BRIEF ARTICLE

Patient-reported outcomes in subjects with neuroendocrine tumors of the pancreas

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Abstract

AIM: To assess the patient-reported outcomes (PROs) of pancreatic neuroendocrine tumor (PNET) patients.

METHODS: Fifty-one consecutive patients (21 male, 30 female, 61.0 ± 10.3 years) with proven PNETs were studied. An SF-12 questionnaire capable of exploring the physical (PCS) and mental (MCS) aspects of daily life was used. Four questionnaires were also used [12 items General Health Questionnaire (GHQ-12) for non-psychotic psychiatric disorders, State Trait Anxiety Inventory (STAI) Y-1 and Y-2 for anxiety and BDI-Ⅱ for depressive symptoms] to explore the psychological aspects of the disease. Forty-four sex- and age-matched Italian normative subjects were included and evaluated using the SF-12, STAI Y-1 and Y-2 questionnaires.

RESULTS: Seven patients refused to participate to the study; they were clinically similar to the 44 participants who agreed to complete the questionnaires. PNET patients had a PCS score (44.7 ± 11.0) were not significantly different from the norms (46.1 ± 9.9, *P* = 0.610), whereas the MCS score was significantly lower in patients (42.4 ± 13.0) as compared to the norms (48.2 ± 9.8, *P* = 0.036). GHQ-12 identified 11 patients (25.0%) as having non-psychotic psychiatric disorders. The STAI scores were similar in the patients and in the normative population. Finally, BDI-Ⅱ identified eight patients (18.2%) with moderate depression and 9 (20.5%) with mild depression whereas 27 patients (61.4%) had no depression.

CONCLUSION: The PNET patients had a good physical but an impaired mental component of their quality of life; in addition, mild or moderate depressive symptoms are present in about 40% of PNET patients.

INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) are a heterogenous group of rare neoplasms, occurring in fewer than one in 100 000 people per year[1]. These tumors have attracted considerable attention in recent years, both because they are relatively easy to palliate and because they demonstrate the chronic effects of the particular hormone whose level is elevated. In about 10%-50% of cases, the tumors are not associated with obvious signs or symptoms of hormone hypersecretion and are called non-functioning tumors[2]. We have recently demonstrated that radical surgery continues to have a central role in the therapeutic approach to PNETs[2], and

that medical treatment has a precise role in functioning neuroendocrine tumors. Even if the survival rate is good, especially in those patients who were resected, there is no extensive data available on the quality of life (QoL) in these patients compared to the general population. In addition, the majority of studies published on this topic until now examined a Scandinavian population[3-10], and it is well known that some differences in perceiving well-being exist among different cultures[11]. Finally, there are no studies specifically focusing on the localization site of neuroendocrine tumors such as PNETs. Therefore, we carried out this prospective study on a large series of subjects with PNETs in order to assess the patient-reported outcomes (PROs), using different questionnaires capable of exploring the physical and mental aspects of their QoL as well as various psychological factors.

