ORIGINAL ARTICLE

Preoperative cognitive function predicts survival in patients with resectable pancreatic ductal adenocarcinoma

Bart M.G. Baekelandt[1], Marianne J. Hjermstad[2,3], Tom Nordby[4], Morten W. Fagerland[5], Elin H. Kure[6], Turid Heiberg[7], Trond Buanes[1,8] & Knut J. Labori[8]

[1]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, [2]Regional Centre for Excellence in Palliative Care, Department of Oncology, Oslo University Hospital, [3]European Palliative Care Research Centre, Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, [4]Department of Gastroenterological Surgery, Østfold Hospital Trust, [5]Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, [6]Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital, Oslo, [7]Østfold University College, Faculty of Health and Social Studies, Halden, and [8]Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital, Norway

Abstract

Background: The purpose of this prospective study was to evaluate whether pre-surgery health-related quality of life (HRQoL) and subjectively rated symptom scores are prognostic factors for survival in patients with resectable pancreatic ductal adenocarcinoma (PDAC).

Methods: Patients undergoing pancreatic resection for PDAC completed the Edmonton Symptom Assessment System (ESAS) and the EORTC QLQ-C30 and QLQ-PAN26 questionnaires preoperatively. Patient, tumor and treatment characteristics, recurrence and survival were registered.

Results: Sixty-six consecutive patients underwent R0/R1 resection for PDAC. Baseline ESAS and EORTC questionnaire compliance was 44/66 (67%) with no statistically significant differences between compliers (n = 44) and non-compliers (n = 22) when comparing clinicopathological parameters and survival. Univariable analyses showed that three symptoms (nausea, dry mouth, cognitive function) and two clinicopathological factors (CA 19-9 > 400 U/ml, lymph node ratio > 0.1) were significantly associated with shorter survival ($p < 0.05$). In multivariable analysis, cognitive function was the only independent predictor for survival: hazard ratio = 0.35 (95%CI 0.13–0.93) for high vs low cognitive function. Median survival times for patients with high and low cognitive function were 21 and 10 months, respectively ($p < 0.001$).

Conclusion: Presurgery cognitive function is a significant independent predictor of survival in patients with resectable PDAC. Thus, presurgery patient reported outcomes may provide as strong prognostic information as clinicopathological factors.

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Correspondence

Knut J. Labori, Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital, Nydalen, N-0424, Oslo, Norway. Tel: +47 23070000. Fax: +47 23072526. E-mail: uxknab@ous-hf.no

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths in Europe and the United States.[1,2] Surgical resection provides the only chance of cure. However, only 15% of patients are amenable for resection.[3] Patients undergoing curative resection have demonstrated 5-year survival rates of approximately 15–20% with a median survival of 16–23 months in different reports.[3–5] Staging and prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) is defined by tumor stages according to the AJCC Cancer Staging Manual (TNM staging system).[6] Multiple previous studies have demonstrated that clinicopathologic factors such as tumor size, histologic differentiation, margin status, and nodal involvement are statistically significant prognostic variables in patients undergoing resection for pancreatic cancer.[5,7,8] Furthermore, nomograms and clinical calculators have been developed to predict outcome in patients with pancreatic cancer.[5,9–11] However, these studies do not include patient reported outcomes (PRO) such as health-

related quality of life (HRQoL) or symptom scores as part of the prognostication. HRQoL related variables have shown to predict survival in several different types of cancers independent of the extent of the disease and other clinicopathologic prognostic factors.[12] The issue of HRQoL as a predictor of survival has been addressed in a few studies, and HRQoL at baseline have shown to give useful prognostic information in patients with advanced pancreatic cancer.[13–18] The primary aim of this prospective study was to assess the prognostic significance of pretreatment HRQoL and symptom scores on survival in a consecutive series of patients with resectable PDAC.

Materials and methods

In October 2008, Oslo University Hospital established a multidisciplinary research program, Thematic Pancreatic Tumour Project (TPTP), on pancreatic tumours including all patients who were referred with solid or cystic pancreatic or periampullary tumours.[19] A database was established containing a prospective sampling of PROs such as symptoms, functioning and HRQoL. Patients undergoing a potentially curative resection for PDAC were identified from the database. Patients with complete presurgery HRQoL and ESAS data were included in this prospective, non-randomized study. Patients were excluded if they were unable to provide informed consent or were unable to understand or cooperate with study conditions.

