

## Pancreatic Diseases: The Need to Assess the Quality of Life

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### Abstract

The patient's overall well-being and ability to function is one of the measures capable of quantifying the impact of disease and treatment. Health-related quality of life, as subjectively perceived by the patient, is becoming a major issue in the evaluation of any therapeutic intervention, mainly in patients with chronic diseases. In this paper, the literature regarding the well-being of patients with pancreatic diseases, both acute and chronic, and of patients who undergo surgery for their benign or malignant pancreatic disease will be reviewed. The conclusions that can be drawn from the studies reviewed are that the quality of life should be routinely assessed for evaluating patients with pancreatic diseases.

**Keywords:** Pancreatitis; Alcoholic; Acute pancreatitis; Pancreatic resection; Pancreatectomy; Quality of life; Questionnaires

### Abbreviations

BDI-II: Beck Depression Inventory-II; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30; GHQ-12: 12 items General Health Questionnaire; PHR: Pancreatic Head Resection; PNETs: Pancreatic Neuro Endocrine Tumors; PROs: Patient-Reported Outcomes; QLQ PAN26: Quality of Life Questionnaire-PAN26; QoL: Quality of Life; SF-12: Medical Outcome Study 12-Item Short-Form Health Survey; SF-36: Medical Outcome Study 36-Item Short-Form Health Survey; STAI: State Trait Anxiety Inventory Y-1 and Y-2

### Introduction

There is a great demand for health services and there is associated pressure to control spending; there is also the need for the National Health Service to better evaluate the cost effectiveness of interventions which improve the quality of life [1]; thus, the patient's overall well-being is one of the measures capable of quantifying the impact of disease and consequent treatment [2]. For these reasons, health-related quality of life, as subjectively perceived by the patient, is becoming a major issue in the evaluation of any therapeutic intervention, mainly in patients with chronic diseases. In this paper, the literature regarding the well-being of patients with pancreatic diseases, both acute and chronic, and of patients who undergo surgery for their own benign or malignant pancreatic disease will be reviewed.

### Acute Pancreatitis

There are few studies on the assessment of the quality of life in patients with acute pancreatitis. All these studies regard patients operated on for acute illness and, in the majority of them, the patient's reported outcomes were evaluated only after a long time interval following discharge [3-8]. The questionnaires used in these six studies were: the Medical Outcome Study 36-Item Short-Form Health Survey (SF-36) in four [4,5,7,8], the Rosser disability and distress index in one [3], and the Karnofsky score, the Rankin score and the Sickness Impact Profile in the remaining one [6]. In one study, the patients completed the questionnaire after 1 year [3], whereas, in the other studies, the questionnaires were completed within 3 years after discharge [4-8]. While the majority of authors have reported a good quality of life for their patients cured of acute pancreatitis [3-7], others have not [8]. Finally, there are no data available on the modification of the patient's reported outcome in medically-treated patients. Thus, we explored the quality of life in 40 patients treated medically during the acute

phase of pancreatitis as well as at 2 and 12 months after discharge from the hospital [9]. The etiology of the pancreatitis was biliary in 31 patients and non-biliary in 9; mild disease was present in 29 patients and severe disease in 11. Thirty patients completed the two surveys at 2 and 12 months after hospital discharge. The Medical Outcome Study 12-Item Short-Form Health Survey (SF-12) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) questionnaires were used for the purpose of the study. We found that the two physical and mental component summaries of the SF-12, all the domains of the EORTC QLQ-C30 (except for physical functioning and cognitive functioning) and some symptom scales of the EORTC QLQ-C30 (fatigue, nausea/vomiting, pain, and constipation) were significantly impaired during the acute phase of pancreatitis. There was a significant improvement in the SF-12 physical component summary, and global health, role functioning, social functioning, nausea/vomiting, pain, dyspnea and financial difficulty (EORTC QLQ-C30) at 2 months after discharge as compared to the basal evaluation. Similar results were found after 12 months except for the mental component score at the 12-month evaluation, which was significantly impaired in acute pancreatitis patients in comparison to the normative population. The etiology of acute pancreatitis did not significantly influence the various domains and symptoms of the two questionnaires either at basal evaluation or during the follow-up period (i.e., 2 and 12 months after discharge). The physical functioning of the EORTC QLQ-C30 at basal evaluation was significantly impaired in patients with severe pancreatitis in comparison to patients with mild pancreatitis. On the basis of these results, we can conclude that two different patterns are recognized in the quality of life of patients with acute pancreatitis; physical impairment is immediately present followed by mental impairment which appears progressively in the follow-up period.