MATERIALS AND METHODS

Patients

Fifty-one consecutive patients with pathological confirmation of PNET who were admitted as outpatients to our Department from January to April 2009 were enrolled in the study. The histological specimens were obtained at surgery in 41 patients and at percutaneous biopsy using computed tomography/ultrasonography/endoscopic ultrasonography in the remaining 10 patients. The epidemiological and clinical data of the 51 patients studied are reported in Table 1. There were 21 males (41.2%) and 30 females (58.8%). The mean age of the patients was 61.0 ± 10.3 years (range, 34-86 years) and the duration of the disease was 5.8 ± 5.2 years (range, 1-28 years). Forty-one patients (80.4%) were married and 10 (19.6%) were single. Thirteen patients had finished elementary school (25.5%), 18 had finished middle school (35.3%), 13 had a high school diploma (25.5%) and seven had a university degree (13.7%). The majority of the patients were still working (38, 74.5%) while 13 were retired (25.5%). Twenty patients in the present series were drinkers (39.2%) while 22 (43.1%) were smokers. Thirty-five patients (68.6%) had one or more comorbidities (arterial hypertension in 21 patients, cardiac diseases in nine patients, chronic obstructive pulmonary diseases in four patients, gastrointestinal diseases such as peptic ulcers, gallstones and/or colon polyposis in eight patients, neuroendocrine diseases such as thyroid or hypophysis diseases in five patients, urogenital diseases in three patients, and other diseases in the remaining four patients) and 41 (80.4%) received drugs for causes not related to the PNET. Forty patients (78.4%) had undergone surgery at least once for causes unrelated to the neuroendocrine neoplasia (cholecystectomy in eight patients, appendectomy in 22 patients, inguinal hernioplasty in seven patients, other abdominal surgery in three patients, tonsillectomy and other otorhinolaryngological procedures in 17 patients, urological surgery in seven patients, gynecologic procedures in 10 patients and other surgical procedures in three patients). Forty-one of the 51 patients (80.4%) underwent surgery for their neuroendocrine pancreatic

Table 1 Demographic and clinical characteristics of the 44 patients who completed the questionnaires (mean ± SD)

	n (%)
Sex	
Males	18 (40.9)
Females	26 (59.1)
Age at interview (yr)	61.0 ± 9.8
Disease duration (yr)	5.8 ± 5.4
Body mass index (kg/m²)	25.9 ± 4.3
Marital status	
Single/Widowed/Divorced	10 (22.7)
Married	34 (77.3)
Diploma	
Elementary school	11 (25.0)
Middle school	18 (40.9)
High school	10 (22.7)
University degree	5 (11.4)
Job	
Current workers	32 (72.7)
Managers	6
Employees	16
Industrial workers	3
Housewives	7
Retired	12 (27.3)
Alcohol habit	
Alcohol drinkers	18 (40.9)
Current drinkers	14
Drinking duration (yr)	40.2 ± 12.5
Smoking habit	
Smokers	20 (45.5)
Actual smokers	5
No. of cigarettes smoked per day	10.6 ± 5.9
Smoking duration (yr)	28.7 ± 13.3
Comorbidities	30 (68.2)
Non disease specific drugs	35 (79.5)
Previous surgery not due to neuroendocrine tumors	33 (77.0)
Surgery due to pancreatic neuroendocrine tumors	35 (79.5)
Pancreatic head resection	8
Distal pancreatectomy	20
Total pancreatectomy	2
Enucleation	5
Status of neuroendocrine tumors	
Disease free	25 (56.8)
Lymph node involvement/liver metastases	19 (43.2)
Specific drugs and treatment	
No drugs	30 (68.2)
Somatostatin analogues alone	9 (20.5)
Somatostatin analogues plus radiometabolic therapy	5 (11.4)
Pain in the month prior to complete the questionnaire	17 (38.6)
Dyspepsia	24 (54.5)
Diabetes	12 (27.3)

Data are reported as absolute and relative frequencies or mean ± SD.

disease: resective surgery was performed in 36 patients and enucleation of the cancer in the remaining 5 patients. At the time of the study, 29 patients were disease-free (56.9%) and the remaining 22 had advanced disease (lymph node involvement or liver metastases). Seventeen patients (33.3%) were currently being treated medically: 11 (21.6%) with somatostatin analogues alone, and 6 (11.8%) with somatostatin analogues and radiometabolic treatment. Nineteen patients (37.3%) had experienced pain in the month prior to the interview whereas 30 patients (58.8%) had dyspeptic symptoms evaluated according to the Rome III criteria[12]. Among the 30 patients with dyspeptic symptoms, the majority (25, 83.3%) had experienced post-

prandial distress syndrome and five had had heartburn (16.7%). Finally, 14 patients (27.5%) had diabetes secondary to pancreatic surgery.