HRQoL and general symptoms were assessed at time of diagnosis of PDAC (baseline, pre-treatment) up to 1 month prior to operation. Surgical complications were classified according to the Clavien-Dindo classification.[20] All patients were followed regularly with history and physical examination to pursuit postoperative complications and symptoms, as previously described.[21] Chest and abdominal CT were performed every six months or if the patients had symptoms suspect of a recurrence. Recurrence was defined as radiological evidence of intra-abdominal soft tissue around the surgical site or of distant metastasis. Overall survival (OS) data from time of surgery were obtained from the National Population Registry in Norway.

Ethical considerations

The TPTP was approved by the Regional Committee for Medical and Health Research Ethics (REC) for registrations of clinical and biochemical data, and PROs. All participants provided written informed consent prior to study start. Confidentiality and data protection were approved by the institutional Data protection officer.

Quality of life and symptom score assessment

The EORTC QLQ-C30 and EORTC QLQ-PAN26 raw scores were calculated using the recommended EORTC procedures.[22] The time frame for both instruments was the past seven days. Scale and item scores were transformed into a continuous scale from 0 to 100, as described in the EORTC Scoring Manual.[22] The EORTC QLQ-C30 consists of five functional scales; physical, role, cognitive, emotional, and social, three symptom scales; fatigue, nausea/vomiting, and pain, and six single items to be scored from 1 ("Not at all") to 4 ("Very much"), supplemented by two questions forming a global health/QoL score going from 1 (poor) to 7 (excellent). The specific pancreatic cancer module; EORTC PAN26 consists of 26 items and supplements the EORTC QLQ-C30.[23] It contains specific symptoms, body image, sexuality, and emotional and social consequences of pancreatic cancer. Each item uses a 4-point scale which range from 1 ("Not at all") to 4 ("Very much"). For the global health score and functional scales, a high score indicates a higher level of functioning and better quality of life, whereas for symptom scales and items a high score indicates a

Table 1 Clinicopathological characteristics for 44 patients with presurgery patient-reported outcome (PRO) data undergoing pancreatic resection for PDAC

Variable	Median (range) or number
Age (years)	68 (34–83)
Gender (male)	20
Pain[a]	25
Preoperative diabetes mellitus	9
Jaundice[a]	30
T1	3
T2	5
T3	36
T4	0
N1	31
Lymph node ratio	0.1 (0–0.75)
R1	29
Diameter (mm)	32 (15–60)
Type of surgery:	
Pancreatoduodenectomy	36
Distal pancreatic resection	4
Total pancreatoduodenectomy	4
Postoperative morbidity	24
Clavien-Dindo $\geq$3	8
Recurrence	38
Site of first recurrence	
Isolated loco-regional	15
Distant	17
Locoregional and distant	6
Disease free survival, months (95%CI)	7 (4–17)
Overall survival, months (95%CI))	16 (13–25)

[a] At time of diagnosis.

higher level of symptoms (i.e., more problems). In the case of missing values within a scale, the missing values were replaced by the mean of the remaining items, provided that at least half of the items were completed.[22]

The Edmonton Symptom Assessment Scale (ESAS) is comprised of a numerical rating scale, with a range from 0 to 10 (0 being the absence of symptoms and 10 being the worst symptoms imaginable).[24] It assesses pain (still/movement), tiredness, nausea, depression, anxiety, drowsiness, appetite, general wellbeing, and shortness of breath.

Statistics

The Mann–Whitney test was used to compare the medians of continuous variables. Dichotomous variables were compared with the Pearson chi-squared test if all expected counts were above five, and the Fisher mid-p test if at least one expected count was less than five. Ordered categorical variables were compared with the exact Wilcoxon-Mann–Whitney test, and unordered categorical variables were compared with the chi-squared test.

PROs were evaluated using univariable Cox regression analyses to determine which parameters showed individual prognostic value for survival. Parameters with a p-value < 0.20 in univariable analyses were included in the multivariable Cox regression model with the stepwise backwards method, where the parameter with the highest p-value is omitted at each step. PRO parameters with statistical significance ($p < 0.05$) were then adjusted for possible core clinical data confounders with Cox regressions analysis.[5] The raw scores from EORTC QLQ-30 on the two questions that together constitute the cognitive function scale were transformed to a score range from 0 to 100%.[22] With two items in the scale, there are seven possible outcome scores; 0%, 16.67, 33.33, 50.0, 66.67, 83.33 and 100%. For the regression analysis cognitive function was categorized into two groups: high (>66.67%, i.e. 83.33% and 100%) and low (≤66.67%, i.e. 16.67%, 33.33%, 50%, 66.67%).

