

# Do Complications After Pancreatoduodenectomy Have an Impact on Long-Term Quality of Life and Functional Outcomes?

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**Objective:** Our aim was to assess whether complications after pancreatoduodenectomy (PD) impact long-term quality of life (QoL) and functional outcomes.

**Background:** There is an increasing number of long-term post-PD survivors, but few studies have evaluated long-term QoL outcomes.

**Methods:** The EORTC QLQ-C30 and QLQ-PAN26 questionnaires were administered to patients who survived >5 years post-PD. Clinical relevance (CR) was scored as small (5–10), moderate (10–20), or large (>20). Patients were stratified based on whether they experienced a complication during the index hospitalization.

**Results:** Of 305 patients >5 years post-PD survivors, with valid contact information, 248 completed the questionnaires, and 231 had complication data available. Twenty-nine percent of patients experienced a complication, of which 17 (7.4%) were grade 1, 27 (11.7%) were grade 2, and 25 (10.8%) were grade 3. Global health status and functional domain scores were similar between both groups. Patients experiencing complications reported lower fatigue (21.4 vs 28.1,  $P < 0.05$ , CR small) and diarrhea (15.9 vs 23.1,  $P < 0.05$ , CR small) symptom scores when compared to patients without complications. Patients experiencing complications also reported lower pancreatic pain (38.2 vs 43.4,  $P < 0.05$ , CR small) and altered bowel habits (30.1 vs 40.7,  $P < 0.01$ , CR moderate) symptom scores. There was a lower prevalence of worrying (36.2% vs 60.5%,  $P < 0.05$ ) and bloating (42.0% vs 56.2%,  $P < 0.05$ ) among PD survivors with complications.

**Conclusions:** Post-PD complication rates were not associated with long-term global QoL or functionality, and may be associated with less severe pancreas-specific symptoms.

**Keywords:** functional outcomes, pancreatoduodenectomy, quality of life

## INTRODUCTION

Improvements in surgical technique and perioperative care for pancreatoduodenectomy (PD) have led to the improvement in perioperative mortality rates in recent years.<sup>1–6</sup> However, PD continues to be associated with high rates of complications driven primarily by persistently high pancreatic fistula rates.<sup>7</sup> Several studies have evaluated how PD affects quality of life

(QoL) using patient-reported outcomes tools.<sup>8–18</sup> However, few of these have assessed the impact of postoperative complications on long-term post-PD QoL.

The studies that have evaluated how complications affect QoL did so with short-term (<1 year) or medium-term (1–5 years) follow-up, and have reported conflicting results. Some showed complications to be associated with significantly worse QoL,<sup>19–22</sup> whereas others did not observe any significant association between post-PD complications and QoL.<sup>23–27</sup> However, understanding how long-term QoL is impacted by complications is increasingly important as we are increasingly performing PD for premalignant lesions and as such, have a higher proportion of long-term PD survivors.<sup>2,4,28</sup> Improving our understanding of how post-PD complications affect long-term QoL may better inform shared decision-making, particularly in patients considering PD for more discretionary indications.

As such, we aimed to evaluate how experiencing postoperative complications impact long-term (>5 years) QoL in a large cohort of patients who have undergone PD using 2 externally validated patient-reported outcomes tools for measuring health-related QoL outcomes, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC-PAN26 questionnaires.<sup>29,30</sup> We hypothesize that similar to intermediate-term follow-up,<sup>27</sup> post-PD complications do not affect QoL at long-term follow-up.

## METHODS

This study was approved by the Mass General Brigham Institutional Review Board (protocol ID: 2014P001951). We

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identified all patients who underwent PD at Massachusetts General Hospital between 1998 and 2011.

### Study Cohort

The inclusion criteria were patients alive at least 5 years after PD, irrespective of whether the operation was for benign or malignant indications. Patients were excluded if they underwent PD for chronic pancreatitis, a subsequent completion pancreatectomy, or did not have valid contact information. The electronic health record was used to obtain preoperative demographic and perioperative clinical variables. Daily progress notes and discharge summaries were used to identify postoperative complications. Complications were graded according to the Clavien-Dindo classification and classified as minor (grades 1 and 2) or major (grade 3 or higher).<sup>31</sup> Patients were classified by the most severe complication grade they experienced. Patients were stratified based on whether they experienced postoperative complications during the index hospitalization.

