The Patient - Patient-Centered Outcomes Research
https://doi.org/10.1007/s40271-020-00412-z

ORIGINAL RESEARCH ARTICLE

The Economic Impact on Australian Patients with Neuroendocrine Tumours

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Abstract

Background and Objective Little is known about the economic burden to patients and families with neuroendocrine tumours (NETs) for medical out-of-pocket expenses and employment decisions. This study was performed to determine the extent and factors influencing the financial consequences of living with NETs and their effect on quality of life.

Methods We undertook an online cross-sectional survey using a targeted approach and collected Australian Medicare claims data. Validated surveys measured health-related quality of life (EuroQol 5-dimension 5-level [EuroQol-5D-5L]) and financial toxicity (COmprehenSive Financial Toxicity [COST]), supplemented with questions on employment and retirement, insurance and out-of-pocket medical expenses. Generalised linear models were performed to assess determinants of quality of life and out-of-pocket expenses recorded by Medicare.

Results The survey was answered by 204 patients with a mean age of 59 years who were diagnosed on average 5.2 years ago. Self-reported mean costs were 1698 Australian dollars ($A) (standard deviation [SD] $A2132) over 3 months (median $A877) and were highest for medical tests (mean $A376 [17% of total costs], SD $A722), travel-related expenses (mean $A289 [13%], SD $A559), and specialist visits (mean $A225 [10%], SD $A342) ($A1 = $US0.69). Imaging scans, surgery and travel expenses were the most common cost burdens reported by patients. Having private health insurance was the key determinant of higher out-of-pocket costs. Poorer quality of life was significantly associated with higher financial toxicity, not working due to cancer, nausea/diarrhoea, two or more co-morbidities and younger age.

Conclusions Medical expenses are substantial for some patients with NETs. Quality of life is adversely affected for patients experiencing financial toxicity and avoiding early retirement is an important issue for supportive care services.

1 Introduction

Neuroendocrine tumours (NETs) are uncommon malignancies often arising in the small intestine, lung, rectum and pancreas [1]. These tumours vary widely in their site of origin and biological behaviour, with some individuals with metastatic disease living for long periods of time. Median overall survival for all patients with NETs is 9.3 years, but this varies significantly by site of origin of tumour, stage of disease at diagnosis, as well as tumour grade. Grade 1 NETs have the highest median overall survival (16.2 years), while grade 3 and 4 NETs have a much poorer survival (10 months) [1]. The annual incidence of NETs has been rising over time, recently reported at seven cases per 100,000 in the USA [1]. In Queensland Australia, the incidence of NETs was 6.7 cases per 100,000 in 2014 [2]. Although NETs are relatively rare, the number of patients living with NETs has resulted in a higher prevalence than oesophageal, gastric, pancreas or hepatobiliary cancers together [3].

Despite the significant economic burden of NETs on health systems [4], little is known about the economic toll on patients and families [5]. Patients with very high medical expenses can face substantial distress and, among those unable to pay for health care, can lead to avoiding medical appointments and poor adherence to medications. This situation is called 'financial toxicity', a broad term that refers to the financial distress or hardship from treatment, specifically for patients with cancer [6]. While there is increasing knowledge on the financial impact on patients with other

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40271-020-00412-z) contains supplementary material, which is available to authorized users.

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Published online: 19 February 2020

Key Points for Decision Makers

Deleterious financial impacts were experienced by some patients with neuroendocrine tumours (NETs), ranging from ongoing and high out-of-pocket expenses to having to retire earlier than desired and refusals of insurance.

Accessing supportive care services to provide occupational support is likely to be an increasingly important aspect of cancer rehabilitation services for NETs patients.

Patients with NETs live with metastatic disease for long periods and appropriate assessment and support for issues such as financial toxicity should occur at all stages of their illness journey.

cancers [7], no research has been undertaken on the financial burden of patients with NETs, and this study aimed to address this gap. To understand the financial burden on patients with NETs, our study addressed three research questions:

1. What are the medical expenses and financial impacts of persons with NETs?
2. What are the main determinants of high costs during the first 2 years after diagnosis? and
3. Do those with high financial strain report poorer quality of life?