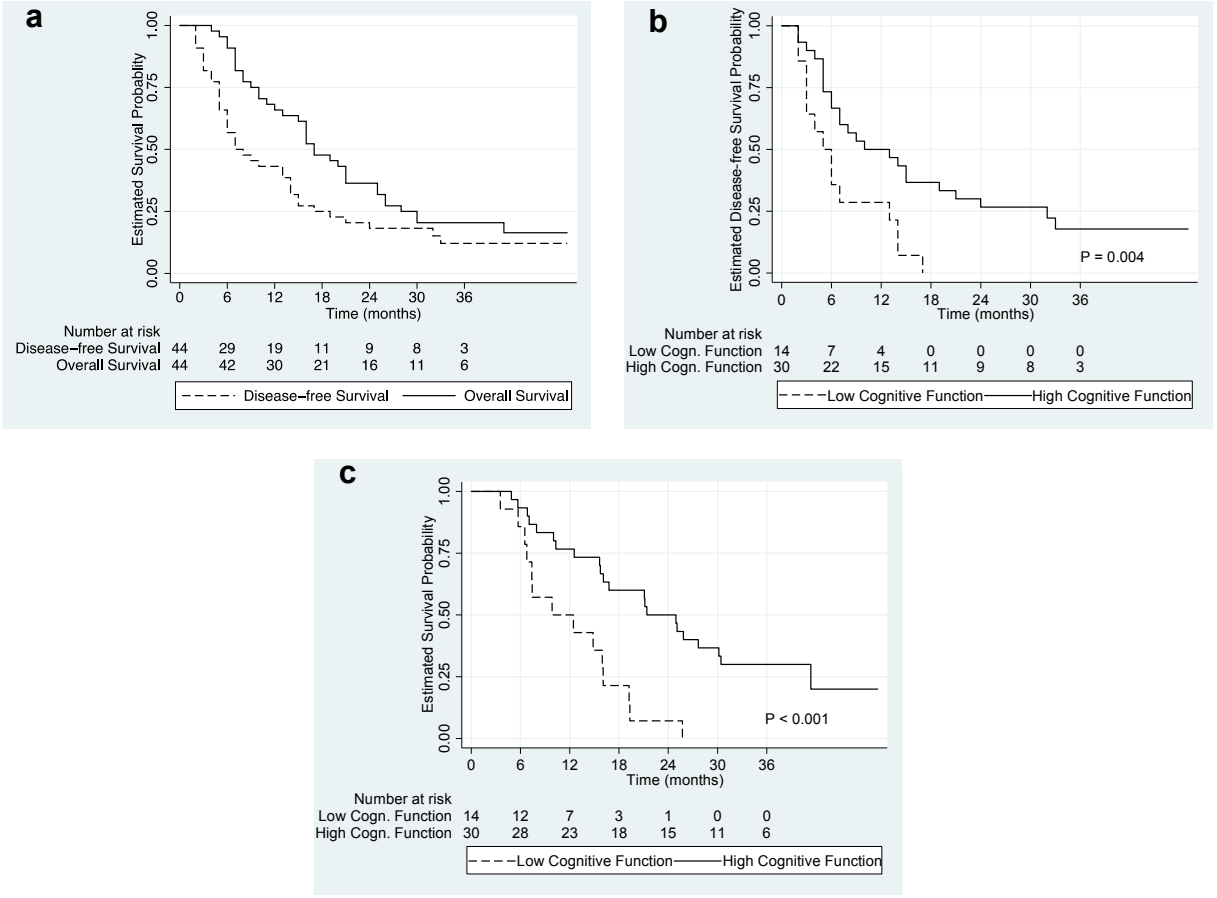

Figure 1 (a) Kaplan-Meier estimate for disease-free (recurrence-free) and overall survival for all 44 patients with complete HRQoL data. (b) Kaplan-Meier estimate for disease-free survival for high and low cognitive function scores. (c) Kaplan-Meier estimate for overall survival for high and low cognitive function scores