### Study Procedure

To minimize nonresponse bias, the principal surgeon who performed the PD contacted patients to initiate study participation and acquire updated mailing information. Five waves of phone calls were made to obtain survey responses. Once verbal agreement to participate in the study was obtained, a packet containing the following items was mailed to patients: recruitment letter, consent for study participation, demographic sheet, EORTC QLQ-C30 questionnaire, the EORTC QLQ PAN26 questionnaire, and a mail-back envelope to return these items upon completion. The demographic fact sheet consisted of a single-page, 10-question survey that aimed to elucidate demographic and socioeconomic details known to potentially influence QoL. It was supplemented with pancreatectomy-relevant questions on diabetes control, need for pancreatic enzyme replacement, and weight changes. The EORTC QLQ-C30 is a well-validated 30-item instrument for evaluating QoL in patients with cancer that contains 9 multi-item scales and 6 single-item scales.<sup>30</sup> The multi-item scales include 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), and a global health status/QoL scale. The 6 single-item scales assess problems commonly reported by cancer patients (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties). The EORTC QLQ PAN26 is an instrument for measuring health-related QoL in patients with pancreatic cancer that has been validated in patients undergoing pancreatic resection.<sup>29</sup> The questionnaire has a 1-week recall period for 26 4-level Likert items comprising 7 multi-item scales (pancreatic pain, digestive symptoms, altered bowel habits, hepatic functioning, body image, health care satisfaction, and sexual dysfunction) and 10 single-item scales (bloating, taste, indigestion, flatulence, low weight, arm/leg weakness, dry mouth, side effects, future health worries, and limits in planning activities). Two independent coders digitalized the responses from the returned questionnaires, and discrepancies were reviewed and corrected until perfect agreement was achieved.

### European Organization for Research and Treatment of Cancer Instrument Internal Validation

Each EORTC subscale underwent linear transformation to provide a score range of 0–100 to standardize the raw score. High scores on the global health status/QoL and functional scales indicate improved QoL and functioning, whereas high scores on the symptoms scales indicate more severe symptoms. In accordance with the EORTC scoring manual, missing data were imputed by aggregating the average score of the items from the same scale as

long as at least half of the items from the scale were answered, and scales with more than half of the questions missing were excluded from the analysis. Previous psychometric assessment of the EORTC instruments within our PD cohort has shown high levels of internal validity, reliability, and responsiveness.<sup>32,33</sup>

### Statistical Analyses

Statistical analysis was performed using STATA software, version 17 (StataCorp, College Station, TX). Stratified data was compared using the Kruskal–Wallis or *t* tests for continuous variables and the  $\chi^2$  test for categorical variables. Statistical significance was accepted at the  $P \leq 0.05$  level. The clinical significance of the score differences on each scale was determined using a validated minimally important clinical difference scale of the EORTC instrument with clinical relevance (CR) interpretation as follows: <5, “no change”; 5–10, “small”; 10–20, “moderate”; and >20, “large.”<sup>34</sup> Overall significance was defined as achieving both statistical and clinical significance.

## RESULTS

### Patient Characteristics

We identified 1266 patients who underwent PD for benign or malignant indications between 1998 and 2011, of whom 374 were still alive. We successfully contacted and mailed packets to 305 patients with valid contact information, receiving 248 completed responses. The response rate is 81% when the denominator is the 305 patients with valid contact information, and 66% when the denominator is all 374 5-years survivors. We had data on index hospitalization postoperative complications in 231 responders, of which 162 (70.1%) were grade 0, 17 (7.4%) were grade 1, 27 (11.7%) were grade 2, and 25 (10.8%) were grade 3 Clavien-Dindo grade complications (Fig. 1). There were no grade 4 complications. Nonresponders were associated with a significantly greater percentage of complications (59.8% vs 34.7%,  $P < 0.001$ ), however, the rates of severe complications in both groups were similar (15.0% vs 10.1%,  $P = 0.165$ ). When comparing the demographic and clinical characteristics of patients who experienced complications and those who did not, there were no significant differences in sex or indication for surgery. However, patients with complications had a significantly higher median age at the time of surgery (64 vs 61 years,  $P < 0.015$ ), a longer median length of initial hospital stay (8 vs 7 days,  $P < 0.001$ ), and higher readmission rates (31.9% vs 13.6%,  $P < 0.001$ ) than patients without complications (Table 1).

The median follow-up time from operation to questionnaire completion was 8.9 years (range 5.3–14.3). Among the 231 responders with postoperative complication data, 124 (53.7%) were female, 147 (63.6%) had a benign indication for surgery, and the median preoperative BMI was 25.1 kg/m<sup>2</sup> (range 16.3–43.7). Pathological diagnoses are shown in Supplemental Table 1, see <http://links.lww.com/AOSO/A312>. At the time of questionnaire completion, the majority of patients were married (69.6%), had children (83.8%), and were retired (61.1%). Overall, 39.6% of patients received chemotherapy, while 32.7% received radiation therapy. Patients with no complications did not significantly differ from patients with complications with regards to receipt of chemotherapy (44.0% vs 26.9%,  $P = 0.125$ ) or radiation therapy (37.3% vs 19.23%,  $P = 0.90$ ).

### Impact of Postoperative Complications on Metabolic Profile After Pancreatic Resection

Patients who experienced complications had a significantly higher median change in BMI compared to those who did not (+0.66 vs -1.34,  $P = 0.0411$ ). There were no significant differences between groups percentage of patients who reported

