

# Quality of life, resource utilisation and health economics assessment in advanced neuroendocrine tumours: a systematic review

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**Quality of life, resource utilisation and health economics assessment in advanced neuroendocrine tumours: a systematic review**

Neuroendocrine tumours (NET) are often diagnosed at an advanced stage when the prognosis is poor for patients, who often experience diminished quality of life (QoL). As new treatments for NET become available, it is important to characterise the associated outcomes, costs and QoL. A comprehensive search was performed to systematically review available data in advanced NET regarding cost of illness/resource utilisation, economic studies/health technology assessment and QoL. Four rounds of sequential review narrowed the search results to 22 relevant studies. Most focused on surgical procedures and diagnostic tools and contained limited information on the costs and consequences of medical therapies. Multiple tools are used to assess health-related QoL in NET, but few analyses have been conducted to assess the comparative impact of available treatment alternatives on QoL. Limitations include English language and the focus on advanced NET; ongoing terminology and classification changes prevented pooled statistical analyses. This systematic review suggests a lack of comparative economic and outcomes data associated with NET treatments. Further research on disease costs, resource utilisation and QoL for patients with advanced NET is warranted.

*Keywords:* quality of life, neuroendocrine, resource utilisation, health technology assessment.

## INTRODUCTION

Neuroendocrine tumours (NET) are a group of diverse malignancies originating from neuroendocrine cells in a variety of anatomical locations throughout the body (Yao *et al.* 2008). Although the worldwide incidence is low (the rate in the United States is approximately 5/100 000) (Hauso *et al.* 2008; Yao *et al.* 2008), the incidence appears

to be increasing, with annual rates of increase ranging from 3.60% in small bowel tumours (Bilimoria *et al.* 2009) to 5.98% in colorectal NET (Kang *et al.* 2007). Given that neuroendocrine cells have the ability to secrete metabolically active substances, NET can cause a variety of distinct clinical syndromes, such as hyperinsulinaemia and carcinoid syndrome (Kaltsas *et al.* 2004). NET may be sporadic or may arise from a variety of diseases, such as multiple endocrine neoplasia type 1 syndrome, von Hippel–Lindau disease, neurofibromatosis type 1 and tuberous sclerosis (Ong *et al.* 2009). The nomenclature and classification of NET have been influenced by their diversity, including tumour behaviour, extent of disease, primary tumour location and presence of symptoms (both from hormones and from tumour mass) (Klimstra *et al.* 2010), resulting in a variety of overlapping and

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inconsistent naming conventions, such as those based on anatomical location (e.g. pancreatic NET), type of hormone produced (e.g. carcinoid tumour) or embryonic tissue origin (e.g. midgut NET).

Patients with NET frequently receive the diagnosis at a late stage. Consequently, survival rates are generally poor, with the median overall survival ranging from 28 months (Halfdanarson *et al.* 2008) to 75 months (Yao *et al.* 2008). Surgery is the primary treatment (used in >80% of NET cases), and it is even used in patients with advanced disease (Corleto *et al.* 2001). For advanced NET of the gastrointestinal (GI) tract and pancreas, a number of systemic therapeutic options are available, including cytotoxic chemotherapy, interferon- $\alpha$ , somatostatin analogues (SSA) and, more recently, targeted biological agents (Table 1). Therapeutic goals include relief of symptoms, biochemical control, objective tumour control and improvement in quality of life (QoL) (Maroun *et al.* 2006).

Although studies of chemotherapy have reported objective response rates as high as 50% among patients with pancreatic NET, such responses are rarely complete, and regimens are associated with considerable toxicity. Interferon- $\alpha$  has demonstrated symptomatic control in up to half of patients and reduces tumour burden in a small proportion; however, because of substantial side effects (e.g. flu-like symptoms, fatigue, depression, autoimmune reactions), the drug is not widely used.

Because high-affinity somatostatin receptors are present in approximately 90% of NET, SSA have been used in the treatment of NET with secretory symptoms (functional

NET), producing improvement in clinical symptoms by inhibiting hormone release (Maroun *et al.* 2006; Dixon & Pasiaka 2007; Eriksson *et al.* 2008). Improvements in clinical symptoms are achieved in 40–80% of patients, with reductions in biomarkers in approximately half of patients. Additionally, SSA may control tumour growth through the inhibition of angiogenesis and other less well understood mechanisms (Dixon & Pasiaka 2007; Eriksson *et al.* 2008). The SSA octreotide long-acting repeatable (LAR) has been shown to increase progression-free survival (PFS) in patients with midgut NET (small bowel and proximal colon) (Rinke *et al.* 2009). Guidelines currently recommend SSA as first-line medical therapy for functional NET (Dixon & Pasiaka 2007). Treatment is typically initiated with an immediate-release formulation (e.g. octreotide), with transition to a longer acting formulation [e.g. octreotide LAR, lanreotide sustained-release (SR)] after efficacy and tolerability have been established (Maroun *et al.* 2006). This reduces the frequency of SSA administration for responding patients from the two to three times per day for an immediate-release SSA to once every 2–4 weeks for the long-acting formulations.

