts, coconut, avocado, banana, raspberries, and soy products (soy sauce, tempeh). Completion of a food and symptom diary should be the first step before assessing the need for dietary change, as any relationship between particular symptoms and food types is likely to be individual.

Diet for weight loss/malnutrition

Patients experiencing weight loss or malnutrition should increase the energy and protein in their diet, as able, according to general clinical guidelines for malnutrition management in cancer patients (J. Arends et al., 2017; Isenring et al. 2013; Kiss et al., 2020), and in consultation with a qualified dietitian (APD).

Dietitian referral and management

If a patient is experiencing symptoms related to their NEN (in particular symptoms of diarrhoea, bloating, abdominal pain/cramps, flushing, and wind/gas) any subsequent occurrence of weight loss and dietary change/restriction should be checked by their treating clinician. If a patient has concerns about their diet in relation to symptoms or they are experiencing weight loss/at risk of malnutrition then a referral to a qualified dietitian should be made, preferably one with expertise in managing NENs.

Diarrhoea management and diet

Diarrhoea is a common symptom experienced by patients diagnosed with and treated for a NEN. The first step to diarrhoea management should be assessing the potential cause of diarrhoea. Potential causes of diarrhoea in NEN patients are presented in Table 1.

Table 1. Potential causes of diarrhoea in patients with a NEN

Cause	Considerations
Carcinoid syndrome/hormonal hypersecretion Link to Chapter 7: Functional NENs (p.4 Carcinoid syndrome)	The hypersecretion of serotonin (carcinoid syndrome) or other hormones that arise from a functional NEN (e.g. VIPoma, gastrinoma) can lead to secretory diarrhoea.
Pancreatic exocrine insufficiency (PEI) and fat malabsorption	Fat malabsorption, resulting from PEI, can lead to excess excretion of fat in the stool, causing diarrhoea and steatorrhoea (appearance of pale, floating, oily stool).
Somatostatin analogue (SSA) treatment Link to Chapter 8: Systemic therapies (SSAs)	Whilst SSA treatment is used to modulate NEN symptoms, including diarrhoea, some patients may experience PEI as an adverse event from SSA treatment, particularly in the first week after injection.
Bile salt malabsorption	Bile salts are reabsorbed by the small bowel during digestion. When reabsorption of bile salts is impaired, often after small bowel surgery, this can lead to watery diarrhoea.

Small intestinal bacterial overgrowth (SIBO)	SIBO is the presence of excessive bacteria in the small bowel, and can lead to symptoms of diarrhoea, pain and bloating. SIBO can occur in people with inflammatory bowel conditions and after bowel surgery.
Infection	Infective causes of diarrhoea should be considered and ruled out during assessment.
Previous gastrointestinal surgery	Surgery to the gastrointestinal system (stomach, small bowel, pancreas, colon) can lead to diarrhoea due to changes in mechanical digestion of food, nutrient/water re-absorption, PEI, bile salt malabsorption and SIBO.
Medications	Antibiotics, Magnesium supplement, Antiemetics

Once the cause of diarrhoea has been assessed, treatment can be planned. Treatment with antibiotics is common for infective causes, and to help treat small intestinal bacterial overgrowth (SIBO). PERT is the most appropriate treatment for the presence of PEI and steatorrhoea. Bile acid reabsorption medication (bile acid sequestrants) may help in suspected cases of bile acid malabsorption. Other medications that may be helpful for diarrhoea management include Telotristat ethyl (Xermelo) for carcinoid syndrome-related diarrhoea, and fibre supplements (e.g. Metamucil, Normafibe) which may be helpful to improve the bulk of stool in some patients.

Dietary management of diarrhoea

Medical assessment and management of diarrhoea should be the first consideration for patients with a NEN, using strategies described above. Diet may also play a role in diarrhoea management and therefore patients with prolonged and severe diarrhoea should be referred to a dietitian for further assessment and advice. Risk of dehydration is a concern for patients with prolonged and severe diarrhoea and therefore patient education on appropriate fluid consumption and use of electrolyte replacement drinks is important in these cases. Assessment of foods that may 'trigger' or exacerbate diarrhoea, and assessment of the presence of underlying food intolerances should occur in consultation with a qualified dietitian, one preferably with expertise in managing NENs. Fibre sources (specifically insoluble fibres) in the diet may require modification to help manage diarrhoea, and reduction in consumption of fermentable foods [low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet] may be helpful to treat SIBO, as assessed by a dietitian. Potential dietary strategies to manage carcinoid syndrome diarrhoea are discussed above in the section 'Diet for carcinoid syndrome'.

Available resources for patients and health professionals

Food and Symptom Diary template (NeuroEndocrine Cancer Australia): https://neuroendocrine.org.au/wp-content/uploads/2020/06/N5058-NECA_NETs-Food-Symptom-Diary-v1.pdf

Nutrition and Neuroendocrine Tumours (NeuroEndocrine Cancer Australia): https://neuroendocrine.org.au/wp-content/uploads/2020/02/190822-NET-Patient-Booklet.pdf

Vitamin and mineral deficiencies in people with neuroendocrine tumours (NeuroEndocrine Cancer Australia): https://neuroendocrine.org.au/wp-content/uploads/2020/02/181128-UFD-Factsheet02-Vitamins.pdf

Clinical Oncology Society of Australia Cancer-Related Malnutrition and Sarcopenia Working Group. Cancer-Related Malnutrition and Sarcopenia Position Statement. Clinical Oncology Society of Australia. August 2020.