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## Chronic Pancreatitis

Recurrent episodes of abdominal pain accompanied by progressive pancreatic exocrine and endocrine insufficiency are usually typical features of chronic pancreatitis [10,11]. The disease is frequently the result of chronic alcohol abuse, even if other etiological factors have been involved in its pathogenesis, such as genetic alterations, autoimmune disorders, and obstructive disease of the biliary tract and the pancreas [12]. Medical treatment is the first option, especially in those patients requiring substitutive therapy for either exocrine or endocrine insufficiency but pain remains the main therapeutic challenge. Although medical management of pain may be one of the therapeutic modalities [13], surgical management has been the main option in the case of intractable pain in the past as well as in the present [14]. In recent years, other therapeutic options, more medically than surgically oriented, have been applied in clinical practice: endoscopic therapy [15], thoracoscopic splanchnicectomy [16], and extracorporeal shockwave lithotripsy [17].

Many studies evaluating the quality of life in chronic pancreatitis patients have recently been published involving both medical and surgical patients [18-21]. Most of them utilized a questionnaire called the Medical Outcome Study 36-Item Short-Form Health Survey (SF-36) [18-20] and one used a questionnaire involving two different modules, the EORTC QLQ-C30 and the Quality of Life Questionnaire Pancreatic Cancer Module (QLQ-PAN26), which had previously been tested on pancreatic cancer patients [21]. All four studies demonstrated that patients with chronic pancreatitis had a substantially impaired quality of life and, most importantly, the impairment of the quality of life in younger patients was higher than in older ones with obvious economic consequences for society [18-21].

Among the various clinical variables examined as possible factors related to chronic pancreatitis, the etiology of chronic pancreatitis (alcoholic vs. non-alcoholic pancreatitis) does not impair the quality of life, and only pain is able to significantly impair all eight domains of the SF-36, thus confirming that pain control is the main therapeutic option for improving the quality of life in patients with chronic pancreatitis, suggesting that much effort should be made in order to identify more efficacious therapies capable of controlling this symptom.

In our study involving Italian patients with chronic pancreatitis [20], neither the type of pancreatic surgery nor endoscopic therapy were able to substantially modify the various physical and mental domains investigated by the SF-36 and this is in contrast to previous studies regarding the various surgical and endoscopic options [4,16,22-29]; the difference may be due to the fact that these latter studies [4,16,22-29] enrolled a highly selected group of patients with a short time interval between the intervention and the assessment of the health-related quality of life or that the data were not adjusted for sex and age.

It is worth noting that diabetes and major alterations of the Wirsung duct (which are expressions of long-standing chronic pancreatitis), as well as a decreased BMI (which is an expression of maldigestion) are able to impair the physical and mental domains [18-20].

An important point is that a percentage of patients, varying from 4 to 10% [20,21], missed responses or refused to complete the questionnaires. In the Italian study [20], it was a rather particular group; in fact we found that patients who refused to complete the questionnaire were mainly male patients, current smokers with a long duration of alcohol consumption, with a long duration of the disease

and free from pain at the time of the study. These patients need an intensive psychological approach in order to counterbalance their unwillingness to improve their relationship with the disease.

Since, in clinical practice, there is the need to utilize a time-saving questionnaire to assess the quality of life, we have recently carried out a study utilizing a short version of the SF-36 questionnaire, called SF-12 [30]. The aim of the study was to establish the validity of the SF-12 questionnaire in patients with chronic pancreatitis and to identify the predictors capable of modifying the physical (PCS) and mental (MCS) component summaries in these patients. One hundred and forty-one patients with proven chronic pancreatitis were studied. The chronic pancreatitis patients had the SF-12 physical (PSC-12) and mental component (MCS-12) summaries significantly related to the PCS-36 and MCS-36 ( $p < 0.001$ ). The presence of pancreatic pain and non-pancreatic surgery accounted for 41.3% in the formation of the PCS-36 score and 37.2% in that of the PCS-12 score, respectively. Gender, BMI and pancreatic pain accounted for 15.3% of the information in the formation of the MCS-36 and for 14.7% in that of the MCS-12; using these clinical variables, the loss of information in applying the SF-12 instead of the SF-36 was very low (4.6% and 0.6% for the PCS and the MCS, respectively). Thus, the SF-12 seems to be a good alternative to the SF-36 in assessing the quality of life in chronic pancreatitis.