Numerous studies that indicate the therapeutic potential of the inhibition of signalling pathways frequently exploited in pancreatic NET have resulted in the clinical development and recent approval of two molecular targeted therapies (Yao 2007; Yao *et al.* 2010, 2011). Everolimus (Novartis, Basel, Switzerland) is an oral inhibitor of mammalian target of rapamycin (mTOR), a central regulator of cell growth/proliferation, angiogenesis and

**Table 1.** Treatment options in patients with neuroendocrine tumours

| Agent                           | Approval status |                                      |  |
|---------------------------------|-----------------|--------------------------------------|--|
|                                 | Symptom control | Tumour control                       |  |
|                                 |                 | Pancreatic NET                       | Well-differentiated NET                      |
| Somatostatin analogues          |                 |                                      |  |
| Octreotide                      | X               |                                      |  |
| Octreotide LAR                  | X               |                                      |  |
| Lanreotide SR                   | X               |                                      |  |
| Chemotherapy                    |                 |                                      |  |
| Streptozocin                    |                 |                                      | Approved in 1982                             |
| 5-Fluorouracil (+ streptozocin) |                 |                                      |  |
| Doxorubicin (+ streptozocin)    |                 |                                      |  |
| Temozolomide                    |                 |                                      |  |
| Targeted therapies              |                 |                                      |  |
| Everolimus                      |                 | US 2011<br>EU 2011<br>Argentina 2011 | Brazil<br>Philippines<br>Chile<br>EU pending |
| Sunitinib                       |                 | EU 2010<br>US 2011                   |  |
| Other agents                    |                 |                                      |  |
| Interferon- $\alpha$            |                 |                                      |  |

LAR, long-acting repeatable; NET, neuroendocrine tumours; SR, sustained-release.

cell metabolism. Activation of mTOR is mediated through several key growth factor receptors (e.g. insulin-like growth factor 1 receptor, epidermal growth factor receptor) that are implicated in the growth of NET (Jensen *et al.* 2008). In a randomised, placebo-controlled, phase III trial of patients with low-grade or intermediate-grade advanced (unresectable or metastatic) pancreatic NET, everolimus plus best supportive care was associated with improvement in PFS compared with best supportive care alone (11.0 vs. 4.6 months), representing a 65% risk reduction ( $P < 0.001$ ) (Yao *et al.* 2011). The benefit was sustained, with 34% of patients progression free at 18 months compared with 9% in the placebo group (Yao *et al.* 2011). Placebo-treated patients whose disease progressed were offered open-label everolimus. Of the 203 patients originally assigned to receive placebo, 148 (73%) crossed over to open-label everolimus. Everolimus also has demonstrated promising activity in combination with octreotide LAR, with a 23% reduction in the estimated risk for progression compared with those who received octreotide LAR plus placebo (Pavel *et al.* 2011). This study was conducted in patients with low-grade or intermediate-grade advanced NET with symptoms from carcinoid syndrome (Pavel *et al.* 2011).

The second recently approved targeted therapy is the multi-targeted tyrosine kinase inhibitor sunitinib (Pfizer, New York, NY, USA). In a randomised, placebo-controlled, phase III trial in patients with well-differentiated advanced (unresectable or metastatic) pancreatic NET, sunitinib plus best supportive care was associated with significant improvement in PFS compared with placebo plus best supportive care [11.4 vs. 5.5 months; hazard ratio, 0.42; 95% confidence interval (CI), 0.26–0.66;  $P < 0.001$ ] (Raymond *et al.* 2011a). The probability of PFS at 6 months was 71.3% in the sunitinib group compared with 43.2% for those receiving placebo (not significant due to adjustment for multiple testing associated with interim analyses) (Raymond *et al.* 2011a). It should be noted that the study was discontinued early on the recommendation of the data and safety monitoring committee because of the greater number of deaths and serious adverse events in the placebo group. The observed PFS was consistent with data from other studies of vascular endothelial growth factor inhibitors in pancreatic NET (Faivre *et al.* 2006; Hobday *et al.* 2007; Kulke *et al.* 2008; Castellano *et al.* 2011; Raymond *et al.* 2011b).