The mean body mass index (BMI) was 25.7 ± 4.1 kg/m^2; in particular, according to the WHO criteria[13], 1 patient (2.0%) was underweight (BMI < 18.5 kg/m^2), 22 (43.1%) had normal weight (BMI between 18.5 and 24.9 kg/m^2), 21 (41.2%) were pre-obese (BMI between 25.0 and 30.0 kg/m^2) and the remaining 7 (13.7%) were obese (BMI > 30 kg/m^2).

Questionnaires

The Italian versions of the SF-12™ Health Survey (SF-12), State Trait Anxiety Inventory (STAI) Y-1 and Y-2, 12 items General Health Questionnaire (GHQ-12), and Beck Depression Inventory-Ⅱ (BDI-Ⅱ) were used for the purpose of the study.

The SF-12 questionnaires had previously been developed and tested on the Italian population in general[14]. It consists of 12 items which generate two summary scales capable of exploring the physical and mental components. High scale scores of the SF-12 physical (PCS) and mental (MCS) component summaries represent a good QoL. The normative population tested with the SF-12 questionnaire included 61 434 Italian subjects; these subjects were randomly sampled from the electoral lists, regardless of their health status[14]. The values of this group represent the average of the health-related QoL of the general Italian population. The stratified mean ± SD values of the PCS and the MCS referring to 44 sex- and age-matched Italian subjects of this population were used as a normative group.

The GHQ-12 is a measure of current mental health and since its development[15], it has been translated into the Italian language and has been used for the Italian population[16,17]. The GHQ-12 has become a commonly used instrument for detecting psychiatric disorders[18]. The scale asks whether the respondent has recently experienced a particular symptom or behavior. Each item is rated on a four-point scale (less than usual, no more than usual, slightly more than usual or much more than usual). The score ranges from 0 to 12[19]; subjects with a score from 0 to 4 have a > 80% probability of having non-psychotic psychiatric disorders and they are generally considered cases (i.e. those subjects who needed psychological support) while those subjects with a score > 4 should be considered not affected by non-psychotic psychiatric disorders[20].

Due to the fact that the GHQ-12 is a general questionnaire regarding the psychological aspects of daily life, we used the following two specific questionnaires: the STAI[21] and the BDI-Ⅱ[22] to better evaluate anxiety disorders and depressive syndrome.

Regarding the assessment of anxiety, both state and trait anxiety can be assessed by using the 40 items of the STAI-Y-1 and Y-2[21]. The state (Y-1) and the trait (Y-2) portions of the inventory each consist of 20 item Likert format statements. The STAI has been extensively validated and the Italian version has already been used[23]. The scores of the two 20 item scales range from 20 to 80 and high scores represent a high level of anxiety[21]. In brief, the state of anxiety can vary in intensity and fluctuate over time depending on the perceived threat. The trait of anxiety is a tendency to perceive a wide range of living conditions as threatening and to react to them with a high intensity; this trend remains latent until it is activated by stress associated with real or imagined dangers. The normative population tested with the STAI questionnaire included 2363 Italian working people sampled regardless of their health status[23]. The stratified mean ± SD values of the STAI Y-1 and the STAI Y-2 used with 44 sex- and age-matched Italian subjects of this population were used as a normative group.

The BDI-Ⅱ[22] is a 21-item self-report instrument which assesses the severity of depressive symptoms in adolescents and adults over the 2 wk prior to its use. Each item is rated on a 4-point scale (0-3) with total scores ranging from 0 to 63. For interpretation of the BDI-Ⅱ, Beck *et al*[22] present a table of scores indicative of: severe (> 28); moderate (score ranging from 20 to 28) and mild (score ranging from 14 to 19) depression. Scores of ≤ 13 suggest an absence of depression. These scores observed in an American population having depressive symptoms can also be used for the respective Italian population[24]. The Italian version of this questionnaire was used[24].

