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ORIGINAL ARTICLE

The impact of cancer treatment on quality of life in patients with pancreatic and periampullary cancer: a propensity score matched analysis

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Abstract

Background: The impact of pancreatic and periampullary cancer treatment on health-related quality of life (HRQoL) is unclear.

Methods: This study merged data from the Netherlands Cancer Registry with EORTC QLQ-C30 and -PAN26 questionnaires at baseline and three-months follow-up of pancreatic and periampullary cancer patients (2015–2018). Propensity score matching (1:3) of group without to group with treatment was performed. Linear mixed model regression analyses were performed to investigate the association between cancer treatment and HRQoL at follow-up.

Results: After matching, 247 of 629 available patients remained (68 (27.5%) no treatment, 179 (72.5%) treatment). Treatment consisted of resection (n = 68 (27.5%)), chemotherapy only (n = 111 (44.9%)), or both (n = 40 (16.2%)). At follow-up, cancer treatment was associated with better global health status (Beta-coefficient 4.8, 95% confidence-interval 0.0–9.5) and less constipation (Beta-coefficient −7.6, 95% confidence-interval −13.8–1.4) compared to no cancer treatment. Median overall survival was longer for the cancer treatment group compared to the no treatment group (15.4 vs. 6.2 months, $p < 0.001$).

Conclusion: Patients undergoing treatment for pancreatic and periampullary cancer reported slight improvement in global HRQoL and less constipation at three months-follow up compared to patients without cancer treatment, while overall survival was also improved.

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Introduction

Patients with pancreatic or periampullary cancer have a grim prognosis with short life-expectancy making health-related quality of life (HRQoL) an important topic.[1] HRQoL is increasingly used in clinical trials as outcome, but also in clinical practice as input for shared decision making. In addition, it was recently shown that HRQoL predicted survival, regardless of patient, tumor, and treatment characteristics.[2] Different treatments have different impact on HRQoL.[3] For example, previous studies have shown that HRQoL may temporarily decrease after resection, and may improve after completion of palliative chemotherapy.[4–8] Moreover, HRQoL is influenced by type of resection (e.g. classical Whipple vs. pylorus-preserving pancreatoduodenectomy) and chemotherapy (e.g. gemcitabine vs. FOLFIRINOX (folic acid, fluorouracil, irinotecan, oxaliplatin) chemotherapy).[9,10] Most HRQoL data are derived from randomized trials with highly selected patients, or from observational studies which rarely include patients without cancer treatment. HRQoL data of patients with pancreatic or periampullary cancer treated in routine clinical practice are scarce.

HRQoL may improve after cancer treatment as a result of reduction of mechanical complaints and/or tumor load, or of diminished fear of the disease itself or its progression. On the other hand, HRQoL may decrease after extensive surgery with often severe morbidity or during and after chemo (radio)therapy due to toxicity and fear of disease recurrence. It is not yet clear what the effect of cancer treatment is on HRQoL compared to no cancer treatment, especially in a population-based setting of patients with pancreatic or periampullary cancer. In order to fully take into account the differences between treatment modalities and potential confounding by indication, adequate statistical matching techniques are required, for which a large number of patients is necessary. Recently, this was made possible with the Dutch Pancreatic Cancer Project (PACAP).

Within PACAP, clinical data and HRQoL data are collected from patients with pancreatic or periampullary cancer.[11] The aim our study was to explore whether patients who underwent cancer treatment (i.e. resection and/or chemo (radio)therapy) differ in HRQoL from patients who did not undergo cancer treatment (i.e. supportive care or no treatment) three months after diagnosis, using a propensity score matched cohort of patients with pancreatic or periampullary cancer.