ESPEN recommendations for cancer-related malnutrition https://www.clinicalnutritionjournal.com/article/S0261-5614(17)30228-5/fulltext

References

Abbott, J. *et al.* (2016) 'Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) is a valid screening tool in chemotherapy outpatients', *Supportive Care in Cancer*, 24(9), pp. 3883–3887. doi: 10.1007/s00520-016-3196-0.

Altieri, B. *et al.* (2018) 'Nutrition and neuroendocrine tumors: An update of the literature', *Reviews in Endocrine and Metabolic Disorders*, 19(2), pp. 159–167. doi: 10.1007/s11154-018-9466-z.

Arends, J. *et al.* (2006) 'ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology', *Clinical Nutrition*, 25(2), pp. 245–259. doi: 10.1016/j.clnu.2006.01.020.

Arends, J. *et al.* (2017) 'ESPEN expert group recommendations for action against cancer-related malnutrition', *Clinical Nutrition*, 36(5), pp. 1187–1196. doi: 10.1016/j.clnu.2017.06.017.

Arends, Jann *et al.* (2017) 'ESPEN guidelines on nutrition in cancer patients', *Clinical Nutrition*, 36(1), pp. 11–48. doi: 10.1016/j.clnu.2016.07.015.

Bauer, J., Capra, S. and Ferguson, M. (2002) 'Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer.', *European journal of clinical nutrition*. Nature Publishing Group, 56(8), pp. 779–785. doi: 10.1038/sj.ejcn.1601412.

Bax, N. D. *et al.* (1996) 'Clinical manifestations of carcinoid disease.', *World journal of surgery*, 20(2), pp. 142–6.

Bell, H. K. *et al.* (2005) 'Cutaneous manifestations of the malignant carcinoid syndrome.', *The British journal of dermatology*, 152(1), pp. 71–5. doi: 10.1111/j.1365-2133.2004.06273.x.

Boléo-Tomé, C. *et al.* (2012) 'Validation of the Malnutrition Universal Screening Tool (MUST) in cancer.', *The British Journal of Nutrition*, 108(2), pp. 343–8. doi: 10.1017/S000711451100571X.

Borre, M. *et al.* (2018) 'Nutritional status and nutritional risk in patients with neuroendocrine tumors', *Scandinavian Journal of Gastroenterology*, 53(3), pp. 284–292. doi: 10.1080/00365521.2018.1430848.

Bouma, G. *et al.* (2016) 'Niacin (Vitamin B3) Supplementation in Serotonin Producing Neuroendocrine Tumor Patients', *Neuroendocrinology*, 103(5), pp. 489–94. doi: 10.1159/000440621.

Caplin, M. E. *et al.* (2014) 'Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors', *New England Journal of Medicine*. Massachusetts Medical Society , 371(3), pp. 224–233. doi: 10.1056/NEJMoa1316158.

Chan, D. *et al*. (2021) 'Computed tomography (CT)-defined sarcopenia and myosteatosis are prevalent in patients with neuroendocrine neoplasms (NENs) treated with peptide receptor radionucleotide therapy (PRRT)', European Journal of Clinical Nutrition, doi: 10.1038/s41430-021-00915-4.

Clement, D. *et al.* (2019) 'Nutritional and vitamin status in patients with neuroendocrine neoplasms.', *World journal of gastroenterology*, 25(10), pp.

1171–1184. doi: 10.3748/wjg.v25.i10.1171.

Creutzfeldt, W. *et al.* (1987) 'Effect of somatostatin analogue (SMS 201-995, Sandostatin) on pancreatic secretion in humans.', *The American Journal of Medicine*. Am J Med, 82(5B), pp. 49–54. doi: 10.1016/0002-9343(87)90426-8.

Ferguson, M. *et al.* (1999) 'Development of a valid and reliable malnutrition screening tool for adult acute hospital patients.', *Nutrition* . Nutrition, 15(6), pp. 458–64. doi: 10.1016/s0899-9007(99)00084-2.

Fiebrich, H.-B. *et al.* (2010) 'Deficiencies in fat-soluble vitamins in long-term users of somatostatin analogue.', *Alimentary Pharmacology & Therapeutics*, 32(11–12), pp. 1398–404. doi: 10.1111/j.1365-2036.2010.04479.x.

Isenring, E. *et al.* (2013) 'Updated evidence-based practice guidelines for the nutritional management of patients receiving radiation therapy and/or chemotherapy. *Nutrition and Dietetics*; 70(4): 312-24.

Jager-Wittenaar, H. and Ottery, F.D. (2017) 'Assessing nutritional status in cancer', *Current Opinion in Clinical Nutrition & Metabolic Care*, 20(5), pp.322-329. Doi: 10.1097/MCO.0000000000000389.