All patients included in our study were fluent in the Italian language and the questionnaires were administered according to the recommendations suggested by the user manuals[14,19,23,24].

Ethics

The study was approved by the Senior Staff Committee of the Department of Digestive Diseases and Internal Medicine of the University of Bologna and was carried out in accordance with the Helsinki Declaration of the World Medical Association. All study participants gave oral informed consent.

Statistical analysis

The descriptive statistics applied were: mean, SD and ranges as well as absolute and relative frequencies. Three-way ANOVA was applied in order to estimate the various effects related to the SF-12 and STAI scores by adjusting for age (increasing trend among the age categories) and gender (males *vs* females). The 95% confidence intervals (95% CIs) of the estimates were also calculated. One-way ANOVA, one-way linear term ANOVA, Pearson correlation, Fisher exact test, Pearson chi-squared and linear-by-linear association chi-square were also applied where appropriate.

All statistical evaluations were carried out by running the SPSS version 13.0 for Windows. Two-tailed *P* values less than 0.05 were considered statistically significant.

RESULTS

Forty-four (86.3%) of the 51 patients answered the questionnaires; the demographic and clinical characteristics of these patients are reported in Table 1. Seven patients

Table 2 Effects of neuroendocrine tumors of the pancreas on the SF-12 physical (PCS) and mental (MCS) component summaries estimated by means of three-way ANOVA adjusted for age (increasing trend among the age classes) and gender

	PCS		MCS	
	Effects (95% CI)	P value	Effects (95% CI)	P value
Overall effects of the disease (patients vs normative group)	-1.16 (-5.66 to 3.34)	0.610	-5.32 (-10.30 to -0.35)	0.036
Effects of the disease within males	-1.17 (-8.01 to 5.68)	0.735	-6.12 (-13.69 to 1.45)	0.112
Effects of the disease within females	-1.15 (-6.99 to 4.69)	0.697	-4.53 (-10.99 to 1.93)	0.167
Interaction between the effects of the disease and gender (males vs females)	-0.02 (-9.02 to 8.97)	0.996	-1.59 (-11.54 to 8.37)	0.752
Interaction between the effects of the disease and age	3.32 (-6.96 to 13.60)	0.522	9.54 (-1.84 to 20.92)	0.099
Interaction between the effects of the disease and age within males	4.10 (-11.88 to 20.09)	0.611	9.24 (-8.44 to 26.93)	0.301
Interaction between the effects of the disease and age within females	2.54 (-10.39 to 15.48)	0.697	9.84 (-4.47 to 24.15)	0.175
Interaction between the effects of the disease and age and gender	1.56 (-19.00 to 22.12)	0.880	-0.59 (-23.35 to 22.17)	0.959

95% CI: 95% confidence interval.

Table 3 Effects of neuroendocrine tumors of the pancreas on the STAI Y-1 (anxiety state) and Y-2 (anxiety trait) estimated by means of three-way ANOVA adjusted for age (increasing trend among the age classes) and gender

	STAI anxiety state (Y-1)		STAI anxiety trait (Y-2)	
	Effects (95% CI)	P value	Effects (95% CI)	P value
Overall effects of the disease (patients vs normative group)	-5.16 (-12.56 to 2.23)	0.169	0.77 (-5.84 to 7.39)	0.817
Effects of the disease within males	-4.66 (-16.98 to 7.67)	0.454	-0.48 (-11.50 to 10.54)	0.932
Effects of the disease within females	-5.66 (-13.84 to 2.51)	0.172	2.02 (-5.29 to 9.33)	0.584
Interaction between the effects of the disease and gender (males vs females)	1.00 (-13.79 to 15.79)	0.893	-2.50 (-15.72 to 10.73)	0.708
Interaction between the effects of the disease and age	7.69 (-7.10 to 22.48)	0.304	-2.58 (-15.81 to 10.64)	0.698
Interaction between the effects of the disease and age within males	5.30 (-19.35 to 29.95)	0.670	-0.05 (-22.09 to 21.99)	0.996
Interaction between the effects of the disease and age within females	10.07 (-6.28 to 26.42)	0.224	-5.12 (-19.74 to 9.51)	0.488
Interaction between the effects of the disease and age and gender	-4.77 (-34.35 to 24.81)	0.749	5.06 (-21.39 to 31.51)	0.704

(13.7%) refused to participate in the study: no significant differences among the demographic and clinical data were found between participants and those who refused to answer the questionnaire (data not shown for brevity).