Table 2 Univariable analysis of the patient-reported outcome (PRO) prognostic variables associated with survival in 44 patients undergoing pancreatic resection for PDAC

PRO parameter	Mean (95%CI)	Haz. ratio (95%CI)	p-value
ESAS			
Pain still	2.4 (1.4–3.4)	1.10 (0.98–1.23)	0.096
Pain movement	2.1 (1.3–3.0)	1.02 (0.91–1.15)	0.688
Fatigue	4.0 (3.1–5.0)	1.11 (0.97–1.27)	0.135
Nausea	1.9 (0.9–2.8)	1.12 (1.00–1.25)	0.050
Breathlessness	1.6 (0.8–2.5)	1.04 (0.92–1.18)	0.493
Dry mouth	3.0 (2.0–4.0)	1.09 (0.98–1.21)	0.105
Appetite	3.0 (2.0–4.1)	1.04 (0.93–1.17)	0.467
Anxiety	2.7 (1.8–3.6)	0.99 (0.87–1.12)	0.874
Sadness	2.3 (1.4–3.2)	1.05 (0.93–1.19)	0.442
All	2.9 (2.1–3.7)	1.05 (0.92–1.19)	0.462
EORTC QLQ30			
Physical functioning	73 (65–80)	0.99 (0.98–1.01)	0.367
Social functioning	62 (50–75)	1.00 (0.99–1.01)	0.685
Role functioning	54 (41–66)	0.99 (0.98–1.00)	0.227
Emotional functioning	75 (67–82)	0.99 (0.98–1.01)	0.390
Cognitive functioning	81 (74–89)	0.98 (0.97–1.00)	0.009
Global QoL	50 (42–59)	0.99 (0.98–1.01)	0.259
Fatigue	52 (40–63)	1.01 (1.00–1.02)	0.212
Nausea-vomiting	19 (12–25)	1.01 (0.99–1.02)	0.240
Pain	35 (25–46)	1.00 (0.99–1.01)	0.942
Dyspnoea	24 (15–34)	1.01 (1.00–1.02)	0.212
Sleeping disturbances	38 (28–49)	1.00 (0.99–1.01)	0.679
Appetite	37 (24–51)	1.00 (0.99–1.01)	0.518
Constipation	14 (4–24)	1.00 (0.99–1.02)	0.550
Diarrhoea	43 (29–57)	1.00 (0.99–1.01)	0.571
Financial impact	4 (0–8)	1.00 (0.97–1.04)	0.941
EORTC PAN26			
Sexuality	54 (40–68)	1.01 (1.00–1.02)	0.325
Satisfaction with care	15 (5–24)	1.00 (0.99–1.02)	0.566
Pancreatic pain	33 (25–41)	1.00 (0.99–1.02)	0.627
Digestive functioning	32 (23–41)	1.00 (0.99–1.01)	0.998
Hepatic symptoms	42 (30–55)	1.00 (0.99–1.01)	0.506
Altered bowel habits	37 (25–49)	1.00 (0.99–1.01)	0.892
Body image	25 (15–36)	1.01 (0.99–1.02)	0.368
Full stomach	37 (25–49)	1.00 (0.99–1.01)	0.432
Taste change	23 (12–34)	1.00 (0.99–1.01)	0.595
Trouble swallowing	38 (26–51)	1.00 (1.00–1.01)	0.366
Flatulence	31 (20–43)	1.01 (1.00–1.02)	0.213
Low weight	24 (12–36)	1.00 (0.99–1.01)	0.890
Weakness	34 (23–45)	1.01 (1.00–1.02)	0.210
Dry mouth	44 (33–56)	1.01 (1.00–1.02)	0.027
Side effects	7 (1–13)	1.00 (0.98–1.02)	0.768
Worry future health	56 (44–67)	1.01 (1.00–1.02)	0.218
Plan activities	39 (24–54)	1.00 (1.00–1.01)	0.422

(*continued on next column*)

Table 2 (*continued*)

The Kaplan-Meier estimator was used to estimate median survival times (with 95% confidence intervals). Kaplan-Meier estimations were calculated for predictors found to have statistical significance. Follow-up time was estimated with the use of the reverse Kaplan-Meier method (the usual method but with an opposite definition of censorship and events).[25]