Methods

Study design

This is an exploratory nested case–control multicenter study within the prospective PACAP cohort study collecting patient reported outcome measures (PROMs) between 2015 and 2018 from 27 participating centers.[11] Clinical data of patients with pancreatic or periampullary cancer were derived from the nationwide population-based Netherlands Cancer Registry (NCR), from date of diagnosis to three months follow-up plus overall survival (OS) data. Data of both registries were linked, as all patients provided written informed consent for participation and linkage of data within PACAP. This study was approved by the Scientific Committee of the Dutch Pancreatic Cancer group and performed in accordance with the STROBE guidelines.[12]

HRQoL data

HRQoL data of the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires (QLQ-C30 and PAN26) at baseline and three-months follow-up were used.[13,14] The cancer-specific EORTC QLQ-C30 questionnaire encompasses global health status, five functioning scales (i.e. physical, role, emotional, cognitive, and social functioning) and eight symptom scales/items (i.e. fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea), and financial difficulties. The pancreatic-specific EORTC QLQ-PAN26 questionnaire includes nine pancreatic- and treatment-related symptoms (pain, eating-related items, cachexia, hepatic symptoms, side-effects, altered bowel habit, ascites, indigestion, and flatulence) and five emotional domains specific to pancreatic cancer (body image, healthcare satisfaction, sexuality, fear of future health and ability to plan future). The items of the EORTC questionnaires employ four response categories, which after linear transformation, form scores ranging from 0 to 100. A higher score on the functional and global scales indicates better HRQoL, whereas for problems and symptoms higher scores indicate worse HRQoL (more problems and symptoms). In addition, a summary score was obtained from the EORTC QLQ-C30 questionnaire, based on the mean of all scale and item scores with the exclusion of global HRQoL and financial impact, and after reversing the scores of the symptom scales.[15] Differences in scores of $\geq$10 were considered clinically relevant.

Clinical data

The NCR data included patient, tumor, and treatment characteristics (i.e. date of diagnosis, age at diagnosis, sex, BMI, number of comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status, pathological diagnosis, tumor location, tumor stage (according to Union for International Cancer Control 7th edition), tumor size, tumor differentiation grade, date of initial treatment, type of pancreatic resection, margin status (microscopically radical resection (R0) and microscopically irradical resection (R1)), (neo)adjuvant/palliative chemo (radio)therapy, biliary drainage, and survival data. Survival data were annually crosschecked with the Municipal Personal Records Database, which contains the vital status of all Dutch inhabitants. OS was defined as time between date of diagnosis and date of death, or censored when alive at the last check of vital status (February 1, 2020).

Study endpoints

The endpoints were the 23 HRQoL subscales scores, including the summary score, and OS.

Intervention and control group

The intervention group (i.e. treatment group) consisted of patients who received cancer treatment (i.e. either neoadjuvant/palliative chemo (radio)therapy or upfront resection of the primary tumor). Patients were included in the treatment group, if cancer treatment started between date of diagnosis and the follow-up questionnaire. Start of cancer treatment was defined as the actual date of the resection or the first chemotherapy admission. Patients were included in the control group (i.e. no treatment group) if they received no cancer treatment, for example supportive care (e.g. only radiotherapy, biliary drainage, pancreatic enzyme replacement therapy) or no treatment at all. Patients were also included in this latter group when cancer treatment was administered after completion of the three-month questionnaire.

For the treatment group, a T0 questionnaire was considered baseline if it was completed before start of treatment. For the no treatment group, the median of the interval between date of diagnosis and date of start cancer treatment from the intervention group (i.e. 32 days) was used to determine whether a T0 questionnaire was baseline (i.e. lower than the median) or follow-up (i.e. higher than the median). For both baseline groups, a subsequent T1 questionnaire, administered three months later, was used for follow-up analyses. If the, T1 questionnaire was not available, but a T0 questionnaire was completed after (the median of) start of cancer treatment, this was used as follow-up questionnaire. In that case, a baseline questionnaire was not available.

Propensity score matching

Propensity score matching was performed to account for possible confounding by indication for cancer treatment. Nearest neighbor (1:3) propensity score-matching was performed to generate matched cases of the no treatment group with the treatment group. A propensity score was generated using logistic regression, based on the covariates age, sex, BMI, number of comorbidities, ECOG performance status, tumor location (i.e. pancreas vs. periampullary), and clinical tumor stage. The within-pair difference was minimized by setting a caliper of 0.2 of the standard deviation of the logit of the propensity score.

