

ORIGINAL ARTICLE

Impact of Post-Operative Complications on Quality of Life After Pancreatectomy

Nsehniitoo Mbah, Russell E Brown, Charles R St. Hill, Matthew R Bower, Susan F Ellis, Charles R Scoggins, Kelly M McMasters, Robert CG Martin

Division of Surgical Oncology, Department of Surgery and James Graham Brown Cancer Center, University of Louisville School of Medicine. Louisville, KY, USA

ABSTRACT

Context Pancreatectomies for malignant and benign diseases are increasingly being performed worldwide. Recent studies, that have evaluated quality of life in pancreatectomy, have reported conflicting outcomes. **Objective** This study was undertaken to analyze the quality of life changes reported by patients with pancreatic cancer undergoing pancreatectomy. **Design** Post-hoc analysis was performed of a clinical trial examining the safety of intraoperative autotransfusion during oncologic resections. **Main outcome measures** Perioperative (90-day) complications were graded prospectively using a validated 5-point scale. Quality of life parameters were recorded prospectively by a single trained interviewer preoperatively, at the first post-operative outpatient visit, and at 6 weeks, 3 months, and 6 months follow-up using the EORTC QLQ-C30 and FACT-An instruments. **Results** Pancreatectomy for adenocarcinoma was performed in 34 patients with a median follow-up of 2 years (range: 1-1.5 years). Major (grade ≥ 3) complications occurred in 12 (35.3%) of patients. Early (<6 month) recurrence was noted in 2 patients (5.9%). Increased severity of fatigue, pain, dyspnea, and loss of appetite over baseline were noted at initial follow-up ($P < 0.05$); however, symptom scores normalized at 6-week follow-up, and remained stable at 6 months. No significant difference was noted in quality of life metrics between patients with or without major complications ($P > 0.11$). A significant ($P = 0.023$) decline in cognitive function vs. baseline was noted at 6-month follow-up after pancreatectomy. Using a repeated-measures generalized linear model, neither age, nor complication occurrence, nor adjuvant therapy, nor early recurrence accounted for this cognitive decline ($P > 0.10$). **Conclusion** Quality of life metrics tend to normalize to preoperative levels after pancreatectomy at 6 weeks post-operatively. The occurrence of major complications does not predict a decreased quality of life. The decrease in self-reported cognitive function at six months in this cohort merits further study.

INTRODUCTION

Through a greater expansion of training and better post-operative care, pancreatectomies for malignant and benign disease are increasingly being performed worldwide. Studies have shown that pancreatectomy is being performed in increasing numbers for various malignant and benign diseases of the pancreas and periampullary region [1]. However, despite the increasing number of pancreatectomies, there are very few studies exploring the quality of life (QoL) in patients undergoing pancreatectomy for benign and especially for malignant disease of the pancreas [2]. Thus more studies are needed for comparative behavior

of the QoL of patients operated on for pancreatic diseases [2].

Recent studies that have evaluated QoL in pancreatectomy have reported conflicting outcomes (Table 1). Huang *et al.* [1] demonstrated that pancreatectomy survivors have near-normal QoL scores. Patti *et al.* [3] and Fink *et al.* [4] found that pancreatectomy patients have mild gastrointestinal symptoms. McLeod *et al.* [5] demonstrated that there was no significant difference between pancreatectomy patients compared to cholecystectomy patients regarding QoL after surgery. Kokoska *et al.* [6] reported an improvement in QoL and survival for pancreatectomy patients compared to non-pancreatectomy patients. Schniewind *et al.* [7] on the other hand concluded that surgical techniques of resection and reconstruction did not affect QoL, but extended lymphadenectomy was associated with impairment in QoL. Despite these studies on QoL, in 2007 Pezzilli *et al.* [8] joined Schmier *et al.* [9] in suggesting the need for more prospective evaluations into the research of QoL. Similarly, only two of these studies [3, 7] have evaluated QoL both pre-operatively and postoperatively, which is a key protocol

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Key words Morbidity; Pancreatectomy; Quality of Life

Abbreviations EORTC: European Organisation for Research and Treatment of Cancer; FACT: Functional Assessment of Cancer Therapy

Correspondence Robert CG Martin II

Division of Surgical Oncology; Upper Gastrointestinal and Hepato-Pancreatico-Biliary Clinic; University of Louisville; 315 East Broadway - Rm 313; Louisville, KY 40202; USA

Phone: +1-502.629.3355; Fax: +1-502.629.3030

E-mail: robert.martin@louisville.edu

Table 1. Published studies on quality of life (QoL) after pancreatic resection.