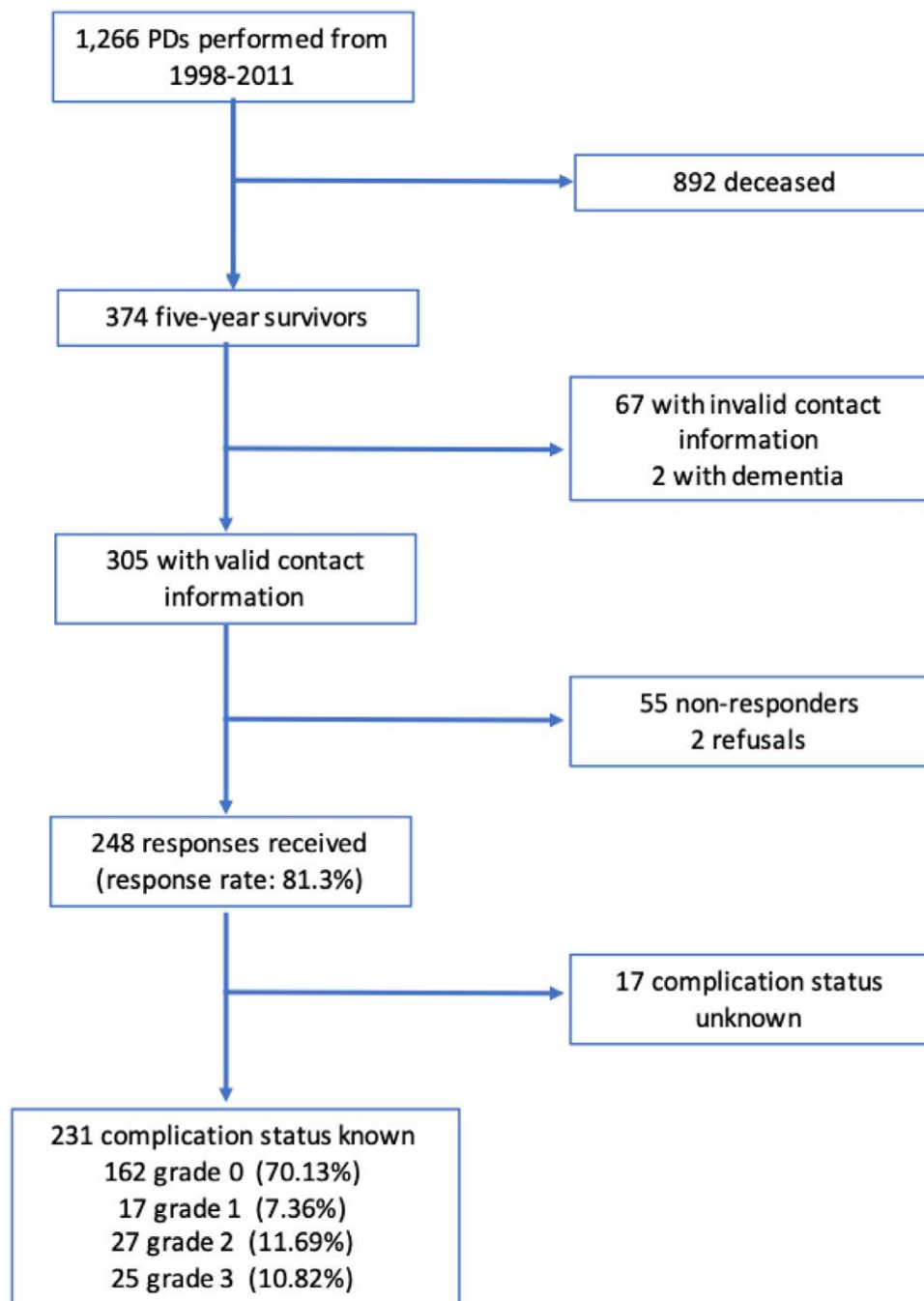


FIGURE 1. Study flow diagram of patients selected for the long-term health-related quality of life study.

taking pancreatic enzymes (46.9% vs 51.2%,  $P = 0.526$ ), antacid medications (58.1% vs 55.1%,  $P = 0.694$ ), or who developed new-onset diabetes after PD (12.7% vs 10.1%,  $P = 0.579$ ).

#### Impact of Postoperative Complications on QoL After Pancreatic Resection

When examining the EORTC QLQ-C30 responses, there were no significant differences in scores on the global health status/QoL or any of the functional scales (physical, role, cognitive, emotional, and social functioning) between patients with and without complications (Fig. 2). However, patients with complications reported better fatigue (21.4 vs 28.2,  $P = 0.0164$ , CR small) and diarrhea scores (15.9 vs 23.1, CR small) on the symptom scales (Fig. 3). Patients experiencing complications also felt

less worried about their future (44.9% vs 60.5%,  $P = 0.029$ ) (Table 2). The groups did not significantly differ in any other symptom (nausea/vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, and diarrhea) or nonsymptom (financial difficulty, feeling tense, feeling irritable, and feeling depressed) scores.