Statistical analyses

Data are presented before and after propensity score matching. Descriptive statistics were used for analysis of patient, tumor, and treatment characteristics, and HRQoL scores. They were reported as proportions for binary or categorical variables, and as mean with standard deviation (SD) for parametric continuous variables and as median with interquartile range (IQR) for non-parametric continuous variables. Matched variables were compared between both groups with Mann–Whitney U tests (i.e. age and BMI were not normally distributed) and chi-squared tests (i.e. sex, comorbidities, performance status, tumor location, and tumor stage were categorical) to test whether groups were well-balanced after matching. Missing data were described, but not imputed. Outcomes were assessed with linear mixed model analyses for the HRQoL outcomes at follow-up, adjusted for baseline HRQoL scores, and with cancer treatment as independent variable. Linear regression analyses were used to assess whether type of first chemotherapy, number of courses, adjustment of chemotherapy regimen (e.g., dose reduction), or adverse events grade 3 or higher were remaining relevant confounders after propensity score matching in the subgroup of patients who received chemotherapy (i.e. <10% change in beta regression coefficient (B) compared to the naive analysis without confounders). This was also performed for type of resection in the subgroup of patients who underwent resection. Outcomes were reported as B with corresponding 95% confidence intervals (CI). Median OS according to presence of cancer treatment was analyzed by means of Kaplan–Meier curves and compared with Log–Rank test. Two-sided p-values of below 0.05 were considered statistically significant.

Results

Study population and clinical characteristics

In total, 629 patients were included of whom 559 (88.9%) in the treatment group and 70 (11.1%) in the no treatment group. A total of 329 patients (52.3%) had a baseline HRQoL measurement, 523 (83.1%) had a follow-up HRQoL measurement, and 235 (37.4%) had both. For 73 of 629 patients (11.6%), the formal three-month questionnaire was not available. However, they had completed a questionnaire after (the median of) start of cancer treatment. This questionnaire was, therefore, used as follow-up questionnaire.

After matching, 247 patients remained of whom 179 (72.5%) in the treatment group and 68 (27.5%) in the no treatment group. Two patients in the no treatment group could not be matched to patients from the treatment group. Baseline characteristics of the total and matched cohorts are shown in Table 1. Compared to the treatment group of the total cohort, the treatment group of the matched cohort was older (66.0 vs. 70.0 years), and more often had worse performance status (ECOG 2–4: 7.7% vs. 17.9%) and higher disease stage (stage IV: 23.3% vs. 49.7%, Table 1).

In the matched cohort, a total of 139 patients (56.3%) had a baseline HRQoL measurement, 182 (73.7%) had a follow-up HRQoL measurement, and 79 (32.0%) had both. For a flow chart of the patient selection and availability of the questionnaires, see Supplementary Figure 1. Of all matched patients, 141 (57.1%) were male, the median age was 70.0 years (IQR 65.0–75.0), and median BMI was 23.4 kg/m^2 (IQR 21.4–25.7). The matched variables did not differ between treatment and no

Table 1 Characteristics of patients with pancreatic and periampullary cancer for the total and matched cohort