As previously noted, NET are often diagnosed at an advanced stage, when the prognosis for patients is poor (Yao *et al.* 2008); these patients experience diminished QoL. Advanced NET likely also pose considerable economic burden on the individual patient as well as on

society, in part because of the unmet need for treatments that can effectively alter and slow the progression of the disease. As new therapies for NET are developed and become available, it is important to characterise and fully understand the current treatment paradigm in terms of the most common therapies, associated outcomes, costs and QoL. This effort is required in any attempt to systematically evaluate the risks, benefits and costs associated with both new and existing treatment options for the broad variety of NET types.

The objective of this study was to systematically review available data in advanced NET within the domains of QoL, cost of illness, resource utilisation and economics.

## METHODS

### Literature search and study selection

To identify citations relevant to the key topics under investigation, a thorough systematic literature search was conducted for the publication range of January 2000 to March 2010 (except for epidemiology, for which the range was January 1990 to March 2010) using 11 databases through a platform maintained by the German Institute of Medical Documentation and Information (DIMDI), an institute within the scope of the German Federal Ministry of Health. The DIMDI Superbase is composed of the following electronic bibliographic databases: Medline EMBASE, EMBASE Alert, BIOSIS Previews, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, NHS-CRD-DARE (database of Abstracts of Reviews of Effectiveness), Health Technology Assessment (HTA) Database, NHS Economic Evaluation Database, Derwent Drug File and Science Citation Index (SciSearch).

A comprehensive search strategy was developed using free-text and combination terms (Table 2). Published English language articles dating to 2000 were the focus of the review. Additionally, the reference lists from identified publications were evaluated to retrieve other relevant publications. Internet searches for abstracts from major clinical conferences (Table 3) and structured searches in HTA databases and supplemental Internet searches of HTA agency websites were performed as well to capture all relevant insights.

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher *et al.* 2009), Figure 1A was generated to describe the search results. The full systematic literature review search results are in Appendix 1 and the search strategy for DIMDI is in Appendix 2. The resultant findings underwent an initial thorough selection process by a staff

medical expert, and irrelevant publications were excluded. A group of six reviewers performed a second screening of individual sections to determine relevance, ensuring that each title had been reviewed by two persons. In cases of disagreement between reviewers, titles were retained. Abstracts of the remaining titles were downloaded and reviewed. Seven content reviewers evaluated the abstracts to further determine relevance, ensuring that each abstract was analysed by at least one reviewer. After the abstracts were selected, citations were divided into relevant categories, and the content reviewers made the final decision on what publications should be identified for

final extraction. Full copies were obtained for all available publications. A supplemental manual search also was performed by reviewing the reference lists of the extracted articles to ensure all relevant articles were captured. After inspection of the full text articles, relevant publications were selected for data extraction and were recorded into extraction tables.

## RESULTS

### Quality of life

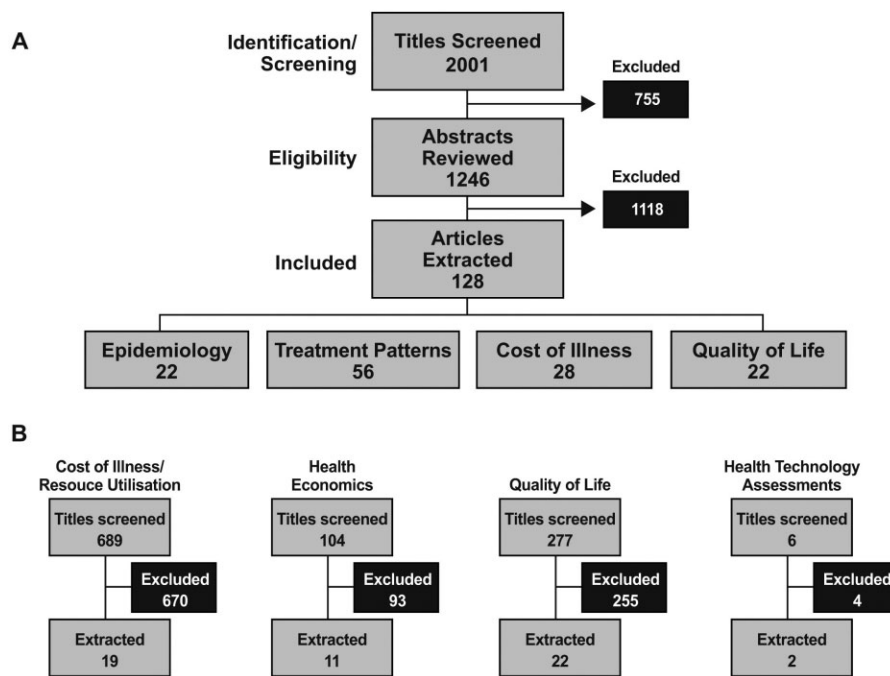
For the final search strategy for QoL, 119 searches were conducted, 277 citations were identified, and 22 full texts (including four abstracts from recent conferences) were appropriate and available for extraction. The 22 articles were published in the United States, Canada and Europe and were based on data primarily from clinical trials and surveys. These studies were conducted broadly across subtypes of advanced NET. Health-related QoL (HRQoL) impact from the disease and from certain treatments, such as SSA and radionuclide therapies, was assessed in various studies. Although QoL is reported in NET studies, the lack of standardisation of measurement tools between studies and the non-NET-specific nature of the tools used made comparing and generalising findings difficult. Table 4 provides a summary of the tools used to assess QoL in patients with NET (Aaronson *et al.* 1993; O'Toole *et al.* 2000; Larsson *et al.* 2001, 2003, 2007; Davies *et al.* 2003, 2006; Major *et al.* 2003; Ramage & Davies 2003; Pasiaka *et al.* 2004; Teunissen *et al.* 2004; Frojd *et al.* 2007, 2009; Haugland *et al.* 2009; Korse *et al.* 2009; Muros *et al.* 2009; Pezzilli *et al.* 2009; Vinik *et al.* 2009, 2011; Baudin *et al.* 2010; Beaumont *et al.* 2010, 2012). Our review showed that a variety of tools was used in patients with NET to assess disease- or treatment-related HRQoL and to evaluate global QoL, functioning, symptoms and mental well-being domains. European Organisation for Treatment and Research of Cancer