We also evaluated the role of the information given by both the SF-12 Health Survey and the EORTC QLQ-C30 questionnaires, and we determined which of these two questionnaires could be considered more efficacious in describing the quality of life of 163 consecutive patients with proven chronic pancreatitis in clinical practice [31]. We found that pancreatic pain was the only clinical variable capable of significantly impairing the SF-12 Health Survey component summaries as well as all the domains of the EORTC QLQ-C30 while body mass index was positively related to the PCS-12 and to the domains of the EORTC QLQ-C30. A high level of reliability of the domains/scores of the two questionnaires in evaluating the quality of life in patients with chronic pancreatitis was found, and two main factors were identified. These two factors were mainly related to the two SF-12 summary components. Thus, from a practical point of view, the SF-12 is more reliable and easier to use in routine clinical practice than the EORTC QLQ-C30.

Finally, we evaluated the outcome for patients with chronic pancreatitis in a 2-year follow-up study by using the SF-12 questionnaire in 83 patients. The interval between the first and the second observation was 2.3 years [32]. In these patients there was a significant increase in the frequency of diabetes mellitus ( $p = 0.008$ ), non-pancreatic surgery ( $p = 0.016$ ) and comorbidities ( $p = 0.004$ ). The PCS-12 and the MCS-12 were not significantly different in comparison to the baseline evaluation. In particular, the PCS-12 score worsened in 17 (20.5%) patients, 44 (53.0%) had a stable PCS-12 score, and the remaining 22 (26.5%) improved their PCS-12 score. Regarding the mental score, 15 (18.1%) patients worsened, 52 (62.7%) had a stable MCS-12 score, and the remaining 16 (19.3%) improved their MCS-12 score. Only age at diagnosis was positively and significantly related to the change of the MCS-12 score. In conclusion, the information given by the quality-of-life assessment should be routinely included in the work-up of patients affected by chronic pancreatitis in order to select those patients with severely impaired physical and mental scores, and to plan an intensive program of medical and psychological follow-up.

## Pancreatic Neuroendocrine Tumors

Pancreatic Neuroendocrine Tumors (PNETs) are a heterogeneous

group of rare neoplasms, occurring in fewer than one in 100,000 people per year [33]. These tumors are relatively easy to palliate and we have recently demonstrated that radical surgery continues to play a central role in the therapeutic approach to PNETs [34] but medical treatment also has a precise role. Even if the survival rate is good, especially in those patients who have been resected, there is no extensive data available on the Quality of Life (QoL) in these patients as compared to the general population. In addition, the majority of studies published on this topic have, until now, examined a Scandinavian population [35-42], and it is well known that some differences in perceiving well-being exist among different cultures [43]. Finally, there are no studies specifically focusing on the localization site of neuroendocrine tumors, such as PNETs. We therefore carried out a 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 [44]. We evaluated the PROs of 51 consecutive patients having PNETs using the SF-12 questionnaire. Four additional questionnaires were also used in order to explore the psychological aspects of the disease, such as the 12 item General Health Questionnaire (GHQ-12), a questionnaire for non-psychotic psychiatric disorders, the State Trait Anxiety Inventory (STAI) Y-1 and Y-2 questionnaires for anxiety and the Beck Depression Inventory-II (BDI-II) questionnaire for depressive symptoms. We found that PNET patients had a PCS score not significantly different from the normative population, whereas the MCS score was significantly lower in patients as compared to the normative population. 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, the 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. We can conclude that 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. This information is of particular importance when we treat these patients, and we need to evaluate their well-being during and after specific treatment.

## Pancreatic Surgery

### Pancreatic head resection

Pancreatic Head Resection (PHR) is a therapy indicated for malignant diseases localized in the head of the pancreas, such as ductal carcinoma and intraductal papillary mucinous neoplasms, and also for tumors arising from the biliary tract and duodenum. Furthermore, patients with benign neoplasms of the pancreas, such as symptomatic serous cystadenoma, and those with mass-forming chronic pancreatitis in which pancreatic cancer cannot be ruled out preoperatively may also benefit from this surgery. This surgical approach continues to have non-negligible morbidity and mortality rates, especially in low-volume centers. Moreover, resection of the duodenum, the biliary tree, and the head of the pancreas might determine impairment of digestion and could also affect the QoL. In addition, in patients operated on for malignant disease, the QoL may also be impaired by recurrence of the disease and the need for adjuvant chemotherapy. The data on clinical outcomes and PROs in patients who underwent PHR for various reasons are based either on a large number of patients enrolled over a long period [45,46] or on a small number of cases enrolled over a short period [28,47,48]. The results of these studies are not conclusive; in patients enrolled over a