Overall analysis of the SF-12 questionnaire in the 44 patients showed that the values of the PCS score are representative of a relatively good physical QoL and they were not significantly different from those of the normative population (PCS: 44.7 ± 11.0 vs 46.1 ± 9.9, $P = 0.610$). The MCS score was significantly lower in patients (42.4 ± 13.0) as compared to the norms (48.2 ± 9.8, $P = 0.036$). Moreover, a stratified analysis (Table 2) failed to show any significant interaction between sex and age and the effect of the disease on the MCS of PNET patients.

Regarding the GHQ-12 questionnaire, we identified 11 patients (25.0%) having non-psychotic psychiatric disorders. Shown in Table 3, the results of the STAI demonstrated that anxiety was similar in patients and the normative population.

Finally, in order to explore the depressive syndrome in detail, the BDI-Ⅱ identified eight patients (18.2%) with moderate depression, nine patients (20.5%) with mild depression and 27 patients (61.4%) with no depression.

We also explored the relationships between the results of the various questionnaire scores. The MCS was highly related ($P < 0.001$) to both anxiety state and trait (STAI Y-1 and Y-2, respectively) whereas the PCS was only significantly related to anxiety trait ($P = 0.043$) but not to the anxiety state ($P = 0.222$). As shown in Table 4, only the STAI scores were significantly associated with the presence of non-psychotic psychiatric disorders as evaluated by the GHQ-12 while both the SF-12 and the STAI were significantly related to the depressive symptoms as assessed by the BDI-Ⅱ. In addition, a significant ($P = 0.011$) positive relationship was also found between the presence of non-psychotic psychiatric disorders and the depressive state (absence of depression: 4/27, 14.8%; mild depression: 2/9, 22.2%; moderate depression: 5/8, 62.5%).

Table 5 shows the possible relationships between the demographic and clinical characteristics of the PNET patients and the results of the questionnaires investigated. MCS significantly improved with age ($P = 0.042$), and anxiety state (STAI Y-1) significantly decreased with age ($P = 0.038$). Workers had an MCS (39.8 ± 13.1) significantly lower than retired people (49.2 ± 10.7, $P = 0.032$). The patients that did not receive non-specific disease drugs had a PCS score (51.7 ± 8.6, $P = 0.032$) significantly higher (42.9 ± 11.70) than those who were taking non-disease specific drugs; PCS was also significantly higher in patients who underwent surgery for PNET (46.4 ± 10.8) compared with those who were not operated on (38.3 ± 10.0, $P = 0.049$). Pain worsened both the STAI Y-1 (patients with pain had a score of 48.9 ± 12.7 and those without 41.5 ± 11.0, $P = 0.046$) and Y-2 (patients with pain had a score of 45.8 ± 12.0 and those without 39.1 ± 9.7, $P = 0.049$) scores. Finally patients with dyspeptic symptoms had a worse MCS (patients with dyspepsia had a score of 38.4 ± 13.2 and those without 47.1 ± 11.4, $P = 0.025$). The frequency of dyspepsia was 37.0% (10/27) in patients without depressive symptoms evaluated with the BDI-Ⅱ, 88.9%

Table 4 Relationships between SF-12 and STAI scores, and GHQ-12 and BDI-II scores in the 44 patients with neuroendocrine tumors of the pancreas (mean ± SD)