Author	Year	No. of patients	QoL instrument	Time point analyzed	Outcome evaluated	Outcome
Huang <i>et al.</i> [1]	2000	192	Standard QoL questionnaire	≥6 months postoperative	Quality of life and outcomes after pancreaticoduodenectomy	Pancreaticoduodenectomy survivors have near normal QoL scores
Patti <i>et al.</i> [3]	1987	10	Computer analysis	Preoperative 10 days and 6 months postoperative	Gastric emptying and gastric function	Survivors had mild gastrointestinal symptoms
Fink <i>et al.</i> [4]	1988	12	Questionnaire	1-7 years postoperative	Gastric emptying and gastric function	Survivors had mild gastrointestinal symptoms
McLeod <i>et al.</i> [5]	1995	NR	Time trade-off technique, direct questioning of objectives, gastrointestinal quality of life index, sickness impact profile, physician global assessment, and Visick scale	Postoperative	Compared the quality of life, nutritional status, and gastrointestinal profiles of post-Whipple patients and post-cholecystectomy patients	No significant differences
Melvin <i>et al.</i> [17]	1998	45	Short Form-36 health survey (SF-36), and nutritional parameters	≥12 months postoperative	Compared pylorus preserved patients and 24 standard resection patients	Favorable outcome for pylorus preserved patient over standard resection
Kokoska <i>et al.</i> [6]	1998	781	Self-reported Karnofsky performance status as a QoL index	Yearly, or more, postoperative	The functional quality of life (QoL) of patients undergoing various treatments for pancreatic cancer using a nationwide, multi-institutional, non-referral patient population.	Resection for local pancreatic cancer had improved QoL and survival than the non-resected
Schmier <i>et al.</i> [9]	1999		Health related QoL	NR	Review on the state of literature on quality of life	More studies recommended base on the limited literature
Schniewind <i>et al.</i> [7]	2006	91	European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and a pancreatic cancer-specific module.	Preoperative and 24 months postoperative	examined quality of life (QoL) after classical partial pancreaticoduodenectomy (PPD) and pylorus-preserving pancreaticoduodenectomy (PPPD) in patients with adenocarcinoma of the pancreatic head, and also evaluated the influence of extended lymphadenectomy (ELA)	The surgical techniques of resection and reconstruction did not affect QoL, but extended lymphadenectomy was associated with an impairment in QoL

NR: not reported

requirement to ensure that a relationship to baseline QoL is possible. Thus the primary goal of this study was to analyze the QoL changes reported by patients with pancreatic cancer undergoing pancreatectomy.

METHODS

Study Design

A prospective evaluation of patients undergoing pancreatectomy for benign or malignant disease was recruited into this observational study of QoL from March 2006 to March 2008. QoL assessment was performed pre-operatively at the time of pre-admission testing, and then again at first follows visit (2-3 post-operative weeks), 6 weeks, 3 months and 6 months.

Patients

Thirty-four patients agreed to participate in this study. This included 26 men (76.5%) and 8 women (23.5%), with a median follow-up of 1.2 years (range: 0.3-2.9 years). Basic data also included the prevalence of comorbidities (n=15, 44.1%), length of stay (median 6 days; range: 5-19 days), and overall operative time

Table 2. Demographic data of the 34 pancreatectomy patients.

Demographics:	
Age, years; median (range)	65 (48-88)
Gender; male:female	26:8 (76.5%:23.5%)
Disease histology:	
- Pancreatic adenocarcinoma	23 (67.6%)
- Others	11 (32.4%)
Procedures:	
- Distal/subtotal pancreas	8 (23.5%)
- Whipple	26 (76.5%)
Post-operative course	
Patients with complication:	
- Overall number	10 (29.4%)
- Patients with major (grade 3 or more)	7 (20.6%)
Number of complication:	
- Overall complications	20
- Major (grade 3 or more)	12
Grade of complication:	
- 1-2	12 (60.0%)
- 3-4	7 (35.0%)
- 5	1 (5.0%)
Received adjuvant chemotherapy	8 (23.5%)
Early recurrence (<6 months)	2 (5.9%)

(median 200 minutes; range: 160-300 minutes). The pancreatic resection group was: Whipple 26 (76.5%), and distal/subtotal pancreas in 8 (23.5%). Adjuvant chemotherapy was administered in 8 patients (23.5%), most often in conjunction with radiotherapy (n=6). A total of 20 complications occurred in 10 patients. Major (grade 3-5) complications occurred in 7 patients. Early (<6 month) recurrence was noted in 2 patients (5.9%) (Tables 2 and 3). All eligible patients completed the questionnaire at the established time points apart from 3 patients (8.8%) that did not complete the 6 month QoL metric due to refusal for participation (n=2) or death (n=1).