2 Material and Methods

2.1 Setting

The study was set in the Australian health system comprising both publicly funded Government services and private providers. Patients attending a public hospital for cancer care generally do not pay out-of-pocket costs; however, any services provided out-of-hospital or in private hospitals often incur co-payments. Citizens can elect to have private health insurance, thus choosing their specialist doctor, and be seen privately in a private hospital; however, for most services, co-payments are necessary as either private health insurers do not cover all services or health providers charge fees over what is reimbursed. High-cost pharmacotherapies that are listed on Medicare's Pharmaceutical Benefits Schedule (PBS) attract a small patient co-payment. Regardless of health insurance status, patients with cancer in Australia can pay significant co-payments for cancer diagnosis and treatment [8] because care is required by private and public providers.

2.2 Sampling and Recruitment

We undertook a national cross-sectional survey of men and women who self-reported they had NETs. Eligible participants were approached in person through hospital clinics and online via newsletters to NETs patient support group members through the Unicorn Foundation. The Unicorn Foundation, a foundation to support patients with NETs, promoted and hosted a web link to the survey by inviting support group members by email and social media. The membership of Unicorn Foundation online support groups during 2017 included approximately 800 members. Oncologists at the Royal Brisbane and Women's Hospital (Queensland), Peter MacCallum Cancer Centre (Victoria), and Royal North Shore Hospital (New South Wales) invited patients to participate in the study during clinic appointments and promoted the survey via flyers. These are large state-based tertiary NETs referral centres and are the major sites in each state delivering peptide receptor radionuclide therapy (PRRT) for NETs patients. To capture a broad cross-section of patients with NETs, no restrictions were made on the time since diagnosis. Ethical clearance was obtained from the Royal Brisbane and Women's Hospital's Human Research Ethics Committees and other sites.

2.3 Survey Questions

A previous Australian survey administered to men with prostate cancer [9] was adapted to include treatments and wording specifically relevant to patients with NETS. On average, the self-reported survey took 30 min to complete and comprised 85 questions over eight domains, including cancer profile, employment, household finances, out-of-pocket medical expenses (past 3 months), financial toxicity, health insurance, quality of life and socio-demographics (Electronic Supplementary Material Appendix 1). Two validated instruments were included: the EuroQol 5-dimension 5-level (EQ-5D-5L) and the COmprehenSive Financial Toxicity (COST) tool. The EQ-5D-5L is a generic health-related quality of life measure and supported by an Australian algorithm and norms [10]. Items include mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The COST tool is an 11-item survey covering financial well-being and related stress and work-related issues during the past 7 days and was validated in a sample of 233 patients with advanced cancers using standard-scale construction techniques and showed high internal consistency and test–retest reliability [11]. For out-of-pocket monetary expenses, participants were asked how much they spent in the previous 3 months due to cancer that was not already covered by Medicare or,

if relevant, their private health insurer. A 3-month period was chosen to limit recall bias of difficult-to-remember cost data. The draft survey was circulated to the study authors, Unicorn Foundation staff and several consumers, with suggested modifications via email made to the structure and wording. The final survey was then pre-tested online with the same group. We asked respondents to release their Medicare claims data to the researchers covering the past 4 years (30 September 2013 to 30 September 2017). The choice of timeframe for Medicare was confined by the Department of Human Services only holding data for this duration before being archived. This administrative data provided information on resource use, health provider charges, Medicare reimbursement, and patient contributions to Medicare-listed medicines and health services. Costs are presented in 2019 Australian dollars ($A) ($A1 = $US0.69) [12].

2.4 Data Collection

Survey data were collected online using an internal survey portal (LabPortal) hosted by QIMR Berghofer Medical Research Institute. The survey period was open from 14 November 2017 to 10 January 2019 to allow time for survey promotion and ethics approvals at multiple sites. Participants could opt to complete a paper-based survey that was posted in the mail with the consent forms and returned in a reply-paid envelope. Participants who agreed for their Medicare data to be shared with the researchers were sent hard copies of the separate Medicare consent form to complete and return in a reply-paid envelope.