**Table 2.** Search terms used in the systematic literature review

| Search terms                                  |
|---|
| Neuroendocrine tumours (general)              |
| Gastroenteropancreatic neuroendocrine tumours |
| Other neuroendocrine tumours                  |
| Incidence/prevalence                          |
| Epidemiology (general)                        |
| Guidelines/consensus                          |
| Hospitalisation                               |
| Treatment patterns/drug utilisation           |
| Survey  |
| Mortality                                     |
| Quality of life                               |
| Cost of illness (direct)/healthcare costs     |
| Work loss/disability                          |
| Health economic analyses                      |
| Resource utilisation and drug utilisation     |
| Hospitalisation                               |
| Ambulatory care                               |
| Unmet needs                                   |
| Octreotide                                    |
| Lanreotide                                    |
| Interferon- $\alpha$                          |
| Chemotherapy                                  |
| Radiotherapy                                  |
| Ablation                                      |
| Registries                                    |
| Surgery                                       |
| Observational studies                         |
| Review  |

**Table 3.** Supplemental searches: grey literature (abstracts, conferences) and Internet

| Conferences   | Websites   |
|---|--|
| ASCO (American Society of Clinical Oncology)                              | <a href="http://www.asco.org/ASCOv2/Meetings/Abstracts">http://www.asco.org/ASCOv2/Meetings/Abstracts</a>  |
| ASHP (American Society of Health-System Pharmacists)                      | <a href="http://www.ashp.org/meetings/">http://www.ashp.org/meetings/</a>  |
| AMCP (Academy of Managed Care Pharmacy)                                   | <a href="http://www.amcp.org/">http://www.amcp.org/</a>  |
| ENETS (European Neuroendocrine Tumor Society)                             | <a href="http://www.neuroendocrine.net/">http://www.neuroendocrine.net/</a>  |
| ESMO (European Society of Medical Oncology)                               | <a href="http://www.esmo.org/education-research/abstracts-virtual-meetings-and-meeting-reports.html">http://www.esmo.org/education-research/abstracts-virtual-meetings-and-meeting-reports.html</a>                              |
| ISPE (International Society for Pharmacoepidemiology)                     | <a href="http://www.pharmacoepi.org/">http://www.pharmacoepi.org/</a>  |
| ISPOR (International Society for Pharmacoeconomics and Outcomes Research) | <a href="http://www.ispor.org/meetings/PastInternational.aspx">http://www.ispor.org/meetings/PastInternational.aspx</a><br><a href="http://www.ispor.org/meetings/PastEuro.aspx">http://www.ispor.org/meetings/PastEuro.aspx</a> |
| NANETS (North American Neuroendocrine Tumor Society)                      | <a href="http://www.nanets.net/">http://www.nanets.net/</a>  |
| NCRI (National Cancer Research Institute)                                 | <a href="http://www.ncri.org.uk/ncriconference/#">http://www.ncri.org.uk/ncriconference/#</a>  |