Results

From November 2008 to December 2011 a total of 66 consecutive patients underwent surgical resection with curative intent for PDAC. Baseline HRQoL and ESAS data were available for 44/66 (67%) patients. There were no statistically significant differences between patients with (n = 44) and without (n = 22) baseline HRQoL data when comparing core clinicopathological parameters and survival (data not shown). Clinicopathological characteristics and outcomes of the 44 patients with complete presurgery PRO data at the time of initial surgery are listed in Table 1. No patients received neoadjuvant chemotherapy or radiotherapy. The procedures performed included pylorus-preserving pancreatoduodenectomy in 32 patients, pancreatoduodenectomy with antrectomy in four, distal pancreatectomy with splenectomy in four and total pancreatectomy with splenectomy in four. Perioperative mortality was zero. The median follow-up period was 39 (95% CI: 31–47) months. Survival is shown in Fig. 1a.

The univariable Cox regression analyses are shown in Table 2. Only six patient reported variables had a p-value < 0.20 and were eligible for the multivariable model. After stepwise backward selection, only cognitive function remained in the model. Based on the results of the prognostic impact of PROs on survival, patients were divided into two groups, i.e. those with high vs those with low cognitive. The hazard ratio of dying was 3.5 (95% CI 1.7–7.3) times higher in the group of patients with low cognitive function compared to the group of patients with high cognitive function (p = 0.001). Patients with low cognitive function and those with high cognitive function had a median disease free survival of 6 [95% CI 30–13] and 12 [95% CI 6–21] months respectively (Fig. 1b). Patients with low cognitive function and those with high cognitive function had a median overall survival of 10 [95% CI 6–16] and 21 [95% CI 16–30] months respectively (Fig. 1c).

Previously explored clinicopathological predictors of survival and high vs low cognitive function were tested with Cox-regression, and the results are shown in Table 3.[5]

Based on the results above, the extent to which patients with low cognitive scores differed in key baseline characteristics from patients with high cognitive scores are shown in Table 4.

Discussion

Most factors used in prognostication of PDAC are known after the patient has undergone resection. Biomarkers to aid in the clinical decision making are still lacking. Only highly elevated preoperative CA 19-9 levels have been associated with low resectability and poor survival rates.[26] PROs have shown to provide distinct prognostic information beyond standard clinical measures in cancer clinical trials.[27] Two studies on resectable pancreatic and periampullary cancer have evaluated the impact of pancreatic resection on longitudinal HRQoL.[28,29] However, to date no studies have determined the prognostic impact of pre-surgery HRQoL on survival in resectable PDAC. The current study, involving a total of 44 patients undergoing resection for PDAC, contributes to the limited amount of data discussing this topic.

The current study demonstrates that only cognitive function was an independent predictor for survival after multivariable analysis. In a German study, self-reported cognitive functioning was prognostic for mortality in elderly onco-surgical patients.[30] However, the patient cohort was heterogeneous regarding cancer site, imposing difficulties in the evaluation of disease specific results. Furthermore, a British study showed that impaired cognitive function was predictive for 6 months mortality after resection for gastric and esophageal cancer.[31] The current study supports that impaired cognitive function is a strong predictor of survival in oncosurgical patients, but specifically relates to PDAC.

An important issue to address is whether impaired cognitive function demands the adjustment of surgical and perioperative therapy in patients with resectable PDAC. Interestingly, one study found that the probability of survival increases significantly if cognitive function improves within 3 months of treatment in patients with advanced stage IV pancreatic cancer.[17] However, which interventions that may improve cognitive function remain to be elucidated. Many commonly used cytotoxic agents are known to drive neurobiological processes contributing to cognitive impairment in cancer patients.[32] However, the mechanism behind cognitive impairment in patients that have not received chemotherapy is yet poorly understood. The stress associated with the diagnosis and staging of cancer, may contribute to abnormal presurgery assessments.[33] Some authors suggests that early detection and intervention for fatigue, anxiety, depression and sleep disturbances holds the possibility of contributing to the reduction of cognitive problems.[32] The current study shows that patients with low cognitive function and thereby shorter survival had a higher probability of presenting with jaundice as a symptom at diagnosis. Preoperative jaundice has shown to be a negative risk factor in PDAC.[8] Interestingly, endoscopic stenting has shown to significantly improve emotional, cognitive and global health scores one month after the procedure in patients with extrahepatic malignant biliary strictures not undergoing surgical resection.[34] However, none of the trials studying the benefits and harms of preoperative biliary stenting report quality of life data.[35,36]