2.5 Data Analysis

Descriptive analyses were performed using frequencies and percentages for categorical data, and means, standard deviations (SDs) and measures of spread for continuous data. The majority of survey outcomes were categorical, while age, time variables, quality-of-life scores, COST scores and out-of-pocket expenses were continuous. The COST scores ranged from 0 to 44 (low to high financial well-being, respectively) and EQ-5D-5L scores ranged from 0 to 1 (low to high health utility, respectively). The population norm for the mean EQ-5D-5L score was 0.91 for a large South Australian community sample [13]. Subgroup analyses were undertaken between participants who were diagnosed within 3 years of completing the survey and at least 3 years ago. This cut-point was where approximately half the respondents were at from the time of their diagnosis (Electronic Supplementary Material Table 1). Pearson's chi-square and Student's *t* tests were used to test for significant differences among subgroups [14]. Skewness was considered for the cost and health utility data and generalised linear models were used to allow for a flexible analytical approach and non-normal cost data [15]. Socio-demographic and treatment variables were assessed in univariate models and were excluded from the multivariable models based on their statistical significance. The final models had a gamma family distribution and log link. Model goodness of fit was based on the Akaike Information Criterion. Statistical significance was determined at $p < 0.05$. All analyses were performed in STATA® SE version 15 (StataCorp LP, College Station, TX, USA).

3 Results

3.1 Responses and Missing Data

Electronic Supplementary Material Table 1 provides a breakdown of the response rates to the survey and Medicare data in relation to diagnosis dates. Overall, there were 204 survey participants, comprising 164 (80%) full and 41 (20%) partial responders. Partial responders were those who did not complete the full eight survey domains. The first five sections of the survey were completed by 175 (85%) participants. As administration was via a web link to the survey, the exact number of eligible persons who were aware of the survey are unknown and the response rate cannot be determined. No notable differences were found between full and partial responders in their cancer profiles, time since diagnosis (±3 years), co-morbidities (±2), employment status, state of residence and financial toxicity lowest tertile scores (Electronic Supplementary Material Table 1).

3.2 Participant Characteristics

The ages of participants varied from 18 to 83 years old (mean 58.7 years old [SD 11.7 years]) (Table 1). Half of the participants were males, and the majority were married (108 [53%]), tertiary educated (122 [59%]) and did not live with dependents (118 [58%]). Household incomes were spread across low (< $A37,000 per year, $n = 36$ [18%]) and higher income levels (> $A87,000 per year, $n = 64$ [32%]). Two-thirds of participants had at least one co-morbid condition or disease risk factor. Three-quarters of the sample had been treated with a somatostatin analogue (156 [76%]), almost half had surgery (95 [47%]), 84 (41%) had radiotherapy with PRRT, 45 (22%) had received chemotherapy and only 14 (6%) had targeted therapies or immunotherapy. The average time since first being diagnosed with NETs was 5.2 years (range < 1–26 years). Those who were older or were treated with somatostatin and/or PRRT and/or targeted therapies were more likely to have been diagnosed over 3 years ago (Table 1).

Table 1 Socio-demographic and medical characteristics ($n = 204$)

Characteristic	Diagnosed < 3 years	Diagnosed ≥ 3 years	Total
Total	91 (45)	113 (55)	204 (100)
Mean age (years) (SD)	56.1 (12.2)	60.9 (10.9)*	58.7 (11.7)
Age (years)			
≤ 40	7 (8)	3 (3)	10 (5)
41–60	42 (46)	36 (32)	78 (38)
≥ 61	25 (27)	51 (45)	76 (37)
Missing	17 (19)	23 (20)	40 (20)
Current relationship status			
Married	47 (51)	61 (54)	108 (53)
Other/missing	44 (49)	52 (45)	95 (47)
Highest education level			
Tertiary	61 (66)	61 (54)	122 (59)
Primary/secondary school	13 (14)	29 (26)	42 (21)
Missing	17 (19)	23 (20)	40 (20)
Living in rural area			
Rural	36 (39)	38 (34)	74 (36)
Urban/missing	55 (61)	75 (56)	130 (63)
Main state treated for NET			
Queensland	40 (44)	51 (45)	91 (45)
New South Wales	25 (27)	29 (26)	54 (26)
Victoria	14 (15)	18 (16)	32 (16)
Other	11 (12)	15 (14)	26 (11)
Site of origin of NET			
Intestine (small and large)	41 (45)	55 (49)	96 (47)
Pancreas	21 (23)	24 (21)	45 (22)
Multiple sites	6 (7)	12 (11)	18 (9)
Appendix/liver/lung	11 (11)	7 (7)	18 (8)
Other/unknown	12 (14)	15 (13)	27 (13)
Treatment received (more than 1 allowed)			
Surgery	37 (41)	58 (51)	95 (47)
Somatostatin analogue (sandostatin, lanreotide)	61 (67)	95 (84)***	156 (76)
PRRT (Lutate)	25 (27)	59 (52)***	84 (41)
Chemotherapy	19 (21)	26 (23)	45 (22)
Radiotherapy	8 (9)	18 (16)	26 (13)
Sunitinib, everolimus, immunotherapy	3 (3)	11 (10)	14 (6)*
Co-morbidities (more than 1 allowed)			
High blood pressure	20 (22)	37 (33)	57 (28)
Depression (including anxiety)	23 (25)	31 (27)	54 (26)
Arthritis	15 (16)	21 (19)	36 (18)
High cholesterol	10 (11)	21 (19)	31 (15)
Diabetes mellitus	12 (13)	17 (15)	29 (14)
Another cancer	11 (12)	13 (12)	24 (12)
Heart disease	6 (7)	11 (10)	17 (8)
None of the above	31 (34)	36 (32)	67 (33)