**Figure 1.** PRISMA flow chart of search strategy. Publications were limited to those from 2000 to the present. (A) The initial search identified 2001 potential abstracts. These findings were screened by medical experts working in sequential fashion to identify erroneous inclusions, and the resultant 1246 abstracts were downloaded and evaluated by seven reviewers to identify the 128 relevant results and to organise them into categories. (B) The cost-of-illness search included the terms *neuroendocrine tumour* and *direct costs* or *indirect costs* (*work loss, disability*). The resource utilisation search included *neuroendocrine tumours* and *resource/drug utilisation* or *ambulatory care* or *hospitalisation*. The health economics search strategy included *neuroendocrine tumour* and *health economic analyses* (*cost-effectiveness, cost-utility, budget impact*). The health technology assessments were categorised by the medical expert screeners. The QoL strategy included *neuroendocrine tumour* and *quality of life*.

(EORTC) QLQ-C30 was the most commonly used tool and was cited in nine of 22 studies.

Current QoL questionnaires do not adequately address specific symptoms and are a burden to patients with NET. Two NET-specific QoL tools have been developed and were in field testing before clinical application at the time of this review. EORTC QLQ-GI NET21 measures GI symptoms, cancer-related factors, psychosocial issues, treatment side effects and other occurrences (e.g. bone pain, sexuality, weight loss and information/communication in GI NET patients) (Ramage & Davies 2003; Davies *et al.* 2006; Vinik *et al.* 2011). The Norfolk QoL-NET measures symptom frequency, symptom severity, activities of daily life, feelings regarding somatostatin injections and general feelings of patients (Vinik *et al.* 2009, 2011). A comparison study of the EORTC QLQ-GI NET21 and the Norfolk QoL-NET scales in 29 patients with diagnoses of NET was recently reported (Vinik *et al.* 2011). Except for the cardiovascular domain, there was a strong correlation between the individual domains and the total scores of the two tests (Vinik *et al.* 2011). Scores also correlated with tumour and serotonin level burden but not with chromogranin A level (Vinik *et al.* 2011). Although individual domains of the Norfolk QoL-NET scale correlated strongly with the total Norfolk QoL-NET score, only the physical functioning, GI and respiratory domains of the Norfolk QoL-NET score predicted the EORTC QLQ-GI NET21 total score (Vinik *et al.* 2011). Unlike the EORTC QLQ-GI NET21, the Norfolk QoL-

NET scale also addresses the impact of treatment with somatostatin analogues (Vinik *et al.* 2011). The results are promising, but these three NET-specific QoL tools have not yet demonstrated evaluative capabilities through longitudinal studies.

Based on the extracted data, specific domains that have registered differences among patients in clinical studies or between patients with NET and healthy samples in observational studies include physical functioning, role functioning, social functioning, emotional functioning, fatigue, insomnia, diarrhoea, mental health, depression, pain, global health and general QoL (Aaronson *et al.* 1993; Larsson *et al.* 2001, 2007; Davies *et al.* 2003, 2006; Ramage & Davies 2003; Haugland *et al.* 2009; Pezzilli *et al.* 2009; Vinik *et al.* 2009). In a study by Haugland *et al.* (2009), the largest gap between patients and the general population was found to be in role-physical limitation scores (the ability to perform activities of daily life), with mean scores 25 points lower for patients with NET. In addition to differences in mental health scores using the general QoL questionnaires, surveys specific for anxiety and depression also show mild or moderate depression in up to 40% of patients with NET compared with healthy subjects (Pezzilli *et al.* 2009).

Across domains, patients with NET have worse HRQoL than do general populations (Larsson *et al.* 2001; Frojd *et al.* 2007; Haugland *et al.* 2009). In general, NET studies of QoL found a strong correlation between improvement in symptoms and improved scores in QoL, as measured