Among the EORTC QLQ-PAN26, patients who experienced complications had significantly better pancreatic pain (38.2 vs 43.4, CR small,  $P = 0.0227$ ) and alterations in bowel habits scores (30.1 vs 40.7, CR small,  $P = 0.0093$ ) on the symptom domain scales (Fig. 4). Patients who had complications also reported better bloating scores (42.0% vs 56.2%,  $P = 0.049$ ) compared to patients without complications (Table 2). There were no other differences between groups on any of the other PAN26 domains (digestive symptoms, hepatic pain, body image,

**TABLE 1.**  
**Characteristics of 5-Year Pancreatoduodenectomy Survivors Based on Postoperative Complications**

	No Complications	Complications	P
N (%)	162 (70.1%)	69 (29.9%)	
Median follow-up, years (IQR)	8.9 (6.9, 11.4)	9.06 (7.2, 10.6)	0.97
Median age at surgery, years (IQR)	61.0 (54.0, 68.0)	64.0 (57.0, 70.0)	0.015*
Females	90 (55.6%)	34 (49.3%)	0.38
Marital status			
Single/never married	10 (6.3%)	2 (3.1%)	0.11
Married	116 (73.0%)	40 (61.5%)	
Widowed	19 (11.9%)	15 (23.1%)	
Separated/divorced	14 (8.8%)	8 (12.3%)	
Race/ethnicity			
Asian	3 (1.9%)	2 (3.3%)	0.22
Black	1 (0.6%)	2 (3.3%)	
White	150 (96.8%)	55 (91.7%)	
Education level			
High school graduate	26 (16.4%)	10 (15.4%)	0.48
College or technical/vocational school	37 (23.3%)	16 (24.6%)	
College Graduate	47 (29.6%)	15 (23.1%)	
Postgraduate or professional degree	46 (28.9%)	20 (30.8%)	
Having children	131 (82.9%)	55 (85.9%)	0.58
Present employment status			
Employed	55 (34.8%)	14 (22.2%)	0.069
Retired	90 (57.0%)	45 (71.4%)	
Not employed	2 (1.3%)	3 (4.8%)	
Disabled	10 (6.3%)	1 (1.6%)	
Median BMI at time of surgery, kg/m <sup>2</sup> (IQR)	25.2 (22.0, 29.9)	24.8 (21.7, 29.1)	0.72
Malignant pathology	57 (35.2%)	27 (39.1%)	0.57
Readmitted to hospital	22 (13.6%)	22 (31.9%)	0.001
Hospital length of stay, median (IQR)	7.0 (6.0, 8.0)	8.0 (7.0, 13.0)	<0.001

\*Indicates statistical significance.  
 IQR indicates interquartile range.

satisfaction with health care, or sexual dissatisfaction) or non-domain scales (indigestion, flatulence, feelings that weight was too low, arm/leg weakness, dry mouth, side effects, future health worries, or limitations in planning activities).

### Subanalysis by Complication Severity

To better understand how complication severity affected long-term QoL, we performed a subanalysis where we stratified patients as experiencing no (grade 0), minor (grade 1 or 2), or major (grade 3) complications. There were 25 (10.8%) patients with major complications, 44 (19.0%) patients with minor complications, and 162 (70.1%) patients with no complications. More severe complications were associated with higher readmission rates, with 36.0% of patients experiencing major complications being readmitted compared to 29.5% of patients with minor complications and 13.6% of patients with no complications ( $P = 0.004$ ). Patients who experienced more severe complications also had significantly longer lengths of initial hospital stay. The median (IQR) duration of initial hospital stay was 12 (7–21) for major complications compared to 7 (6–11) for minor complications and 7 (6–8) for no complications ( $P = 0.0001$ ).

When this subanalysis was performed on the EORTC data, more severe complications were associated with better fatigue scores on the EORTC QLQ-C30 questionnaire. The average fatigue score in patients with major complications was 17.13 compared to 23.81 for patients with minor complications and 28.16 in patients with no complications ( $P = 0.0479$ ). On the EORTC QLQ-PAN26 questionnaire, patients with more severe complications had better scores on the altered bowel habits scales, with patients experiencing major complications having an average score of 25.3 compared to patients with minor complications and no complications having average scores of 32.9 and 40.7, respectively ( $P = 0.0396$ ).

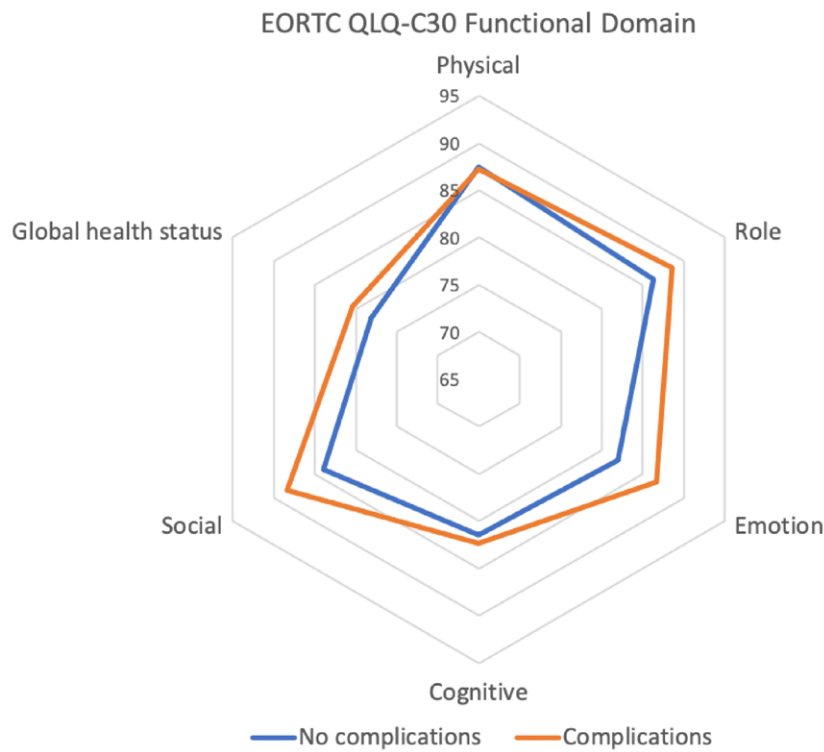
### Subanalysis by Benign Versus Malignant Disease