All data are given as *n* (%) unless otherwise stated

NET neuroendocrine tumour, *PRRT* radiotherapy with peptide receptor radionuclide therapy, *SD* standard deviation

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

3.3 Response to Financial Situation and Financial Toxicity

One in five participants sought financial advice after their cancer diagnosis. Eighty-one (40%) participants reported spending more money on the cost of treating cancer than expected, 35 (17%) said this caused significant stress to them and their family, 62 (31%) reported that cost was a consideration in choosing their cancer treatment course and eight (4%) participants did not proceed with treatment due to cost (Electronic Supplementary Material Figure 1). For financial toxicity, the overall mean score was 22.1 (SD 10.6; $n = 175$). Twenty-five percent of participants (44/175) were in the lowest tertile of the COST score, indicating poorer financial well-being.

3.4 Employment and Insurance Experiences

Relatively more participants were retired at the time of the survey than were currently employed (Table 2). Of those who were retired, 43 (44%) did so early due to their cancer. Among current workers, substantial time off work was taken due to cancer, while nearly one-third reported the cancer had prevented them from securing employment and another third had decreased their work hours. A small proportion of participants said colleagues treated them differently (27 [17%]) or they were overlooked for promotion (11 [7%]), while 25 (16%) participants had not told their employers or work colleagues about their cancer. Of those currently working, over one-third said they would retire early due to their cancer. Two-thirds of participants had private health insurance and 69 (34%) were treated in both private and public hospitals. Of those privately insured, insurance did not cover expected expenses for a high proportion of participants (77 [58%]). Between 2 and 25% of participants had been refused some type of insurance product (Table 2).

3.5 Self-Reported Out-of-Pocket Medical Expenses

Out-of-pocket expenses over the past 3 months were mostly spread evenly across direct and indirect medical expenses (Fig. 1). The most common expenses were for transport, medications, doctors' visits and hospital stays, although not all participants experienced all these expenses. Total mean costs were $A1698 (SD $A2132) over 3 months (median $A877). The highest costs were for medical tests (mean $A376 [17%], SD $A722), travel-related expenses (mean $A289 [13%], SD $A559) and specialist visits (mean $A225 (10%), SD $A342). Since their diagnosis, the most common highest expense category was for positron emission tomography (PET) and magnetic resonance imaging (MRI) scans, reported by 30% of patients. Rural patients reported travel and accommodation expenses as their largest expense more frequently (21 [30%]) than urban patients (10 [13%]). Participants with private health insurance paid proportionally more out of pocket than those without private health for medical tests (18% vs. 7%) and specialist visits (11% vs. 5%) and less for transport and travel (9% vs. 31%) (Electronic Supplementary Material Figure S2). Since their NETs diagnosis, only 16 (9%) patients had no perceived treatment complications and the remainder commonly experienced fatigue (138 [68%]), diarrhoea (108 [53%]), nausea (92 [45%]) and hot sweats (67 [33%]). Sixty percent of participants ($n = 100$) reported purchasing alternative therapies (e.g. vitamins, tonics, herbal therapies) as a result of their cancer at a mean cost of $A3190 (SD $A12,274, median $A500, interquartile range $A1935).

3.6 Medicare Data on Out-of-Pocket Expenses

Medicare data pertaining to transactions through the Medicare Benefits Schedule (MBS) and PBS records over 4 years were analysed for patients who were at least 2 years out from their diagnosis ($n = 54$). The range of out-of-pocket costs per person over 4 years was $A38 to $A24,277 (mean $A6153, SD $A5014) (Table 3). Co-payments for medicines were significantly less than for medical procedures but higher than doctors' appointments, imaging and pathology testing. Pharmaceuticals were the highest costs to the Commonwealth Government (mean $A74,400, maximum $A229,799) (Table 3). Medicare out-of-pocket costs were three-fold higher in participants with private health insurance ($p < 0.001$) and two-fold higher for those with incomes > $A87,000 per year ($p = 0.54$) (Table 4).