Clinical characteristics	Total cohort		Matched cohort		
	Intervention group (n = 559)	Control group (n = 70)	Intervention group (n = 179)	Control group (n = 68)	P value[a]
Male (n, %)	309 (55.3)	39 (55.7)	103 (57.5)	38 (55.9)	0.886
Age at diagnosis (median, IQR)	66.0 (60.0–72.0)	71.0 (65.0–77.0)	70.0 (65.0–74.0)	70.5 (65.0–76.8)	0.366
BMI (median, IQR)	24.1 (21.6–26.5)	23.4 (21.6–25.8)	23.4 (21.3–25.9)	23.4 (21.6–25.7)	0.973
Comorbidities (n, %)[b]					0.912
0 categories	237 (42.4)	32 (45.7)	78 (43.6)	31 (45.6)	
1 category	163 (29.2)	18 (25.7)	52 (29.1)	18 (26.5)	
2 or more categories	75 (13.4)	12 (17.1)	32 (17.9)	11 (16.2)	
Unknown	84 (15.0)	8 (11.4)	17 (9.5)	8 (11.8)	
ECOG performance status (n, %)					0.689
0	228 (40.8)	17 (24.3)	54 (30.2)	17 (25.0)	
1	157 (28.1)	18 (25.7)	52 (29.1)	18 (26.5)	
2-4	43 (7.7)	18 (25.7)	32 (17.9)	16 (23.5)	
Unknown	131 (23.4)	17 (24.3)	41 (22.9)	17 (25.0)	
Follow-up in months (median, IQR)	17.2 (10.9–23.6)	6.1 (3.3–9.8)	14.9 (7.6–20.7)	6.3 (3.3–10.0)	
Mortality rate (n, %)	358 (64.0)	67 (95.7)	138 (77.1)	65 (95.6)	
Months to death (median, IQR)	12.7 (8.4–19.3)	5.9 (3.1–9.4)	11.6 (6.4–18.0)	6.0 (3.2–9.5)	
Tumor characteristics					
Location (n, %)					0.803
Pancreas	441 (78.9)	65 (92.9)	163 (91.1)	63 (92.6)	
Periampullary	118 (21.1)	5 (7.1)	16 (8.9)	5 (7.4)	
Stage (n, %)					0.803
IA/IB	61 (10.9)	9 (12.9)	25 (14.0)	9 (13.2)	
IIA/IIB	162 (29.0)	5 (7.1)	8 (4.5)	5 (7.4)	
III	206 (36.9)	19 (27.1)	57 (31.8)	19 (27.9)	
IV	130 (23.3)	37 (52.9)	89 (49.7)	35 (51.5)	
Treatment characteristics					
Resection (n, %)	*n = 327*	NA	*n = 68*	NA	
Pancreatoduodenectomy	293 (89.6)[c]		59 (86.8)[c]		
Other pancreatectomy	34 (10.4)[c]		9 (13.2)[c]		
Resection margin (n, %)	*n = 327*	NA	*n = 68*	NA	
R0	201/323 (62.2)[c]		35 (51.5)[c]		
R1	122/323 (37.8)[c]		33 (48.5)[c]		
Radiotherapy (n, %)	50 (8.9)	3 (4.3)	17 (9.5)	3 (4.4)	
Chemotherapy (n, %)	*n = 447*	NA	*n = 151*	NA	
Neo-adjuvant only	28 (6.3)[d]		5 (3.3)[d]		
Adjuvant only	157 (35.1)[d]		31 (20.5)[d]		
Neo-adjuvant and adjuvant	35 (7.8)[d]		6 (4.0)[d]		
Chemotherapy, no resection	227 (50.8)[d]		109 (72.2)[d]		
Type of first chemotherapy (n, %)	*n = 447*	NA	*n = 151*	NA	
Gemcitabine only	105 (23.5)[d]		30 (19.9)[d]		
Gemcitabine in combination[e]	106 (23.7)[d]		41 (27.2)[d]		
FOLFIRINOX	214 (47.9)[d]		78 (51.7)[d]		
Other	22 (4.9)[d]		2 (1.3)[d]		

Table 1 (*continued*)

Clinical characteristics	Total cohort		Matched cohort		
	Intervention group (n = 559)	Control group (n = 70)	Intervention group (n = 179)	Control group (n = 68)	P value[a]
Chemotherapy courses (n, %)	*n = 447*	NA	*n = 151*	NA	
1-4	139/381 (36.5)[d]		61/138 (44.2)[d]		
5-8	192/381 (50.4)[d]		58/138 (42.0)[d]		
≥9	50/381 (13.1)[d]		19/138 (13.8)[d]		
Adjustment of chemotherapy (n, %)	*n = 447* 187/248 (75.4)[d]	NA	*n = 151* 67/86 (77.9)[d]	NA	
Adverse event chemotherapy (n,%)	*n = 447* 143/374 (38.2)[d]	NA	*n = 151* 48/133 (36.1)[d]	NA	
Biliary drainage (n, %)	262 (46.9)	34 (48.6)	72 (40.2)	33 (48.5)	