Kiss, N. *et al.* (2020) 'Cancer-Related Malnutrition and Sarcopenia Position Statement', Clinical Oncology Society of Australia Cancer-Related Malnutrition and Sarcopenia Working Group.

Kondrup, J. *et al.* (2003) 'Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials', *Clinical Nutrition*, 22(3), pp. 321–336. doi: 10.1016/S0261-5614(02)00214-5.

Laing, E. Kiss, N. *et al*. (2020) 'Nutritional Complications and the Management of Patients with Gastroenteropancreatic Neuroendocrine Tumors', *Neuroendocrinology*. Karger Publishers, 110(5), pp. 430–442. doi: 10.1159/000503634.

Laing, E. Gough, K. *et al*. (2022) 'Prevalence of malnutrition and nutrition-related complications in patients with gastroenteropancreatic neuroendocrine tumours', Journal of Neuroendocrinology. Wiley, pre-print e.13116. doi: 10.1111/jne.13116. Available at https://onlinelibrary.wiley.com/doi/10.1111.jne.13116

Laing, E. Kiss, N. *et al.* (2022) 'Exploring health professional knowledge and management of nutritional complications in neuroendocrine cancer patients: Results of an international multidisciplinary survey', Clinical Nutrition ESPEN. Article in press. Doi: 10.1016/j.clnesp.2022.02.124. Available at: https://clinicalnutritionespen.com/article/S2405-4577(22)00174-7/fulltext

Lamarca, A. *et al.* (2018) 'Somatostatin analogue-induced pancreatic exocrine insufficiency in patients with neuroendocrine tumors: results of a prospective observational study', *Expert Review of Gastroenterology & Hepatology*. Taylor & Francis, 12(7), pp. 723–731. doi: 10.1080/17474124.2018.1489232.

Lembcke, B. *et al.* (1987) 'Effect of the Somatostatin Analogue Sandostatin (SMS 201–995) on Gastrointestinal, Pancreatic and Biliary Function and Hormone Release in Normal Men', *Digestion*. Karger Publishers, 36(2), pp. 108–124. doi: 10.1159/000199408.

Lind, A., Wängberg, B. and Ellegård, L. (2016) 'Vitamin D and vitamin B12 deficiencies are common in patients with midgut carcinoid (SI-NET)', *European Journal of Clinical Nutrition*, 70(9), pp. 990–994. doi: 10.1038/ejcn.2016.40.

Lindkvist, B. (2013) 'Diagnosis and treatment of pancreatic exocrine insufficiency.', *World journal of gastroenterology*. World J Gastroenterol, 19(42), pp. 7258–66. doi: 10.3748/wjg.v19.i42.7258.

Maasberg, S. *et al.* (2017) 'Malnutrition Predicts Clinical Outcome in Patients with Neuroendocrine Neoplasia.', *Neuroendocrinology*, 104(1), pp. 11–25. doi: 10.1159/000442983.

Marshall, K. M. *et al.* (2019) 'Prevalence of malnutrition and impact on clinical outcomes in cancer services: A comparison of two time points', *Clinical Nutrition*, 38(2), pp. 644–651.

Massironi, S. *et al.* (2017) 'Impact of Vitamin D on the Clinical Outcome of Gastro-Entero-Pancreatic Neuroendocrine Neoplasms: Report on a Series from a Single Institute', *Neuroendocrinology*. Karger Publishers, 105(4), pp. 403–411. doi: 10.1159/000456619.

NHMRC (2006) 'Niacin', in *Nutrient Reference Values for Australia and New Zealand Including Recommended Dietary Intakes*, pp. 79–84.

Nitenberg, G. and Raynard, B. (2000) 'Nutritional support of the cancer patient: Issues and dilemmas', *Critical Reviews in Oncology/Hematology*, pp. 137–168. doi: 10.1016/S1040-8428(00)00048-2.

Qureshi, S. A. *et al.* (2016) 'Screening for malnutrition in patients with gastro-entero-pancreatic neuroendocrine tumours: a cross-sectional study.', *BMJ open*. British Medical Journal Publishing Group, 6(5), p. e010765. doi: 10.1136/bmjopen-2015-010765.

Robbins, H. L. *et al.* (2018) 'Supplementation of Vitamin D Deficiency in Patients with Neuroendocrine Tumors Using Over-the-Counter Vitamin D3 Preparations', *Nutrition and Cancer*. Taylor & Francis, 70(5), pp. 748–754. doi: 10.1080/01635581.2018.1470650.

Shah, G. M. *et al.* (2005) 'Biochemical assessment of niacin deficiency among carcinoid cancer patients.', *The American Journal of Gastroenterology*, 100(10), pp. 2307–14. doi: 10.1111/j.1572-0241.2005.00268.

Singh, S. *et al.* (2017) 'Patient-Reported Burden of a Neuroendocrine Tumor (NET) Diagnosis: Results From the First Global Survey of Patients With NETs', *Journal of Global Oncology*. American Society of Clinical Oncology, 3(1), pp. 43–53. doi: 10.1200/JGO.2015.002980.