Surgery

The decision to perform pancreatic resection was at the surgeon's discretion. The procedure was carried out following the protocol as described by Martin *et al.* [10].

Comorbidities were defined as significant cardiac (past coronary infraction), pulmonary, renal, or pancreatic dysfunction. Additional organ resection excluded cholecystectomy and included colon resection, gastric, or any other solid organ in combination with pancreatic resection. Therefore, cholecystectomy at the time of pancreatic resection was not considered as an additional organ.

Postoperative complications and the length of hospital stays were recorded and graded by using our standard classification scale of complications which has been reported previously [11]. For patients with more than one complication, comparisons of in-hospital and 90-day postoperative complications were evaluated by assigning the complication with the highest severity for each patient. Complications were defined by publishing criteria [10]. A postoperative death was defined as any patient death that occurred within 90 days postoperatively. Anemia was defined as the day of discharge hemoglobin. Anemia was categorized according to values <10 g/dL and ≥10 g/dL, based on the fact this is a more clinically relevant value in post pancreatectomy patients [12], and occurred in 17 (50.0%) patients.

Table 3. Complications.

Type of complications	Grade
Hematologic (n=3)	1, 2, 3
Pancreatic leak (n=1)	2
Ileus (n=2)	3, 3
Atelectasis/pneumonia (n=3)	2, 2, 3
Myocardial infarction (n=1)	5
Small bowel obstruction (n=1)	3
Liver abscess (n=1)	3
Abdominal fluid collection (n=2)	2, 3
Clostridium difficile (n=2)	2, 2
Wound (n=2)	2, 2
Acute renal failure (n=2)	2, 2

Study Procedures

This study was observational; no study-specific treatment was provided to these patients through this investigation. We used a pre-post test design to assess a patient's symptoms and concerns before and after pancreatic resection. Quality of life parameters were recorded prospectively by a single trained interviewer preoperatively, at the first post-operative outpatient visit, and at the 6-week, 3-month, and 6-month follow-up using the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30: <http://groups.eortc.be>) instrument and the Functional Assessment of Cancer Therapy FACT-Anemia (FACT-An: <http://www.facit.org>) [12]. The reason for the use of these QoL measures was based on our past experience with these instruments and the sensitivity of identifying clinically relevant QoL effects following abdominal surgery [13, 14].

Upon enrollment, the study coordinator, research assistant, or investigator completed the treatment history and demographics. At this time the patients completed a baseline questionnaire battery consisting of EORTC QLQ-C30 and FACT-An. Upon discharge after pancreatectomy, each patient completed the Functional Health and Symptom Index (FHSI-8) [14, 15], which includes questions that are applicable to the hospitalization (the data of this questionnaire are not presented in the present study). At the remaining time points, each patient completed the EORTC QLQ-C30 questionnaire. Clinical events (type of surgery, complications, and repeat hospitalization) were documented at the 4 follow-up time-points. These visits coincided with the scheduled follow-up appointments and did not burden the patient. If a patient missed an appointment or continued follow-up elsewhere, the follow-up questionnaire was mailed to the patient. For those patients that survived less than 6 months after surgery, QoL assessment was continued until the last follow-up visit by the patient. All questionnaires were completed in English.

The quality of the data obtained from each patient was evaluated when the patient completed all questionnaire forms at each visit. The study coordinator, research assistant, or investigator who had enrolled the patient reviewed each form immediately after receiving them to identify any missing data.

The quality of data entry is evaluated by the use of range checks on all variables and by double data entry for small portion (10%) of the data. This process allowed for the evaluation of the accuracy of the data entered by the primary data entry assistant.

QoL Instrument

The FACT-An is a validated instrument for assessing QoL in patient with anemia following pancreatectomy. This instrument is a 47-item self-report instrument that incorporates the 27 FACT-G and 20-item anemic subscale. The 27-item FACT-G measures QoL in 4 life domains: physical (7 items), social (7 items), emotional (6 items), and functional (7 items). The additional 20

items relate to anemia due to loss of blood. The patients circle on a scale of 0 (not at all) to 4 (very much) how true was each statement. The scores were adjusted so that lower scores indicated higher QoL on all the items.