long period, the survival rate evaluated retrospectively suffers from changes in their care whereas studies carried out over a short period do not have definitive conclusions. Thus, we undertook a multicenter prospective study to evaluate, over a 24-month follow-up, the clinical outcomes and the PROs of patients who consecutively underwent PHR over a 1-year period in order to identify which parameters were probably linked to their QoL. One hundred and ninety-seven patients with benign and malignant pathologies who underwent PHR were studied [49]. A dedicated clinical form and the EORTC QLQ C-30 were administered at evaluation times (immediately before surgery and 6, 12, 18, and 24 months after discharge). One hundred and ninety-seven sex- and age-matched normative populations were also included in the study as a reference group. Of the 197 patients studied 164 (83.2%) had malignant disease and 33 had benign disease (16.8%). At initial evaluation, global health was significantly lower ( $p=0.001$ ) in the study population as compared to the normative population. At the end of the study, the QoL was not significantly different from the normative population, although the QoL of the 30 patients with benign disease was significantly better than that of the 72 patients with malignant disease.

Before PHR, the QoL was impaired in study patients as compared to the normative population whereas, following PHR, it significantly improved in the 24 months after surgery. This is further confirmation of the utility of patient well-being assessment in evaluating the results of a therapeutic approach.

### Total pancreatectomy

**Total pancreatectomy for chronic pancreatitis:** Intractable pain is one of the main indications for a surgical approach in chronic pancreatitis. When other treatment measures have failed, a total pancreatectomy is indicated, albeit diabetes is a complication. To treat the diabetes, islet autotransplantation may be a therapeutic option. The quality of life was evaluated in both the preoperative and the postoperative periods (mean follow-up 9 months) using the SF-12 questionnaire [50] in 33 patients who underwent an extensive pancreatectomy with islet autotransplantation for pancreatitis. In these patients, the authors also evaluated data pertaining to daily oral morphine equivalents. The preoperative quality of life scores showed a mean of 25 for the physical component and 32 for the mental health component. Postoperatively, the physical component score increased significantly at 6 months and at 12 months as did the mental health component score. The data of the SF-12 were also confirmed by the decreased number of morphine equivalents utilized by the patients. Thus, a total pancreatectomy for chronic pancreatitis associated with islet autotransplantation should be considered as an effective surgical option for intractable pain in chronic pancreatitis because the quality of life of patients improves and narcotic use decreases.

**Total pancreatectomy for other pancreatic disease:** Using the EORTC QLQ-C30, we studied the QoL of 20 patients who underwent a total pancreatectomy [51]. Of the 20 patients who underwent a total pancreatectomy, 7 were affected by ductal adenocarcinoma and the remaining 13 by other pancreatic diseases (8 intraductal papillary mucinous neoplasias, 2 well-differentiated neuroendocrine carcinomas, 2 pancreatic metastases from renal cell cancer and 1 chronic pancreatitis). The median follow-up period was 23 months. The pancreatic diabetes was well controlled and no patients died from complications secondary to severe hypoglycemia. The patients assumed pancreatic enzyme supplements, and weight loss was observed in 11 patients with a median weight loss of 15 kg. The results of the QoL can be summarized in this way: global health, physical role,

emotional role, cognitive role and social functioning had a high score, and these values represented a high quality-of-life status. Low scale scores were observed for symptoms and financial impact of the disease. As expected, we found that long-term survival was significantly better in patients affected by non-ductal adenocarcinoma than in those affected by ductal adenocarcinoma and that, in selected cases, a total pancreatectomy can be safely proposed to patients, keeping in mind that adequate medical support and appropriate education regarding the effects of the pancreatic state, should allow good control of endocrine and exocrine pancreatic insufficiency which are the major determinants of a good quality of life.

## Conclusive Remarks

The following conclusions can be drawn from the studies. It is necessary to choose a widely accepted questionnaire regarding the quality of life in order to render the various studies in different populations with pancreatic diseases comparable. At present, the SF-12 questionnaire seems to be the instrument of choice for assessing the quality of life in clinical practice. The QoL should be routinely assessed for evaluating our patients.

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