Since patients undergoing resection of benign versus malignant pancreatic disease may have different QoL measurements at baseline, we separately analyzed outcomes in patients with benign and malignant disease (Supplemental Table 2, see <http://links.lww.com/AOSO/A312>). On EORTC QLQ-C30, patients with malignant disease experiencing complications reported worse financial difficulty (24.0 vs 9.1, CR moderate,  $P = 0.0048$ ) than those who did not experience complications, whereas patients with benign disease who experienced complications reported improved global health status/QoL (82.9 vs 77.3, CR small,  $P = 0.042$ ), social functioning (90.7 vs 83.3, CR small,  $P = 0.034$ ), fatigue (19.0 vs 28.7, CR small,  $P = 0.0062$ ), dyspnea (8.13 vs 16.5, CR small,  $P = 0.025$ ), appetite loss (3.3 vs 9.4, CR small,  $P = 0.022$ ), and diarrhea (13.3 vs 23.3, CR moderate,  $P = 0.013$ ) in comparison to those who did not experience complications. On EORTC QLQ-PAN26, patients with malignant disease experiencing complications reported less bloating (29.6% vs 57.9%,  $P = 0.016$ ) than those who did not experience complications, while patients with benign disease who experienced complications reported improved bowel habits (23.0 vs 39.5, CR moderate,  $P = 0.0013$ ) and less worries about weight being too low (11.9% vs 28.6%,  $P = 0.032$ ) or having to limit planning activities in advance (16.7% vs 36.2%,  $P = 0.020$ ).

## DISCUSSION

The widespread use of cross-sectional imaging has led to increased detection of incidental pancreatic lesions, and in turn, leading to the increased utilization of PD for resection.<sup>35</sup> While these lesions are considered potentially malignant, the vast majority of patients who undergo resection are eventually found to have nonmalignant lesions.<sup>2,28,35–37</sup> As such, there is an increasing proportion of long-term PD survivors. Unfortunately,





EORTC QLQ-C30 Functional Domain	No complications		Complications		p-value	Clinical relevance
	Mean	SD	Mean	SD		
Physical	87.5	16.4	87.3	17.5	.47	No change
Role	86.3	20.2	88.6	20.21	.22	No change
Emotion	82	17.9	86.7	16.7	.037	No change
Cognitive	81.4	21.4	82.3	21.5	.39	No change
Social	84	22.5	88.4	22.3	.085	No change
Global health status	78.1	18	80.4	18.9	.19	No change

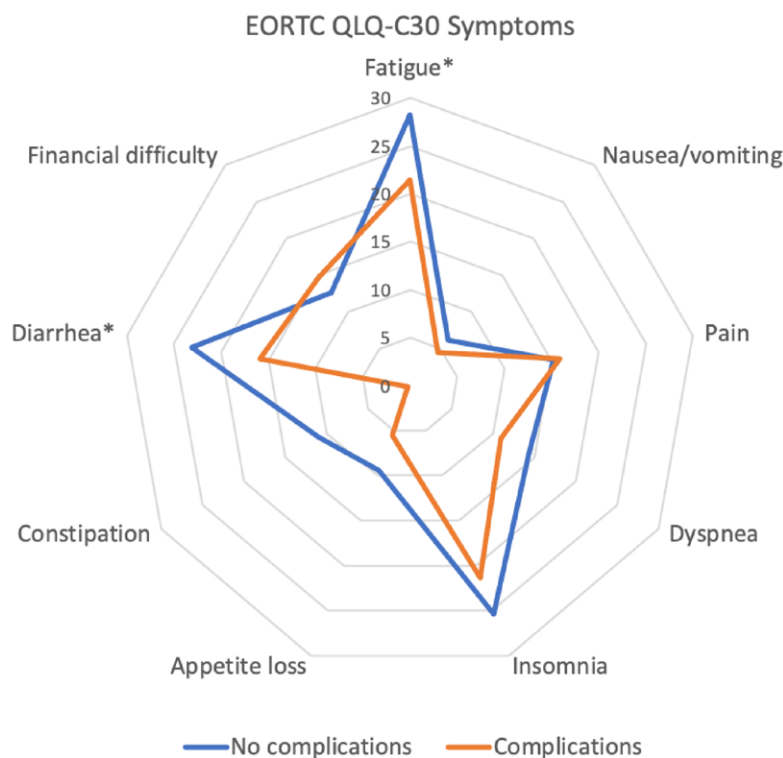
**FIGURE 2.** Comparison of the EORTC QLQ-C30 functional domain scales between 5-year pancreaticoduodenectomy survivors with and without postoperative complications. \*Indicates statistical significance. CR indicates clinical relevance.