	SF-12		STAI	
	PCS	MCS	Anxiety state (Y-1)	Anxiety trait (Y-2)
GHQ-12[1]				
Subjects without non-psychotic psychiatric disorders (score ≤ 4, n = 33)	46.1 ± 9.8	44.4 ± 11.8	42.3 ± 10.9	39.1 ± 10.1
Subjects with psychotic psychiatric disorders (score > 4, n = 11)	40.6 ± 13.9	36.1 ± 15.0	50.7 ± 13.9	49.6 ± 10.3
P value	0.156	0.066	0.043	0.005
BDI-Ⅱ[2]				
Absence of depression (score ≤ 13, n = 27)	48.2 ± 8.8	47.3 ± 10.3	39.1 ± 9.1	36.1 ± 8.1
Mild depression (score 14-19, n = 9)	40.0 ± 11.8	40.1 ± 14.8	44.2 ± 7.7	43.6 ± 4.6
Moderate depression (score 20-28, n = 8)	38.4 ± 13.3	28.2 ± 8.3	62.3 ± 7.2	58.8 ± 4.3
Severe depression (score > 28, n = 0)	-	-	-	-
P value	0.010	< 0.001	< 0.001	< 0.001

[1]One-way ANOVA; [2]ANOVA linear term.

Table 5 Relationship between demographic and clinical characteristics of the 44 patients who completed the questionnaires and the results of the questionnaires used (in bold the significant associations)

	P					
	SF-12 PCS	SF-12 MCS	GHQ-12	STAI Y-1	STAI Y-2	BDI-II
Gender (males *vs* females)	0.589[1]	0.630[1]	0.480[2]	0.317[1]	0.214[1]	0.387[3]
Age at interview	0.113[4]	**0.042[4] (r = 0.309)**	0.351[1]	**0.038[4] (r = -0.314)**	0.309[4]	0.525[5]
Disease duration	0.962[4]	0.751[4]	0.912[1]	0.669[4]	0.752[4]	0.856[5]
BMI	0.766[4]	0.185[4]	0.125[1]	0.241[4]	0.514[4]	0.723[5]
Marital status (single *vs* married)	0.181[1]	0.093[1]	0.237[2]	0.110[1]	0.556[1]	0.443[3]
Diploma (trend from elementary school to university degree)	0.185[5]	0.916[5]	0.648[3]	0.705[5]	0.373[5]	0.405[3]
Job (workers *vs* retired)	0.240[1]	**0.032[1] (-9.4 ± 4.23)**	0.240[2]	0.054[1]	0.057[1]	0.227[3]
Alcohol habit (drinkers *vs* non-drinkers)	0.407[1]	0.745[1]	0.480[2]	0.653[1]	0.724[1]	0.930[3]
Smoking habit (smokers *vs* non-smokers)	0.349[1]	0.465[1]	0.294[2]	0.124[1]	0.122[1]	0.601[3]
Comorbidities (present *vs* absent)	0.651[1]	0.923[1]	1.000[2]	0.435[1]	0.202[1]	0.402[3]
Non-disease specific drugs (yes *vs* no)	**0.032[1] (-8.7 ± 3.9)**	0.322[1]	0.085[2]	0.369[1]	0.152[1]	0.140[3]
Previous surgery not due to neuroendocrine tumors (yes *vs* no)	0.775[1]	0.238[1]	0.241[2]	0.439[1]	0.437[1]	0.321[3]
Surgery due to pancreatic neuroendocrine tumors (yes *vs* no)	**0.049[1] (8.1 ± 4.0)**	0.778[1]	0.669[2]	0.987[1]	0.880[1]	0.957[3]
Disease status (disease free patients *vs* patients having lymph node involvement or liver metastases)	0.875[1]	0.454[1]	1.000[2]	0.300[1]	0.169[1]	0.105[3]
Specific treatment (yes *vs* no)	0.816[1]	0.454[1]	0.722[2]	0.925[1]	0.733[1]	0.985[3]
Pain in the last month (present *vs* absent)	0.152[1]	0.371[1]	0.075[2]	**0.046[1] (7.4 ± 3.6)**	**0.049[1] (6.7 ± 3.3)**	0.190[3]
Dyspepsia (present *vs* absent)	0.115[1]	**0.025[1] (-8.7 ± 3.8)**	0.728[2]	0.199[1]	0.195[1]	**0.015[3,6]**
Diabetes (present *vs* absent)	0.908[1]	0.263[1]	0.457[2]	0.883[1]	0.581[1]	0.938[3]