**Table 4.** Quality-of-life (QoL) instruments used in patients with neuroendocrine tumours

| QoL measurement tool  | Scale of measurement  |
|---|---|
| BDI-II (Beck Depression Inventory-II)   | Depressive symptoms   |
| HADs (Hospital Anxiety and Depression Scale)  | Anxiety<br>Depression   |
| EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30)        | Functional scales<br>– Physical<br>– Role<br>– Cognitive<br>– Emotional<br>– Social<br>Symptom scales<br>– Fatigue<br>– Pain<br>– Nausea<br>Global health and QoL scale<br>Single-item scales<br>– Dyspnoea<br>– Appetite loss<br>– Sleep disturbance<br>– Constipation<br>– Diarrhoea<br>– Perceived financial impact of the disease and the treatment |
| EORTC QLQ-GI NET (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-GINET21) | Gastrointestinal symptoms<br>Cancer-related worries<br>Psychological issues<br>Treatment side effects<br>Individual issues: bone pain, sexuality, weight loss, information  |
| FACT-G (Functional Assessment of Cancer Therapy-General)  | Physical well-being<br>Functional well-being<br>Social/family well-being<br>Emotional well-being  |
| GHQ-12 (12-item General Health Questionnaire)   | Psychological symptoms<br>Psychological behaviours  |
| GHQ-30 (30-item General Health Questionnaire)   | Psychological symptoms<br>Psychological behaviours  |
| Karnofsky Index   | Ability to carry out normal activity<br>Ability to work<br>Ability to live at home<br>Ability to care for most personal needs<br>Ability to care for self   |
| NET 35 (Neuroendocrine Tumors 35)   | Disease symptoms<br>Social<br>Emotional<br>Functional<br>Financial  |
| Norfolk QOL-NET   | Symptom frequency<br>Symptom severity<br>Activities of daily living<br>Somatostatin injections<br>Feelings  |
| Nottingham Health Profile   | Physical mobility<br>Social isolation<br>Pain<br>Emotional reactions<br>Energy<br>Sleep   |
| PAIS (Psychosocial Adjustment to Illness Scale)   | Psychological<br>Social   |
| PROMIS-29 (Patient-Reported Outcomes Measurement Information System)  | Pain<br>Fatigue<br>Depression   |
| SF-12 (12-Item Short-Form Health Survey)  | Physical<br>Mental  |
| SF-36 (i.e. RAND-36) (36-Item Short-Form Health Survey)   | Physical<br>Mental  |
| VAS (Visual Analogue Scale for Quality of Life)   | Physical<br>Symptoms<br>Sensation of well-being<br>Family relationships   |

using various HRQoL instruments (Vinik *et al.* 2011). Patients with carcinoid syndrome report poorer QoL than do those who do not have carcinoid syndrome (Beaumont *et al.* 2012). This finding seems to corroborate the general observation that symptom burden correlates with patient QoL. In addition to symptom burden, a study by Vinik *et al.* (2011) suggests that tumour burden may have a negative impact on patient QoL. In both the EORTC QLQ-C30 GI.NET21 and the Norfolk QoL-NET questionnaires, QoL correlated significantly with tumour burden ( $r = 0.5$  and  $r = 0.52$ , respectively;  $P = 0.005$  and  $P = 0.004$ , respectively) (Vinik *et al.* 2011). Two studies assessed HRQoL in relation to tumour response to specific radionuclide treatments (Teunissen *et al.* 2004; Muros *et al.* 2009). Although evidence suggests radionuclide therapies improve HRQoL, these findings must be confirmed by larger trials. It should be noted that neither of these studies collected utility data.

#### **Cost of illness/resource utilisation, economic studies/health technology assessment**

In total, 150 searches were conducted for cost of illness, 143 searches were conducted for resource utilisation and drug utilisation/hospitalisation/ambulatory care, 689 citations were identified, and 19 articles were appropriate and available for extraction. For health economic studies, 62 searches were conducted, 104 citations were identified, and 10 articles (including two from the cost of illness/resource utilisation section) were appropriate and available for extraction. In total, six citations were identified, and two articles were appropriate and available for extraction. Figure 1B provides the final search strategy for cost of illness, resource utilisation, health economics and HTAs.

There is a lack of consistent and comprehensive documentation of resource utilisation in the management of NET, and one could argue that diagnosis and surgical resection (primary treatment) and therapeutics should be treated as separate categories. The extent of burden of illness for surgical resection depends on disease location (e.g. lung and pancreatic resections are very different from one another, but an insulinoma resection and a pancreatic adenocarcinoma resection are similar), whereas the burden of illness during therapy depends more on tumour type and on symptoms associated with secretory proteins.

#### **Diagnosis and surgical resection**

Numerous localisation, diagnostic and post-treatment procedures, as well as hospital lengths of stay, were

reported in the literature. Resource utilisation for diagnosis differs according to the location of the NET. For example, in a retrospective study of patients with pancreatic NET, tumour location was frequently confirmed radiologically by ultrasound, contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI). Upper GI endoscopy, colonoscopy and staging laparoscopy also were used if radiological confirmation proved inconclusive. Radiolabelled octreotide scans were used to define the site and functional status of the tumour (Abu *et al.* 2009).