PD remains associated with significant morbidity despite improvements in perioperative care.<sup>7</sup> In order for patients with discretionary pathology to make informed clinical decisions, it is crucial that they understand how complications may affect their long-term QoL. Multiple studies have assessed how experiencing postoperative complications after PD affects short-term (<1 year) and medium-term (1–5 year) QoL.<sup>19–27</sup> To our knowledge, none have evaluated how complications may affect long-term (>5 years) QoL, which is particularly important given the increasing number of long-term post-PD survivors. In this study, we assessed how index hospitalization complications affect QoL in 231 patients surviving at least 5 years after PD (median follow-up 9.1 years) using previous responses we obtained on the EORTC QLQ-C30 and EORTC QLQ-PAN26 instruments.<sup>32,33</sup> We observed that patients who experienced postoperative complications had similar long-term global QoL and functioning compared to patients without complications, while also reporting lower fatigue, diarrhea, pancreatic pain, altered bowel habits, worrying, and bloating.

Our work adds to the growing literature of evaluating how complications affect QoL after pancreatic resection. Some studies have shown complications not to significantly affect

QoL,<sup>23–27,38</sup> whereas others have shown complications to be associated with significantly worse QoL.<sup>19–22</sup> The study with the longest follow-up had a median follow-up time of 28 months and observed a limited effect of postoperative procedure-related complications on long-term QoL.<sup>27</sup> However, this study used the SF-36 questionnaire to assess QoL rather than the pancreas-specific EORTC QLQ-PAN26 instrument. We previously observed that the use of a pancreas-specific questionnaire may capture information missed by a general QoL instrument.<sup>33</sup> The few studies that actually did utilize pancreas-specific instruments to assess how complications affect QoL after pancreatic resection have conflicting results.<sup>21–24</sup> Our study is unique in that it utilized pancreas-specific instruments to assess postpancreatectomy QoL in patients with long-term follow-up (>5 years from PD, median follow-up of 9.1 years) and found that global QoL and functional scores were no different between patients with and without postoperative complications.

In a cohort of 73 patients, Eshuis et al<sup>22</sup> observed worse outcomes on multiple EORTC QLQ-PAN26 (digestive symptoms, hepatic symptoms, and health care satisfaction) and EORTC QLQ-C30 (global health status, physical functioning, role functioning, cognitive functioning, fatigue, nausea/vomiting, and



EORTC QLQ-C30 Symptom Domain	No complications		Complications		p-value	Clinical relevance
	Mean	SD	Mean	SD		
Fatigue	28.2	22.0	21.4	20.4	.016	Small
Nausea/vomiting	6.2	12.2	4.5	10.3	.16	No change
Pain	15.2	20.1	15.9	21.8	.41	No change
Dyspnea	14.3	23.6	11.0	20.4	.16	No change
Insomnia	25.4	27.9	21.4	25.1	.16	No change
Appetite loss	9.4	18.8	5.5	17.0	.069	No change
Constipation	10.9	21.1	0.3	0.9	.031	No change
Diarrhea	23.1	25.4	15.9	23.7	.026	Small
Financial difficulty	12.7	23.4	14.7	25.6	.29	No change

**FIGURE 3.** Comparison of the EORTC QLQ-C30 symptom domain scales between 5-year pancreaticoduodenectomy survivors with and without postoperative complications. \*Indicates statistical significance. CR indicates clinical relevance.

dyspnea) domains 2 weeks after surgery in patients with delayed gastric emptying. Similarly, Eaton et al<sup>21</sup> observed severe pancreatic complications to be associated with clinically important worsening in multiple EORTC QLQ-PAN26 (body image, sexual dysfunction) and EORTC QLQ-C30 (physical functioning, role functioning, emotional functioning, social functioning, dyspnea, constipation, and financial difficulties) domains 60 days postresection in a cohort of 260 patients. Although both of these studies contrast our results, a recent systematic review concluded that although QoL after pancreatic resection may decline in the early postoperative period, it tends to gradually return to baseline and remain stable over time.<sup>39</sup> This finding is congruent with our study that demonstrated that global QoL scores and symptom scales were no worse in the long-term, even after minor and major postoperative complications.

Johansen et al<sup>23</sup> performed a retrospective cohort study of 245 patients who underwent PD and observed no significant

differences between patients who experienced severe postoperative complications and those who did not on any EORTC QLQ-C30 or QLQ-PAN26 domains. Our study is different from theirs in several ways. First, the majority (64%) of our patients underwent resection for benign indications, whereas only a minority (11%) of their patients underwent a resection for benign tumors. As such, their latest time point for assessing QoL was 12 months after PD. In contrast, we assessed QoL at least 5 years after PD which is more pertinent to patients undergoing the procedure for premalignant indications. Moreover, 31% of patients undergoing PD may experience other late-onset complications (appearing >90 days after surgery) unrelated to cancer recurrence, such as incisional hernia, cholangitis, pancreatitis, small bowel obstruction, and peptic ulcer disease.<sup>40</sup> Some of these complications, such as exocrine and endocrine pancreatic insufficiency, are known to affect QoL in patients after pancreatic resection.<sup>41,42</sup> Indeed, we previously observed