[1]One-way ANOVA (effect estimates; mean ± SE); [2]Fisher exact test; [3]Liner-by-linear association chi-square (frequencies); [4]Pearson correlation (regression coefficient; r); [5]One-way linear term ANOVA; [6]Frequency of dyspepsia: according to BDI-II: absence of depression (score ≤ 13) 10/27 (37.0%); mild depression (score 14-19) 8/9 (88.9%); moderate depression (score 20-28) 6/8 (75.0%). In order to quantify the relationships, the various effect estimates - evaluated according to the statistical analysis applied - have been reported in parentheses.

(8/9) in those with mild depressive symptoms, and 75% (6/8) in those with moderate depressive symptoms (*P* = 0.015).

DISCUSSION

The correct management of neuroendocrine tumors of the pancreas includes diagnosis, management of the functional hormonal syndrome when present and management of the potentially malignant tumor. Control of the hormonal syndrome, when present, is achieved preoperatively in order to stabilize patient status for the operation[25] whereas, in the case of recurrence and in the case of a non-surgical approach to these tumors, medical treatment is the main option[26].

In the present study, approximately 57% of the patients were disease-free at the time of the interview whereas, as previously reported[2], patients with advanced disease were treated medically. Thus, especially in this latter group of subjects, PRO assessment seems to be important for evaluating the impact of this chronic disease[27] in order to understand how biology interacts with cultural, social, interpersonal and psychological aspects. In fact, QoL also plays a central role in how the variety of symptoms and the medical management of disease are perceived by those affected. However, there are a limited number of studies evaluating the patient point of view regarding his own disease[3-10,28]. All

these studies evaluated the QoL in patients with various neuroendocrine tumors of the gastrointestinal tract and almost all[3-6,8-10,28] used the European Organisation for Research and Treatment of Cancer Quality of life Questionnaire-C30 (EORTC) questionnaire for quantifying the QoL of the patients; only one study explored the PROs using a different questionnaire such as the SF-36[7]. Only two studies compared the EORTC results of neuroendocrine tumor patients with a normative population[6,9], but the patients enrolled had carcinoid tumors which represent only a part of the neuroendocrine tumors of the gastrointestinal tract. Thus, we focused our attention on the PROs in a well defined group of patients, i.e. those with a diagnosis of PNET. For this purpose, we utilized the SF-12 questionnaire. The choice of this questionnaire in evaluating the PROs was based on the following assumptions: the simplicity of this questionnaire (it is based on 12 questions only whereas the EORTC contains 30 questions); the two SF-12 component summaries have a high level of reliability in evaluating the QoL similar to that of the domains/scores of the EORTC questionnaire[29]; it is also possible to compare the data of patients with a nationwide normative population (there is no Italian normative population for EORTC) and, finally, SF-12 has been already tested in patients with neuroendocrine tumors of the ileum[30]. Thus, from a practical point of view, the SF-12 questionnaire is more reliable and easier to use in routine clinical practice than the EORTC. Only a few studies have also explored psychological aspects of the disease, mainly using the Hospital Anxiety and Depression Scale (HADS) for evaluating this topic[3,6,7,9,10]. Thus, we planned the present study in order to evaluate not only the presence of generic psychological distress by using the GHQ-12 questionnaire but also to determine whether the psychological distress eventually present is related to anxiety or depressive syndrome, and to compare these psychological aspects to those of the normative Italian population. For this purpose, we utilized two specific questionnaires, the STAI and the BDI-Ⅱ, which are largely used in this setting.