Thus, imaging techniques constitute an important part of the diagnostic process for patients with NET. However, each has its strengths and weaknesses, and the number and type of imaging studies necessary for definitive diagnosis and localisation vary, depending on tumour location. Somatostatin receptor scintigraphy (SRS) has become a key technique for NET detection because of its high sensitivity and specificity, but it has poor spatial resolution. Therefore, SRS must be used in conjunction with other imaging techniques, such as CT and MRI, for preoperative tumour localisation. Those imaging techniques include ultrasound, endoscopy, angiography, X-ray (Grover *et al.* 2004) and radionuclide bone scanning (Grover *et al.* 2004; Johnson *et al.* 2006). Dimitroulopoulos *et al.* (2004) examined the diagnostic sensitivity, accuracy, and cost-effectiveness of SRS compared with conventional imaging methods (chest X-ray, upper abdominal ultrasound, chest CT and upper and lower abdominal CT) in patients with gastroenteropancreatic carcinoid tumours. Although primary and metastatic tumour sites were detected more frequently using SRS (71.0%) than conventional imaging methods (61.3%), imaging combinations (i.e. chest X-ray/upper abdominal CT/SRS and chest CT/upper abdominal CT/SRS) yielded the highest sensitivity (88.8% for each combination) in terms of the number of detected lesions. The combinations of X-ray/upper abdominal ultrasonography/SRS and chest CT/upper abdominal ultrasonography/SRS had nearly similar results (sensitivities of 82%). Of these four combinations, the X-ray/upper abdominal ultrasonography/SRS presented the lowest cost at 1183.93 Euro, and chest CT/upper abdominal CT/SRS had the highest cost at 1362.75 Euro (Dimitroulopoulos *et al.* 2004).

Among the various surgical and resection methods used in patients with NET, conventional wisdom suggests that patients with multiple metastases should not be considered for resection. However, studies in patients with multiple metastases (including hepatic) have suggested that surgical resection in select patients with advanced, multiple metastatic NET may have acceptable risks

(Norton *et al.* 2003; Abu *et al.* 2009). Although surgical resection increases the healthcare costs for patients with NET, the potential survival benefits should be considered. On the other hand, the use of laparoscopic versus traditional open surgery is still being investigated; some studies suggest an increased chance of fistulas in those patients who undergo laparoscopic pancreatic surgery; all report favourable survival (Fernandez-Cruz *et al.* 2001; Norton *et al.* 2003; Jaroszewski *et al.* 2004; Mazzaglia *et al.* 2007).

The reporting of post-treatment procedures and hospital lengths of stay was more consistent. Studies have found that mean and median hospital stays are as follows: mean of 5 days after enucleation or distal pancreatectomy in patients with pancreatic NET (Fernandez-Cruz *et al.* 2001); median of 10 days after isolated hepatic infusion (Grover *et al.* 2004); mean of 4.5 days for patients with insulinoma after laparoscopic resection without complications (Jaroszewski *et al.* 2004); mean of 11.8 days for laparoscopic and 17 days for open surgery in patients with insulinoma (Liu *et al.* 2007); and mean of 11.5 days after aggressive resection in patients with pancreatic NET (Teh *et al.* 2007).

### Therapeutics

Given the relatively few approved pharmacological therapies for NET, the two HTAs uncovered by the search related primarily to diagnosis, staging and surgical techniques. The literature review identified an HTA for octreotide therapy that presented a budget impact analysis for the therapy in endocrine, oncological and GI disorders in the Canadian health system (Murphy *et al.* 2008). Although the HTA evaluated the efficacy of octreotide in patients with gastroenteropancreatic NET, the findings were insufficient for drawing economic conclusions (Murphy *et al.* 2008). The only indication with sufficient data was pancreatic surgery, and octreotide demonstrated clear benefit compared with placebo (Murphy *et al.* 2008). Another relevant economics-focused publication by Schonfeld *et al.* (1998) was identified through the reference manual search in extracted articles. Although the article did not meet our eligibility requirements in terms of publication date, it proved to be relevant and thus was included. This study presented results from a Markov model that evaluated the cost-effectiveness of octreotide treatment in patients with carcinoid syndrome and VIPoma. Results showed that in these patients octreotide was cost-effective and doubled survival time (Schonfeld *et al.* 1998). In a 1998 study in patients with VIPoma, the average cost per year of survival with octreotide was

\$29 300, whereas the average cost per year of survival without octreotide was \$60 600 (Schonfeld *et al.* 1998).

Other therapeutic options for the treatment of patients with NET include mTOR inhibitors, tyrosine kinase inhibitors, peptide receptor radionuclide therapy, chemotherapy, radiotherapy, interferon, transplantation, artery ligation, percutaneous cryoablation and percutaneous ethanol injection. Although numerous studies have investigated the efficacy of these therapies in patients with NET, the healthcare economics and cost of illness have not been explored.