Table 3 High cognitive function adjusted for possible clinicopathological confounders in univariable and multivariable analysis

Parameter	Median (range) or number	Haz. ratio	Univariable p-value	Haz. ratio	Multivariable p-value
High Cognitive Function	30	0.29 (0.14–0.60)	0.001	0.35 (0.13–0.93)	0.036
Age > 70 years	16	0.94 (0.48–1.88)	0.869	–	–
Gender (male)	20	1.49 (0.77–2.88)	0.231	–	–
Karnofsky[a]	90 (60–100)	0.98 (0.94–1.02)	0.245	–	–
Pain[a]	25	0.88 (0.45–1.70)	0.704	–	–
Diabetes mellitus[a]	9	1.35 (0.61–2.98)	0.461	–	–
Jaundice	31	0.75 (0.37–1.53)	0.431	–	–
CA-19-9 > 400[b]	9[a]	2.68 (1.18–6.09)	0.019	1.11 (0.40–3.07)	0.846
Tumor diameter	3.25 (15–60)	1.21 (0.90–1.62)	0.215	–	–
T3 status	36	0.81 (0.35–1.85)	0.615	–	–
Tumor grade	16	1.26 (0.64–2.48)	0.500	–	–
Lymph node ratio > 0.1	23	2.06 (1.05–4.03)	0.036	1.47 (0.59–3.63)	0.410
R1 status	28	1.49 (0.74–3.00)	0.260	–	–

[a] At time of diagnosis.
[b] N = 37, missing CA19-9 serum values from 7 of 44 patients.

Table 4 Baseline characteristics for 14 patients with low cognitive function and 30 patients with high cognitive function

Variable	Low cognitive function N = 14 median (range) or number	High cognitive function N = 30 median (range) or number	p-value
Age	68 (34–79)	67 (43–83)	0.772
Gender (male)	6	14	0.818
Pain[a]	8	17	0.977
Diabetes mellitus[a]	4	5	0.333[b]
Jaundice[a]	13	18	0.023[b]
Serum-bilirubin[a]	43.5 (7–347)	15.5 (5–306)	0.075
Karnofsky score[a]	85 (80–100)	90 (60–100)	0.087
ECOG score[a]	1 (0–1)	1 (0–2)	0.842
T-status			
T1-rate	1	2	
T2-rate	0	5	
T3-rate	13	23	
Lymph node ratio	0.17 (0–0.75)	0.055 (0–0.43)	0.008
R1-rate	10	18	0.474
Tumor diameter	3.25 (20–55)	3.2 (15–60)	0.586
Type of surgery:			
Pancreatoduodenectomy	11	25	0.549[b]
Distal pancreatic resection	0	4	0.191[b]
Total pancreatoduodenectomy	3	1	0.048[b]
Adjuvant chemotherapy, initiation	9	23	0.390
Adjuvant chemotherapy, completion	6	15	0.660
Recurrence	14	24	0.093[b]
Type of recurrence:			
Isolated loco-regional	2	13	0.066[b]
Distant	10	7	0.002
Locoregional and distant	2	4	0.823[b]
Postoperative morbidity (any grade)	8	16	0.818
Clavien-Dindo $\geq$3	2	6	0.656

[a] At time of diagnosis.
[b] Fisher mid-p test.

Several limitations of the current study must be acknowledged. First, the study reports data from a single center which may affect the generalizability of the findings. Second, the current study only includes self-reported cognitive function and objective methods for assessing cognitive function were not performed. It may be that more objectively based measures such as the Mini Mental State Examination (MMSE) may increase the generalizability of the findings.[37] However, the current results of shorter survival with poor cognitive function are supported in elderly oncosurgical patients, using the MMSE and the EORTC QLQ-C30.[30] Lastly, the study sample size is small, and a larger scale study to confirm the findings of the current study will be necessary.

In conclusion, in the present sample, presurgery cognitive function was a significant independent predictor of survival in patients with resectable PDAC, while other PROs were significant in the univariable analyses. Thus, presurgery PROs may provide as strong prognostic information as clinicopathological factors in patients with resectable PDAC.

Acknowledgements

The ESAS, EORTC QLQ-C30 and EORTC QLQ-PAN26 questionnaires are not included.

Conflicts of interest

None declared.

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