Intervention group = cancer treatment group. Control group = no cancer treatment group. BMI = body mass index, ECOG = eastern cooperative oncology group, FOLFIRINOX = folinic acid, fluorouracil, irinotecan, oxaliplatin. NA = not applicable.
[a] P value of the matched variables to show balance between both groups in the matched cohort.
[b] Comorbidity categories are previous malignancy, cardiovascular, neurological, pulmonary, diabetes mellitus, renal, liver, ulcer disease, rheumatic, and HIV/AIDS.
[c] Proportion of patients who underwent resection in the intervention group.
[d] Proportion of patients who underwent chemotherapy in the intervention group.
[e] Gemcitabine + nab-paclitaxel and gemcitabine + capecitabine.

treatment groups (Table 1). In total, 68 patients (27.5%) underwent resection of the tumor, 111 (44.9%) received chemotherapy only, and 40 (16.2%) received both. In the treatment group, median time to first cancer treatment was 32.0 days (IQR 21.0–48.0). Overall, median follow-up time was 11.7 months (IQR 5.8–19.6), 203 patients (82.2%) died, and median time to death was 9.2 months (IQR 5.0–15.9).

Impact of cancer treatment

Table 2 depicts the HRQoL scores of the matched cohort and the clinically relevant differences between the treatment and no treatment group. For most of the subscales, patients in the no treatment group reported a worse HRQoL at baseline that improved over time (Table 2). Clinically relevant improvement (i.e. ≥10 points) was more often found in the no treatment group than in the treatment group for different subscales, including the summary score (Table 2). Median OS was longer for the treatment group (15.4 (IQR 7.6–23.4) vs. 6.2 (IQR 3.3–9.7) months, p < 0.001, Fig. 1).

Associations of cancer treatment with HRQoL

For the matched cohort with baseline and follow-up questionnaires (n = 191), the association between follow-up HRQoL scores and cancer treatment, investigated with linear mixed model analysis, is shown in Table 3. The treatment group had better global health status scores (B 4.8, 95% CI 0.0–9.5, p = 0.048) and constipation scores (B −7.6, 95% CI -13.8 to −1.4, p = 0.017) compared to the no treatment group, yet the observed differences were not clinically relevant (i.e. <10 difference in scores between groups). No association was found between the both patient groups and the other 21 HRQoL scores, including the summary score (reference no treatment group: B 1.0, 95% CI -2.3 - 4.4, p = 0.540, Table 3).

For patients who underwent chemotherapy, the type of first chemotherapy, number of cycles, adjustment of chemotherapy regimen, or adverse events grade 3 or higher were not relevant confounders for follow-up HRQoL scores in multivariable linear regression analyses, including adjustment for baseline HRQoL (i.e. change beta regression coefficients ranged from 1.3 to 8.9%). Similarly, for patients who underwent resection, type of resection was not a relevant confounder (i.e. change beta regression coefficient was 3.2%).

Discussion

This multicenter study in patients with pancreatic and periampullary cancer found that cancer treatment was independently associated with slightly better global health status and constipation follow-up scores compared to no cancer treatment, after adjustment for baseline differences. Other HRQoL scores were similar between the groups. OS of patients with cancer treatment was better than without cancer treatment, even though no change or only a slight change was observed in HRQoL.