### DISCUSSION

The management of advanced NET tumours is challenging. Although the recent approval of everolimus and sunitinib represent important therapeutic advances, there are substantial gaps in the published literature in the understanding of several key domains relevant to advanced NET, particularly with respect to economic and outcomes research studies and objective HTAs. Although the literature on NET in general is extensive (particularly in terms of epidemiology, pathophysiology and prognosis), there is a paucity of information specific to advanced NET and an even greater shortfall in the literature with adequate specificity across the numerous subtypes and categories of NET. The heterogeneous nature of the disease and the rarity of many subtypes, along with the lack of consensus in terms of nomenclature and classification within the disease, have likely contributed to this shortfall. Nonetheless, the articles obtained and the data extracted confirm a substantial unmet need for new treatments that can positively impact outcomes and QoL and an unmet need for clarity concerning current treatments best able to improve patient outcomes across the spectrum of NET, including patient QoL, PFS and overall survival. Additional data (e.g. cost/outcomes impact of treatment alternatives) are needed to facilitate objective judgments about the merits of the various treatment options and strategies and to evaluate new treatments in the context of current practice.

An extensive list of non-disease-specific QoL tools has been used in NET, and three relatively newer specific tools for patients with functional NET are under development and will likely provide richer, more relevant and valuable data for patients with NET. Although these QoL tools are available and have been used within NET populations, data concerning the comparative impact of treatment alternatives across different NET types are minimal. To date, no utility data in patients with NET have been published. Although there is some evidence to suggest



a correlation between disease symptoms and tumour burden with QoL, more research is warranted to understand the impact of disease progression on QoL.

With regard to resource utilisation and economic studies, there is little comprehensive documentation on the resources used in (both in terms of the cost of disease diagnosis and the cost of interventions), and insufficient literature on the costs associated with, the management of NET. The direct and indirect cost drivers for disease interventions and disease progression are largely undefined. Furthermore, the available cost-effectiveness-specific literature is limited to sparse qualitative information focusing on specific therapies and patient subgroups.

A limitation of this study is that the literature search was restricted to articles published in English; therefore, it is possible that information is missing, particularly in the areas of cost of illness and QoL. In addition, there may be specialty conferences that do not have online abstract search engines but that may contain relevant abstracts. Although dual independent review was undertaken to assess article titles, abstracts and article texts were reviewed by single reviewers only. Because dual independent review was not applied in these stages of the review, certain biases are unavoidable and might have influenced the overall findings. Another important potential limitation is that this review focussed specifically on advanced NET. Although the purpose of this literature review was to focus on advanced disease, it is possible that relevant data were inadvertently overlooked because of the exclusion of articles that did not mention the word 'advanced' in the title or the abstract. Further, differences in NET terminology and changes in the World Health Organization classification system pose challenges in making cross-study comparisons because many studies focussed on specific NET subtypes. This circumstance prevented pooled statistical analyses.

The results of this systematic review illustrate the paucity of data regarding the burden of illness for patients with NET. We recommend that future clinical trials consider including QoL and economic analyses in their study designs. In particular, the ideal trial design would include both a general QoL survey such as the Short Form-36 form and a NET-specific survey such as the Norfolk QoL-NET to help validate the Norfolk survey and to provide longitudinal data on QoL in NET. With regard to resource utilisation, the diagnostic and surgical teams should coordinate with post-surgical clinicians to maximise the information derived from diagnostic and pre-surgical imaging studies. For example, scintigraphic results may help identify patients with non-secretory NET who may benefit from the anti-tumour effects of octreotide therapy (Rinke

*et al.* 2009; Anthony *et al.* 2010; Boudreaux *et al.* 2010; Oberg *et al.* 2010; Kulke *et al.* 2011). In addition, more research must be conducted to better define resource utilisation at the various stages of disease progression, particularly after the initial diagnosis in patients with advanced disease.

In conclusion, there is an unmet need not only for more effective treatments in NET but also for appropriate and robust data to guide the development and application of new and existing treatments. Although the published literature in the area of NET is substantial, there is a lack of treatment-specific and comparative economic and outcomes research data associated with commonly used treatments. Further research relating to the cost of disease, resource utilisation and evidence-based treatment guidelines for patients with advanced NET is warranted to facilitate effective treatment of these patients.

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## Competing interests

Ian Chau is an advisor for Novartis, and his institution has received research funding from Novartis.

Roman Casciano and Jacob Willet are employees of LA-SER Analytica, a consultancy that received funding from Novartis for the research.

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## Author contributions

All authors were involved in the conception, design, writing and final approval of the manuscript.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Appendix S1.** Systematic literature review search results.

**Appendix S2.** Search Strategy for DIMDI (German Institute of Meidical Documentation and Information).