ORIGINAL ARTICLE

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

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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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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.