The European organization for Research and Treatment of Cancer (EORTC) core questionnaire used in this investigation has been described in a previous publication [12].

ETHICS

The study protocol was approved by the institutional review board (IRB), and all patients were provided with written informed consent. The study protocol and the patient care conforms to the ethical guidelines of the "World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008. Only patients who wished to be consented and followed for QoL were included in this study and not all pancreatic resections at our institutions were included during this time interval.

STATISTICS

Post-hoc analysis of a clinical trial was performed examining the safety of intraoperative autotransfusion during oncologic resection. Frequencies, as well as median and range or mean and SD, are used as descriptive statistics. All P values are based on 2-sided tests. The generalized linear models by using JMP V4.1 (SAS, Inc., Cary, NC, USA) were applied in order to analyze data. The repeated-measure design was used when different time points were involved in the analysis.

RESULTS

EORTC QLQ-C30 Questionnaire

Using EORTC QLQ-C30, increased severity of fatigue (P=0.032), pain (P=0.043), dyspnea (P=0.022), and loss of appetite (P=0.012) over baseline (pre-operative) were noted at initial follow-up; however, symptom scores normalized at 6 weeks follow-up, and remained stable at 6 months. A significant (P=0.022) decline in cognitive function vs. baseline was noted at 6 months follow-up after pancreatectomy. This was demonstrated to be predominantly related to the patients who had started and were undergoing adjuvant chemotherapy. Using a repeated-measures generalized linear model, neither age, nor complication occurrence, nor adjuvant therapy, nor early recurrence accounted for this cognitive decline (P>0.101). Moreover, no significant difference was noted in all EORTC QLQ-C30 QoL metrics between patients with or without major complications (P>0.113) at any time points (Figure 1).

FACT Questionnaire

The behavior or FACT anemia scores in patients undergoing pancreatectomy with and without anemia are shown in Figure 2a. In the anemic group the FACT-physical score (GP) showed a significant decrease in QoL at the first postoperative visit (P=0.023), with a return to baseline at 6 weeks and stability at 6 months when compared with the patients' baseline QoL. For the anemic group, QoL was decreased compared to baseline at the first postoperative visit (P=0.038) and further declined at 6 weeks with a return to baseline at 3 months and improvement at 6 months (Figure 2b). A high score in the FACT-social category (GS) denotes an increase in QoL parameters. For the anemic group, there was a decline in QoL at the 1st post operative visit, 6 weeks and 3 months with a return to baseline at 6 months. For the non-anemic group, at 1st post operative visit there was not an effect. However, there was a decline in QoL at 6 weeks, 3 months and a more dramatic (P=0.031) decrease at 6 months (Figure 2c). For FACT-emotional (GE), there was improvement in QoL for the anemic groups at 1st postoperative visit, 6 weeks, and 3 months with a slight decline at 6 months postoperative periods. However, the QoL at 6 months postoperative period was better than baseline. For the non-anemic group, there was little decline on the QoL at 1st postoperative visit, a significant decline at 6 weeks (P=0.027) but with a return to better QoL values at 3 and 6 months postoperative periods (Figure 2d). For the FACT-function QoL effect (GF), a high score denotes an increase in QoL parameters. Baseline values for QoL compared to first postoperative visit for the anemic group show a decline at both the 6 week and 3 months postoperative period, with a return to baseline at 6 months. For the non-anemic group, there was significant decline in QoL at the first postoperative visit, the 6 weeks, 3 months and 6 months follow-ups. (Figure 2e).

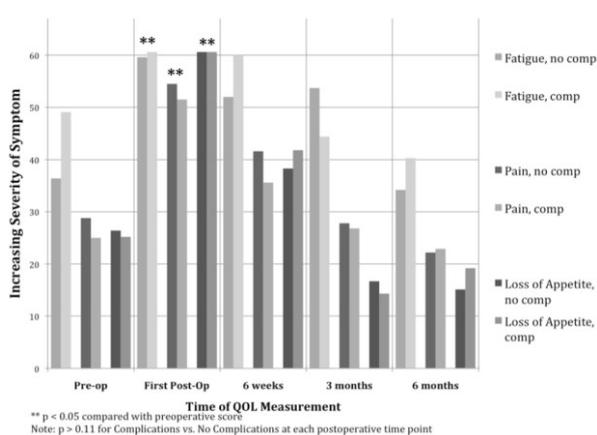


Figure 1. QoL over time for patients after pancreatectomy. Comparison of patients with or without major complications. Mean values are shown.