3.7 Quality-of-Life Impacts

The overall mean health-related quality of life score for the EQ-5D-5L ($n = 164$) was 0.65 (SD 0.23). There were no differences by time since diagnosis (±3 years) or by treatments received: somatostatin analogue (mean 0.64, SD 0.24), surgery (mean 0.63, SD 0.26) or PRRT (mean 0.66, SD 0.23). Poorer quality-of-life scores were significantly associated with a poorer financial toxicity score, two or more co-morbidities, younger age, not working due to cancer and nausea/diarrhoea (Table 4).

4 Discussion

Our study found deleterious financial impacts were experienced by some patients with NETs. These ranged from ongoing and rising out-of-pocket expenses to having to retire earlier than desired and refusals of insurance. While acknowledging these findings are from a select group of patients with NETs, we show there is wide variability in

Table 2 Employment, retirement and insurance impacts

Impact	Diagnosed < 3 years	Diagnosed ≥ 3 years	Total
Current working status			
Employed	49 (54)	27 (24)	76 (37)
Unemployed due to cancer	8 (9)	10 (9)	18 (9)
Retired early due to cancer	10 (11)	33 (29)	43 (21)
Retired due to other reason	20 (22)	34 (30)***	54 (26)
Other/missing	4 (4)	9 (8)	13 (6)
Time off work due to cancer (weeks)[a] (mean [SD])	18.4 (23.4)	51.9 (84.4)*	29.5 (54.0)
Has cancer prevented you from securing alternative employment?[b]—yes	15 (21)	26 (33)	41 (27)
Major change at work since cancer ($n = 156$)			
My hours decreased	22 (29)	21 (26)	43 (28)
My hours increased	1 (1)	4 (5)	5 (3)
My income has changed	24 (32)	33 (41)	57 (37)
My work tasks or responsibilities changed	15 (20)	10 (12)	25 (16)
I changed my employer	5 (7)	10 (12)	15 (10)
None of the above	34 (45)	41 (51)	75 (48)
Experiences at work since diagnosis of cancer ($n = 156$)			
My colleagues treat me differently in the workplace	16 (21)	11 (14)	27 (17)
I have been overlooked for a promotion	3 (4)	8 (10)	11 (7)
I have been demoted	0 (0)	4 (5)*	4 (3)
I have been offered voluntary redundancy	1 (1)	4 (5)	5 (3)
I have not told my employer or colleagues I have cancer	10 (13)	15 (19)	25 (16)
My workplace colleagues have treated me with respect	41 (54)	33 (41)	74 (47)
None of the above	20 (26)	33 (41)*	53 (34)
Expected retirement age (years)[a] (mean [SD])	64.3 (6.6)	64.2 (8.1)	64.3 (7.1)
Has this age changed because of your cancer?[a]			
No, I still expect to retire at this age	24 (49)	11 (41)	35 (46)
Yes, my cancer has meant I have delayed retirement	3 (6)	5 (19)	8 (11)
Yes, my cancer has meant I will retire early	20 (41)	9 (33)	29 (38)
If yes, can you afford to retire at this age?[a]—yes	19 (39)	9 (33)	28 (37)
Do you have private insurance?—yes	63 (69)	69 (61)	132 (65)
Where were you treated for your cancer?			
In a public hospital	23 (25)	31 (27)	54 (26)
In a private hospital	22 (24)	14 (12)	36 (18)
In a mixture of public and private hospitals	27 (30)	42 (37)	69 (34)
Have you ever changed your health insurer to gain benefits?—yes	8 (13)	3 (4)	11 (8)
How difficult was any claim you made for an insurance policy?			
Not difficult at all	15 (24)	17 (25)	32 (24)
A little difficult	6 (10)	9 (13)	15 (11)
Somewhat difficult	5 (8)	7 (10)	12 (10)
Did your private insurance cover you for everything you expected?—no	37 (59)	40 (58)	77 (58)
Did your private insurance influence treatment choice?—yes	13 (21)	18 (26)	31 (23)
Have you ever been refused insurance because of cancer?			
Health insurance—yes	1 (1)	7 (6)	8 (4)
Life insurance—yes	7 (8)	20 (18)	27 (13)
Income protection insurance—yes	8 (9)	16 (14)	24 (12)
Travel insurance—yes	14 (15)	37 (33)	51 (25)
Other type of refused insurance—yes	1 (1)	3 (3)	4 (2)