**TABLE 2.**  
**Comparison of the EORTC QLQ-C30 and EORTC QLQ-PAN26 Nondomain Scales Between 5-Year Pancreatoduodenectomy Survivors With and Without Postoperative Complications**

	No Complications	Complications	P
EORTC QLQ-C30			
Felt tense	43.8%	36.2%	0.284
Worried	60.5%	36.2%	0.029*
Felt irritable	43.2%	36.2%	0.324
Felt depressed	42.0%	33.3%	0.219
EORTC QLQ-Pan26			
Bloated	56.2%	42.0%	0.049*
Food and drink taste different than usual	20.4%	18.8%	0.79
Indigestion	55.6%	47.8%	0.281
Flatulence	77.2%	65.2%	0.059
Worried about weight being too low	31.5%	24.6%	0.296
Felt weak in arms and legs	48.8%	39.1%	0.179
Dry mouth	45.1%	46.4%	0.854
Troubled with side effects from treatment	64.8%	60.9%	0.568
Worried about health in the future	74.7%	68.1%	0.304
Limited in planning activities in advance	35.8%	23.2%	0.06

\*Indicates statistical significance.

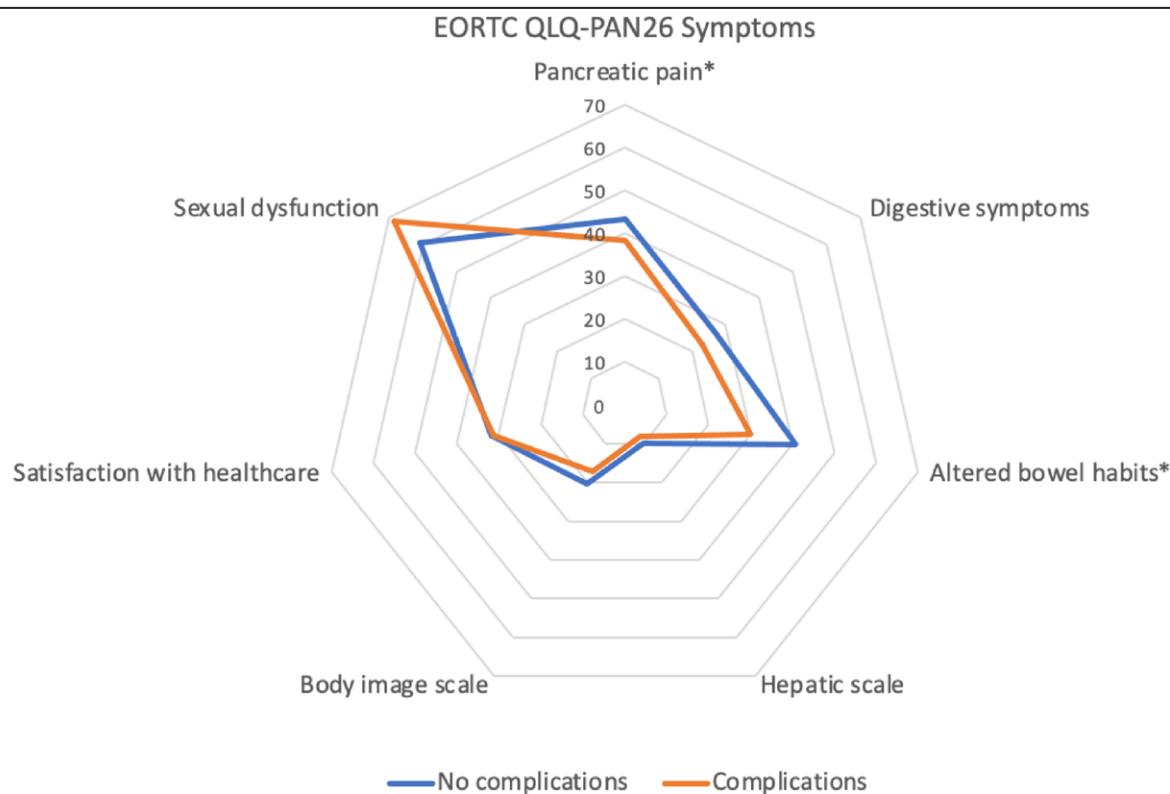
negative effects of new-onset post-PD exocrine insufficiency (defined as needing pancreatic enzymes) and endocrine insufficiency (defined as new diabetes diagnosis) to have a negative on long-term QoL.<sup>32</sup> Broadly evaluating how complications affect long-term QoL may allow us to better understand the impact of late-onset complications.