* P<0.05 compared with preoperative score. Note: P>0.113 for complications vs. no complications at each postoperative time point.

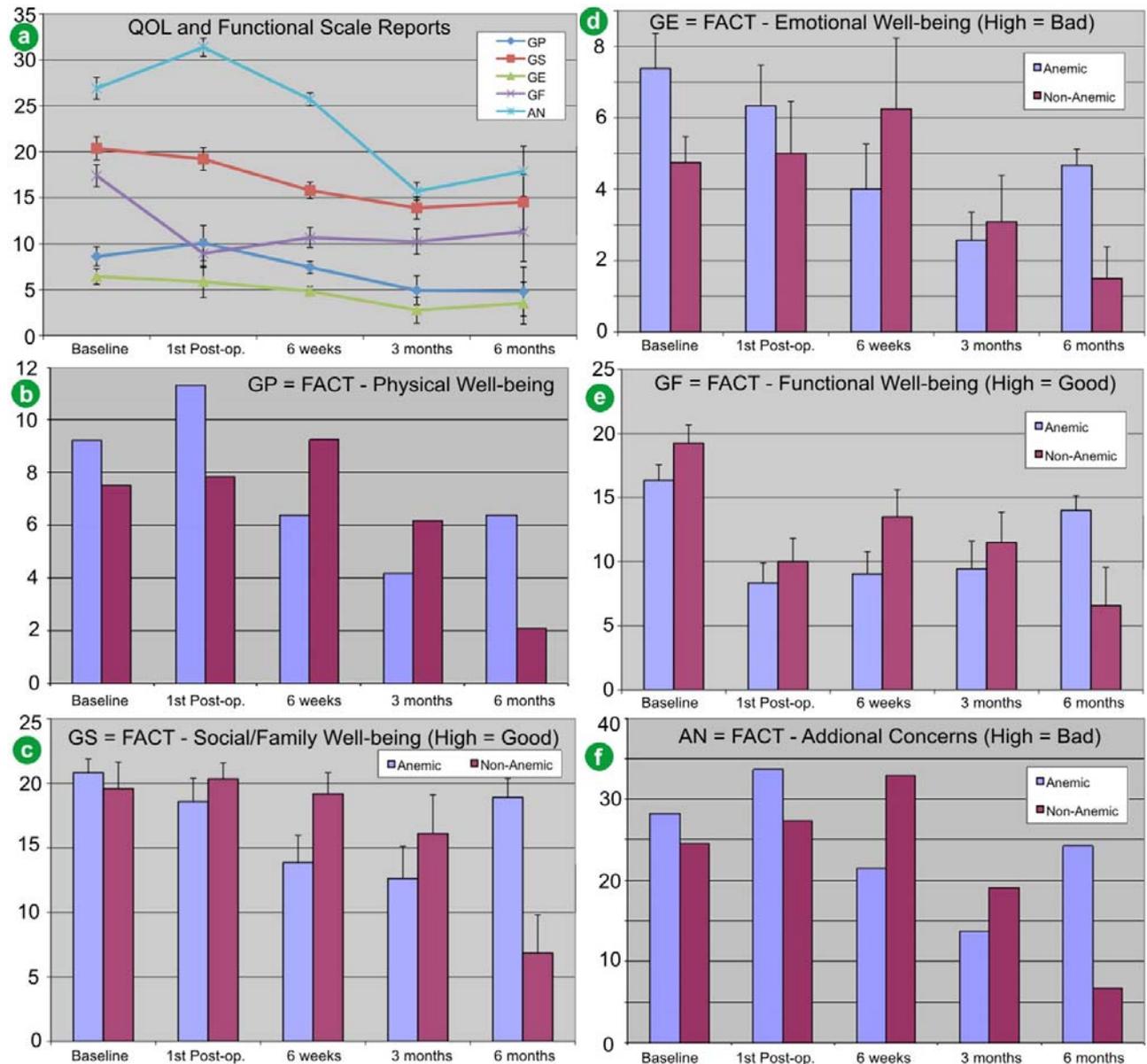


Figure 2. FACT. Anemia scores in patients undergoing pancreatectomy with and without anemia (mean±SD). **a.** QoL and functional scale reports in the overall population. **b.** Physical well-being (GP: high=bad). **c.** Social/family sell-being. (GS: high=good). **d.** Emotional well-being (GE: high=bad). **e.** Functional well-being (GF: high=good). **f.** Additional concerns (AN: high=bad).