The values of the SF-12 summary scores as compared to the norms showed that the 44 patients in the present study seemed to perceive their physical QoL as relatively good even if they had a tumor, and this finding agreed with previous reports[4,5,9,10] whereas mental aspects were significantly impaired as compared to the norms. This seems to be due to the disease itself and is not related to the effects of gender and age. In fact, we carried out a stratified analysis which showed no significant interaction between age and sex, and the effect of the disease. We also attempted to identify the factors capable of modifying the mental component of QoL of patients with PNET. Surprisingly, we found that our patients were not affected by anxiety, but mild and moderate depressive symptoms were present in about 40% of the patients studied. Our data differed from those previously published which showed that patients with neuroendocrine tumors had anxiety and depression in varying proportions from low, as reported by Larsson et al[4], to high, as reported by Fröjd et al[10]. These results may be due to the fact that we compared the data to the general population. In fact, when we analyzed the questionnaire score within the group of patients without comparison to the normative population, we found that the MCS and the anxiety state were better in older patients, and that workers had an MCS significantly lower than retired people. PCS was significantly higher in patients that did not receive non-disease specific drugs as compared to those who were taking non-disease specific drugs; this score was also significantly higher in patients who underwent surgery for PNET as compared to those who were not operated on. Furthermore, we also found that pain worsened both the anxiety state and trait (STAI Y-1 and Y-2) scores. Finally, patients with dyspeptic symptoms had worse MCS scores and they also presented with more depressive symptoms than those without. In clinical practice, these red flags should also be taken into consideration; even if the tumor does not affect physical condition (only 2% of patients were underweight), the workers were worried about their condition which could limit their daily activity and they probably needed psychological support.

Furthermore, these patients needed more intensive medical treatment for alleviating the pain flares and the dyspeptic symptoms.

Finally, the seven patients who refused to participate in the study were similar in demographic and clinical variables to the 44 subjects who completed the questionnaires; thus, we can assume that the results obtained can be extended to the entire Italian PNET population, at least under our experimental conditions.

In conclusion, knowledge of the patient's reported outcome in patients with PNET may help in decision-making providing important information about the long-term effects of depressive symptoms in cancer survivors, and help to identify potential adjustment problems. Current workers and especially those with dyspeptic symptoms are those patients who need specific and intensive medical and psychological support because of the presence of depressive symptoms.

COMMENTS

Background
Pancreatic neuroendocrine tumors (PNETs) are generally slow growing and patients may have prolonged survival. There are no studies specifically focusing on the localization site of neuroendocrine tumors such as PNETs.

Research frontiers
patient-reported outcome (PRO) assessment is important for evaluating the impact of this chronic disease in order to understand how biology interacts with the cultural, social, interpersonal and psychological aspects. In fact, quality of life (QoL) also plays a central role in how the variety of symptoms and the medical management of the disease are perceived by those affected.

Innovations and breakthroughs
Of the patients affected by PNETs, current workers and especially those with dyspeptic symptoms are those subjects who need a specific and intensive medical and psychological support because of the presence of depressive symptoms.

Applications

Knowledge of the patient's reported outcome in patients with PNETs may help in decision-making providing important information about the long-term effects of depressive symptoms in cancer survivors, and help to identify potential adjustment problems.

Terminology

Patient-reported outcomes provide a means of gaining an insight into the way patients perceive their health and the impact that treatments or adjustments to lifestyle have on their QoL.

Peer review

The paper by Pezzilli *et al* assessed the physical and mental status of patients with PNETs. They conclude that patients had a comparable physical but a lower mental score than these 44 individuals. The idea is rather innovative and the results are interesting.

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