Our observation that complications do not adversely affect QoL after PD supports those from other studies.<sup>23–27,33,38</sup> Moreover, postoperative complications have also been shown to have no negative impacts on long-term QoL in patients undergoing esophagectomy.<sup>43–45</sup> These results might reflect the Halo effect, a cognitive bias whereby a positive impression of 1 attribute makes it more likely for a related attribute to be viewed favorably. It is possible that overcoming postoperative complications developed resilience that helped patients perceive life and subsequent challenges with a more positive outlook. If true, this Halo effect might extend to other adverse events, including operations. Indeed, we previously observed that post-PD patients had improved long-term QoL compared to controls who did not undergo resection.<sup>33</sup> Surgery has also been associated with more favorable long-term QoL in other disease settings, such as open versus endovascular repair of abdominal aortic aneurysms,<sup>46–48</sup> and esophagectomy versus endoscopy for resection of high-grade esophageal dysplasia.<sup>49,50</sup> Together, these results suggest that patients can have a normal, or perhaps even better, long-term QoL after they overcome the immediate associated with surgery and perioperative complications. Future studies should evaluate interventions that help patients cope with these challenges.<sup>51</sup>

This study has multiple strengths. First, we believe this is the first study to assess the impact of postoperative complications on long-term (>5 years) post-PD QoL with a median follow-up of 9.1 years. Second, we used the EORTC QLQ-PAN26 instrument, an externally validated instrument for assessing pancreas-specific health-related QoL that has already been internally validated with our cohort of patients.<sup>33</sup> Our response rates were also high (81.3%), which compares favorably to other studies and helps mitigate the potential confounding effects of response bias.<sup>19,23,24,27</sup> Third, the group with complications had similar rates of malignancy to the group without complications and both groups had a similar proportion of patients who received chemotherapy and radiation. This may mitigate the effects a cancer diagnosis or cancer-related treatment has on QoL as more advanced pancreatic cancer has been shown to have unfavorable impacts on QoL.<sup>52</sup> Moreover, we separately analyzed patients with benign and malignant indications, and other than

financial toxicity being worse in patients with malignant indications, no other outcomes were worse when patients experienced complications.

Our results must be interpreted in the context of their limitations. First, our rate of complication rates may have been underestimated due to the retrospective nature of the study. Second, we observed that responders had lower rates of severe complications than nonresponders. Patients experiencing severe complications may have been more reluctant to respond, in line with oncology trials that have demonstrated clinical deterioration to be a risk factor for study attrition.<sup>53</sup> Third, our cohort includes no patients with grade 4 complications. This may be because the long-term physical sequela associated with grade 4 complications such as an ICU admission decreased the likelihood of patients reaching 5 years of follow-up. We acknowledge that these severe complications may also have long-term emotional sequela that we were unable to capture. Fourth, as a function of our inclusion criteria to only include long-term survivors, we do not capture patients who did not survive to the 5-year mark, and these patients may have experienced worse postoperative QoL. This study also lacks baseline or longitudinal QoL data, information that would help clarify at what point QoL starts improving after the initial postoperative decline. Fifth, our study may not be as generalizable to contemporary patients undergoing pancreatic resection for pancreatic cancer since neoadjuvant chemotherapy is increasingly becoming the standard of care and the majority of our patient population received adjuvant therapy.<sup>54,55</sup> However, a recent study did not observe an association between adjuvant chemotherapy and QoL.<sup>23</sup> Other studies have noted similar findings for neoadjuvant chemotherapy in gastrointestinal cancers.<sup>56,57</sup> Together, these results provide optimism that patients undergoing PD can be restored to a good QoL regardless of the order of cancer treatment. Sixth, the minimally important clinical difference classification we used has only been validated for the EORTC QLQ-C30 instrument and not the PAN26 instrument. Therefore, it is possible that some of the statistically significant differences we observed within the PAN26 instrument were also clinically significant. Although no consensus has been established on what constitutes a clinically significant difference on the PAN26 instrument, results from recent studies suggest that our interpretation of CR in this instrument is appropriate.<sup>58</sup> Lastly, both EORTC QLQ-C30 and PAN26 were developed to assess QoL in patients with cancer. As a result, QoL scores may be different in patients with cancer compared to those with benign disease. Reassuringly, our conclusions were



EORTC QLQ-PAN26 Symptom Domain	No complications		Complications		p-value	Clinical relevance
	Mean	SD	Mean	SD		
Pancreatic pain	43.4	18.9	38.2	14.3	.023	Small
Digestive symptoms	27.1	29.6	22.9	28.3	.16	No change
Altered bowel habit	40.7	31.1	30.1	29.0	.0093	Moderate
Hepatic scale	9.8	14.1	8.0	14.6	.19	No change
Body image scale	20.2	23.6	17.2	21.7	.19	No change
Satisfaction with healthcare	31.8	33.6	31.2	33.8	.45	No change
Sexual dysfunction	60.7	37.7	68.7	37.0	.087	No change

**FIGURE 4.** Comparison of the EORTC QLQ-PAN26 symptom domain scales between 5-year pancreaticoduodenectomy survivors with and without postoperative complications. \*Indicates statistical significance. CR indicates clinical relevance.

the same when we looked at the cohort stratified by benign versus malignant indication.

In conclusion, this study demonstrated that post-PD complication rates during the index hospitalization were not associated with long-term global QoL or functionality, and may be associated with less severe pancreas-specific symptoms. This result may better inform shared decision-making and reduce the nihilism surrounding potentially lifesaving pancreatic surgery. Further studies are needed to corroborate these results and should consider reporting complications using the comprehensive complication index for a more granular view.<sup>59</sup>

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