All data are given as *n* (%) unless otherwise stated; figures do not add to 100% due to missing or other categories not presented

SD standard deviation

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

[a]Only included current working status: employed

[b]Removed current working status, retired for other reasons

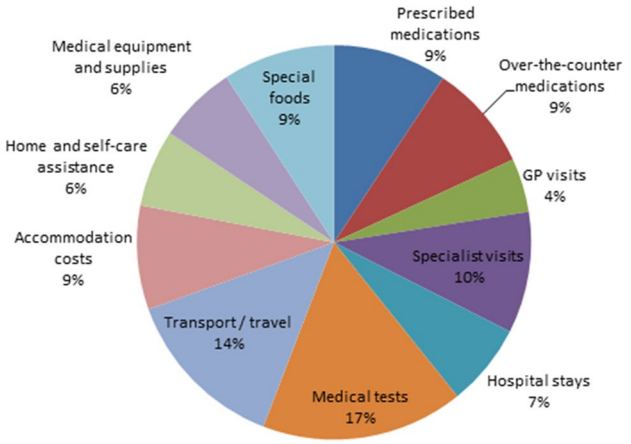

Fig. 1 Proportion of mean out-of-pocket expenses over the past 3 months. Hospital stays include hospitalisations for procedures and treatments. Questions regarding out-of-pocket costs for items purchased for managing complications and for alternative therapies were asked separately in the survey, covering the time since diagnosis

out-of-pocket medical costs, with some individuals facing very high costs within 2 years of diagnosis. In this mid-age sample, most study participants were well-educated, had metastatic disease (as represented by the treatments they received) and two-thirds were privately insured, but having NETs affected employment experiences, retirement plans, income levels and health-related quality of life.

There are few cost-of-illness studies on NETs [4]. A systematic review by Grande et al. [4] highlighted four earlier US studies assessing treatment costs of NETs [16, 17] or treatment-related adverse events [18, 19]. Three additional studies have provided updated health system costs (including newer therapies) in Canada [20], the USA [21] and Sweden [22]. Health system costs of NETs are significant and have been reported to be a mean of €25,500 (2013 values) per patient over 1 year (including lost productivity in individuals under 65 years old) [22], $US99,691 for first-year costs in somatostatin analogue users and $US158,397 in targeted therapy (e.g., everolimus or sunitinib) users (2014 values)

Table 3 Health provider charges, government benefits and patient out-of-pocket costs over 4 years ($n = 54$[a])

Costs	n[a]	Mean	SD	Median	25th percentile	75th percentile	Minimum	Maximum
MBS charges	54	18,516	13,865	14,905	11,095	23,227	1690	84,140
MBS benefits	54	14,318	9979	11,722	9585	18,444	1690	65,161
Appointments	54	4926	2196	4351	3314	6259	1118	9911
Procedures	53	3332	6989	1799	890	3370	78	49,765
Diagnostic imaging	54	3959	3031	3292	2172	4804	219	18,008
Pathology services	54	1948	1260	1722	1053	2419	73	6283
Other	30	387	370	285	77	586	12	1522
MBS out-of-pocket costs	50	4533	4456	3769	1062	5897	32	20,835
Appointments	49	1381	894	1282	763	1924	32	3869
Procedures[b]	40	2900	3462	2059	650	3492	10	15,946
Diagnostic imaging	34	807	1148	446	165	812	51	6168
Pathology	36	364	393	257	60	474	4	1572
Other	14	173	170	111	32	276	5	548
PBS charges	51	74,400	49,824	78,499	31,368	106,559	458	229,799
PBS benefits	50	73,776	48,922	78,811	30,437	102,295	10	226,542
Somatostatin	18	44,665	24,863	40,246	33,598	47,200	13,200	111,149
PBS out-of-pocket costs	51	2070	1627	1654	687	3258	38	8186
Somatostatin	18	353	321	288	106	492	6	1236
Total charges	54	88,782	54,027	92,879	44,799	123,991	3868	246,888
Total benefits	54	82,630	52,509	88,229	38,088	116,576	3830	243,534
Total out-of-pocket costs	54	6153	5014	5300	3044	7514	38	24,277

Only patients with at least 2 years' medicare data post-diagnosis were included (4 years of costs were included: 30 September 2013–30 September 2017); all values are given in Australian dollars