This study demonstrated that receiving cancer treatment was associated with a better global health status and constipation score on average over time, although this did not reach the target set for clinical relevance which would require ≥10 points difference. However, recently studies have been published that show that the cut-off value of 10 is controversial. For example, a EORTC study specific to ovarian cancer demonstrated that anchor-based minimal important differences for most scales ranged from 4 to 10 points.[16,17] In our study, while unadjusted

Table 2 Mean health-related quality of life scores with standard deviations and delta scores in the matched cohort at baseline and follow up

	Intervention group (n = 179)			Control group (n = 68)			Between groups
	Baseline (n = 102)	Follow-up (n = 134)	Delta	Baseline (n = 35)	Follow-up (n = 45)	Delta	Delta
EORTC QLQ-C30							
Summary score[a]	72.8 (16.8)	74.6 (15.6)	1.8	62.2 (20.1)	77.0 (17.0)	**14.8**	**−13.0**
Global health status[a]	62.3 (22.5)	65.8 (20.2)	3.5	53.3 (20.6)	67.4 (20.0)	**14.1**	**−10.6**
Physical functioning[a]	76.6 (20.7)	72.7 (20.7)	−3.9	61.1 (28.8)	69.4 (24.3)	8.3	**−12.2**
Role functioning[a]	66.2 (29.6)	62.0 (29.7)	−4.2	49.5 (34.4)	62.9 (35.6)	**13.4**	**−17.6**
Emotional functioning[a]	71.6 (22.7)	78.5 (19.1)	6.9	63.8 (26.2)	80.9 (20.5)	**17.1**	**−10.2**
Cognitive functioning[a]	81.4 (22.7)	84.0 (20.2)	2.6	72.9 (28.3)	82.6 (23.0)	**9.7**	−7.1
Social functioning[a]	72.5 (27.6)	71.4 (25.2)	−1.1	60.5 (29.5)	76.0 (29.6)	**15.5**	**−16.6**
Fatigue[b]	41.0 (27.3)	46.5 (26.4)	5.5	59.7 (26.7)	37.9 (31.0)	**−21.8**	**27.3**
Nausea and vomiting[b]	18.3 (27.0)	18.1 (25.6)	−0.2	27.6 (30.5)	12.9 (22.4)	**−14.7**	**14.5**
Pain[b]	33.3 (28.4)	27.2 (27.7)	−6.1	46.7 (32.3)	28.4 (24.8)	**−18.3**	**12.2**
Dyspnea[b]	12.2 (22.0)	16.0 (24.4)	3.8	21.0 (23.0)	12.4 (24.2)	−8.6	**12.4**
Insomnia[b]	33.7 (32.0)	23.1 (29.5)	**−10.6**	41.0 (32.4)	18.9 (27.3)	**−22.1**	**11.5**
Appetite loss[b]	41.8 (35.3)	35.3 (33.3)	−6.5	50.5 (35.6)	27.4 (31.2)	**−23.1**	**16.6**
Constipation[b]	24.8 (30.4)	14.1 (25.3)	**−10.7**	33.3 (37.0)	19.7 (28.1)	**−13.6**	2.9
Diarrhea[b]	18.0 (25.6)	23.8 (30.3)	5.8	24.5 (32.1)	15.2 (28.3)	−9.3	**15.1**
Financial difficulties[b]	6.5 (19.4)	9.0 (22.1)	2.5	5.9 (15.3)	7.8 (21.6)	1.9	0.6
EORTC QLQ-PAN26							
Pain[b]	38.4 (28.1)	23.8 (21.5)	**−14.6**	43.5 (28.2)	26.3 (25.6)	**−17.2**	2.6
Digestive complaints[b]	35.3 (31.7)	35.8 (30.0)	0.5	43.1 (32.9)	27.3 (32.6)	**−15.8**	**16.3**
Altered bowel habit[b]	31.0 (25.2)	37.7 (26.4)	6.7	43.1 (27.6)	26.1 (20.1)	**−17.0**	**23.7**
Hepatic symptoms[b]	22.4 (30.1)	10.4 (20.1)	**−12.0**	25.5 (29.4)	9.5 (18.8)	**−16.0**	4.0
Body image[b]	26.6 (26.9)	26.0 (25.3)	−0.6	28.1 (28.2)	22.7 (24.1)	−5.4	4.8
Healthcare satisfaction[b]	65.0 (30.2)	63.8 (29.2)	−1.2	62.7 (25.0)	64.2 (29.9)	1.5	−2.7
Sexuality[b]	46.7 (37.5)	57.8 (36.0)	**11.1**	55.9 (40.3)	48.2 (39.7)	−7.7	**18.8**