For FACT-additional (AN), in the anemic group, there was a significant decline in QoL at the 1st post operative visit with a return to baseline at 6 weeks and throughout the 6-month follow-up period. For the non-anemic group, there was a significant decline in QoL at 6 weeks post operative visit (P=0.023) with a return to baseline at 3 and improvement at 6 months (Figure 2f).

DISCUSSION

Despite the increasing number of pancreatectomies being performed, there is still the general impression that very little is known about the quality of life of a patient after this procedure [2]. Therefore, it is imperative to analyze the QoL changes reported by patients with pancreatic cancer undergoing pancreatectomy. Such findings may provide insight to adjuvant therapies still considered controversial in the treatment of pancreatic cancer.

In this prospective, longitudinal QoL study, we reported 34 pancreatic resection cases in our center. All patients completed this same survey preoperatively and then at four postoperative time points, allowing for measurement of changes in QoL over 6 months. Although other studies have reported QoL outcomes, this has been done in comparison with other procedures such as cholecystectomy [1, 5], gastric emptying [3, 4], or standard procedure *versus* pylorus-preserving procedures.

This report focuses on the QoL changes after pancreatic surgery. Eight major (grade ≥3) complications occurred in 7 patients; however, no significant difference was noted in QoL metrics between patients with or without complication. Increased severity of fatigue, pain, dyspnea, and loss of appetite compared to baseline was noted at initial follow-up; however, symptom scores normalized at 6

weeks follow-up, and remained stable at 6 months. A significant decline in cognitive function *vs.* baseline was noted at 6 months of follow-up after pancreatectomy; neither age, complication, adjuvant therapy, nor early recurrence explained this cognitive decline.

Although little has been published on QoL after pancreatectomy, some comparisons can be made between our report and those from the existing literature. Similar to most of the reports (Table 1), there is little change, or usually a return to a normal QoL, following pancreatectomy. In addition, this report demonstrated that symptoms scores remained stable at 6 months. This report compared with the report of Melvin *et al.* in their review of 45 pancreatectomy survivals showed some differences in regard to cognitive function. They used SF-36 to compare pylorus-preserving pancreatectomy and standard resection to a normal standard of age-matched control subjects from the U.S. population [1]. After analysis, they concluded that there were no differences in mental health between groups. In our study, using EORTC QLQ-30 with a postoperative time of 6 months, a significant decline in cognitive function *vs.* baseline was noted at 6 months follow-up after pancreatectomy. With the use of a repeated-measures generalized linear model, neither age, complication, adjuvant therapy, nor early recurrence explained this cognitive decline. This difference may have been because of the QoL instrument used, variables in the studies or most importantly the time point analyzed; in our case 6 months *vs.* 12 months for Melvin *et al.* [16]. Most importantly, the two studies analyzed different aspects in the QoL debate.

With pancreatectomy gaining acceptance and being increasingly performed in the treatment of pancreatic cancer, more consistent QoL surgical standards need to be established and more comparative studies need to be conducted. With pancreatectomy survivors in multimodality care and/on either adjuvant therapy or neoadjuvant therapy or both therapies, maximizing disease-free survival and/or overall survival limiting permanent QoL defects is imperative. Furthermore, minimizing the time for chemotherapy interruption is also important. This study, unlike the few other studies on pancreatectomy regarding QoL, shows the return to normalcy at 6 weeks and stability at 6 months. This could be helpful in determining the time to resume chemotherapy, thus accepting the concept of “time to resumption of chemotherapy” or “time to the induction of postoperative chemotherapy” as 8 weeks after pancreatic resection. This concept is important for collaborating as well as for educating other oncology specialties in the benefit as well as the limited QoL effect that pancreatic resection induces. Setting this time goal or, more importantly, this surgical standard in recovery is yet another potential quality measure that pancreaticoduodenal surgeons should consider as we proceed in overall patient outcome.

The limitation of this study is related to the small sample size of patients. A possibility exists that a larger sample size may create more variance in these results, but because of the close range of scores, this variance would probably be small. Even with this limitation, this study represents a solid foundation in which additional quality standards can be set as well as strived for in all pancreatic resection.

In conclusion, QoL metrics tend to normalize to preoperative levels after pancreatectomy. The occurrence of major complications does not predict a decrease QoL. The decrease in self-reported cognitive function at six months in this cohort merits further study.

Conflict of interest The authors have no potential conflict of interest

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