MBS Medicare Benefits Schedule, *PBS* Pharmaceutical Benefits Schedule, *SD* standard deviation

[a] n is < 54 when patients had zero costs in that subgroup

[b] Procedures that involve overnight hospital stays may be covered by private health insurance, and therefore may be overestimated here

Table 4 Unadjusted and adjusted analyses of out-of-pocket expenses and health-related quality of life

OOPs and quality of life	*n*	Unadjusted OOPs ($A)			Adjusted OOPs ($A) (*n* = 52)		
		Mean	95% CI	*p* value	Mean	95% CI	*p* value
Out-of-pocket costs (Medicare)							
Private health insurance							
No	11	2031	1124–2939	Ref.	2415	1113–3177	
Yes	43	7207	5700–8714	< 0.001	7342	5803–8881	< 0.001
Income ($A per year)							
< 37,000	12	4006	2091–5922	Ref.			
37,000–87,000	19	5962	3927–7998	0.19	5872	4349–7395	
> 87,000	19	7980	5291–10,668	0.02	6732	4481–8983	0.54
		Unadjusted scores			**Adjusted scores (*n* = 160)**		
Quality of life (EQ-5D-5L)							
Financial toxicity (lowest tertile of COST-FACIT)							
No	131	0.71	0.67–0.75	Ref.	0.69	0.65–0.73	
Yes	44	0.47	0.41–0.54	< 0.001	0.53	0.45–0.61	0.01
Number of co-morbidities							
0	54	0.73	0.67–0.79	Ref.			
1	45	0.67	0.61–0.74	0.23	0.69	0.66–0.73	Ref.
≥ 2	65	0.58	0.52–0.63	< 0.001	0.59	0.53–0.66	0.02
Age (years)							
> 60	76	0.71	0.65–0.76	Ref.	0.71	0.66–0.76	Ref.
≤ 60	88	0.61	0.56–0.66	0.01	0.61	0.55–0.60	0.02
Income ($A per year)							
< 37,000	34	0.57	0.49–0.65	Ref.			
37,000–87,000	59	0.64	0.58–0.70	0.21			
> 87,000	60	0.72	0.66–0.78	0.004			
Complications							
None	16	0.81	0.69–0.92	Ref.	0.71	0.66–0.76	Ref.
Other	27	0.74	0.66–0.83	0.39			
Nausea and diarrhoea	117	0.61	0.57–0.66	0.002	0.63	0.60–0.67	0.01
Not working due to cancer[a]							
No	119	0.70	0.66–0.74	Ref.	0.69	0.65–0.72	Ref.
Yes	45	0.54	0.47–0.60	< 0.001	0.56	0.47–0.65	0.03

EQ-5D-5L EuroQol 5-dimension 5-level, *COST-FACIT* COmprehenSive Financial Toxicity–Functional Assessment of Chronic Illness Therapy, *OOPs* out-of-pocket expenses, *Ref.* reference

[a]This means retired early or unemployed due to cancer

[21]. To our knowledge, this is the second study to quantify the personal financial burdens in patients with NETs [23]. Our previous work in patients with newly diagnosed breast, prostate, colorectal or lung cancer or melanoma showed Medicare-reported out-of-pocket costs over 2 years were a mean of $A3514 (SD $A4325) and ranged from $A0 to > $A50,000 [8]. Similar to our previous study, those with private health insurance pay significantly more for health services as private doctors tend to charge higher fees, leading to higher gaps for patients, relative to publicly provided services. The current study suggests the impact for patients with NETs may be similar to those with other major cancers in the shorter term but are ongoing in the longer term as shown by the last 3-monthly costs (median $A877 in patients on average 5.2 years after diagnosis). High long-term costs were also reported by Hallet et al. [20], who found higher health system costs for persons with NETs than those for colorectal cancer for continuing pharmaceutical therapies, doctors' appointments and inpatient episodes of care [20].

Individuals can face considerable financial consequences after a diagnosis of cancer, particularly if they are unable to work or retire earlier than expected [23, 24]. In our study, 28% of participants decreased their work hours and 44% of workers reported they had retired due to NETs. This contrasts to findings by Singh et al. [23], where 24% decreased their work hours and 82% had stopped working due to their NETs [23]. Our earlier work found that patients with colorectal cancer who stopped work or decreased work hours at

12 months after diagnosis were significantly likely to experience financial strain [25]. Further, Mehnert et al. [24] found that patients with cancer and a desire to retire early were more likely to have longer sick leave periods, less favourable workplace environments, lower work ability, more psychological distress and poorer quality of life. A study by Beesley et al. [26] showed that a lack of information on financial entitlements (Medicare, health fund claims and travel allowances) was one of the worse-ranking aspects of coordinated care [26].

Patients live with NETs over a relatively long period and, although they have advanced disease, may otherwise be medically stable and relatively well. Our study supports the increased awareness of NETs among health professionals and the general public, necessary to advocate for support through patient groups and cancer organisations. Unlike patients with other types of cancers, financial stress may not be transient and appropriate assessment and support for this issue should be considered at all stages during the illness journey. Decisions about retirement or reducing employment should be made with full information to avoid premature cessation of work, known to exacerbate financial toxicity [26] and poorer quality of life [27]. Considering the financial position of NETs patients, accessing supportive care services to provide occupational support is likely to be an increasingly important aspect of cancer rehabilitation services. Our work further supports the integration of protocols including informed financial consent into multidisciplinary team care to encourage discussion with social workers and establish pathways for financial support.

The study participants had a very high PRRT rate. Despite Australian NETs patients having relatively good access to PRRT, the rate is significantly higher than in the NETs population generally. This is largely due to the study's three recruiting sites being the major referral centres for PRRT in the three most populous states in Australia. These centres are publicly funded to provide this service at no cost to patients, as distinct to the USA or some centres in Europe where patients need to pay. This means that PRRT for NETs patients in Australia is predominantly delivered in high-volume specialist centres with expertise in their tumour, although many patients have to travel long distances to access treatment and have high travel-related costs.

This study has several limitations, mostly relating to the sampling methods and cross-sectional design. The study was not population-based and generalisability to all patients with NETs is reduced. There are no Australian-wide studies on NET patients to compare patient characteristics and there are no data on the current prevalence of NETs in Australia. The study is cross-sectional and therefore a snapshot of information. A longitudinal assessment would be valuable in learning the long-term implications of financial stress in patients with NETs. In addition, there was higher participation among those with private health insurance (65%) than in the general population (47%). Also, some participants may have been more interested and engaged with the topic, and potentially had higher-than-normal medical expenses. Although the out-of-pocket expense findings will be Australian-specific, the financial burden, quality of life and employment experiences of patients with NETs will be reasonably generalisable. We cannot rule out inaccuracies of participant recall of the expenses. However, recall bias was minimised by limiting the out-of-pocket questions to the previous 3 months, with shorter recall periods for cost data being more accurate and reliable. These limitations should be viewed alongside the study strengths. Our survey captured a sample of 204 patients with an uncommon cancer covering a broad spectrum of ages, geographic regions and socio-economic status and provided a range of financial experiences. Finally, we relied on self-report of having NETs and, except for those providing Medicare data with pharmaceutical treatments that indicated to NETs, there was no way of verifying the diagnosis among respondents. However, a targeted approach was taken and we have no reason to believe that respondents did not have NETs.

5 Conclusions

This study highlights the dual problem of cumulative out-of-pocket costs and early unanticipated retirement from the workforce. Financial hardship did exist for some individuals in our study and many had a reduced capacity to work, which contributed to their financial distress. A prospective study itemising costs in more detail by treatment and treatment sector would help provide a clearer understanding of where costs may be reduced for patients.

Acknowledgements The project concept was devised at the Commonwealth Neuroendocrine Tumour Collaboration (CommNETs) 2016 Annual Scientific Meeting. We thank the participants of the study and the Unicorn Foundation for assistance with developing and promoting the survey.

Author contributions LG, TME and DKW designed the study and the main survey tool. KW, SL, JL, MM, NP, JM and DKW provided clinical expertise and feedback to the survey, recruited patients and reviewed the draft manuscript. LGG and TME performed the data analyses and DKW assisted with data interpretation. ES provided critical feedback on the manuscript. All authors read, wrote and provided input to the draft results.

Funding The Unicorn Foundation funded the project. Funding was also received through a research grant from Ipsen Australia.

Data Availability Statement The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

Conflict of interest David K. Wyld received funding from Ipsen Australia. Louisa G. Gordon, Thomas M. Elliott, Kate Wakelin, Simone Leyden, John Leyden, Michael Michael, Nick Pavlakis, Jan Mumford and Eva Segelov have no conflicts of interest directly relevant to the content of this article.

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