Intervention group = cancer treatment group. Control group = no cancer treatment group. EORTC = european organization for research and treatment of cancer, QLQ = quality of life questionnaire. Delta = follow-up HRQoL score minus baseline HRQoL; improvement in HRQoL in the functioning scales is a positive delta, whereas in the symptom scales a negative delta. Between groups delta = delta intervention group minus delta control group. Bold indicates a clinically relevant difference of 10 points.
[a] Higher scores represent better HRQoL.
[b] Higher scores represent worse HRQoL.

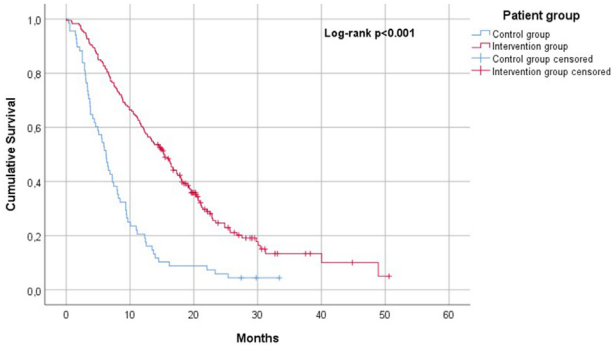

Figure 1 Overall survival by cancer treatment

global health status and constipation scores where similar between the patient groups at follow-up, both baseline scores were worse for the no treatment group. The global health status score is derived from two questions in which patients are asked to rate their overall health and overall quality of life on a 7-point scale.[13] At baseline, patients may be disappointed that cancer treatment is not possible and therefore score lower on these two global health status factors than patients who are relieved they can receive cancer treatment, or it could be related to their WHO performance status. The association with constipation may be related to opioid-related side effects since it is widely known that opioids may induce constipation.[18] Patients without treatment reported worse (unadjusted) pain scores than patients with cancer treatment. Therefore, it is likely they received more

Table 3 Linear mixed model analysis of the relation between HRQoL scores (dependent variable) and cancer treatment (independent variable) of patients with pancreatic and periampullary adenocarcinoma from the matched cohort with baseline and follow-up HRQoL (n = 191)

HRQoL scores	B (95% CI)[a]	P value
EORTC QLQ-C30		
Summary score	1.0 (–2.3–4.4)	0.540
Global health status	**4.8 (0.0–9.5)**	**0.048**
Physical functioning	0.7 (–2.7–4.1)	0.691
Role functioning	1.8 (–4.7–8.4)	0.579
Emotional functioning	1.0 (–2.8–4.9)	0.604
Cognitive functioning	1.2 (–2.8–5.2)	0.558
Social functioning	0.3 (–5.0–5.7)	0.900
Fatigue	0.0 (–5.8–5.9)	0.999
Nausea and vomiting	–3.5 (–9.2–2.3)	0.234
Pain	–3.9 (–10.0–2.3)	0.218
Dyspnea	3.7 (–0.6–8.0)	0.089
Insomnia	0.4 (–5.6–6.4)	0.891
Appetite loss	–0.4 (–8.3–7.6)	0.929
Constipation	**–7.6 (-13.8–-1.4)**	**0.017**
Diarrhea	0.4 (–6.2–7.1)	0.895
Financial difficulties	1.9 (–1.9–5.8)	0.328
EORTC QLQ-PAN26		
Pancreatic pain	–4.1 (–10.7–1.5)	0.137
Digestive complaints	–1.4 (–8.1–5.2)	0.670
Hepatic symptoms	–1.6 (–7.8–4.5)	0.598
Body image	–3.4 (–9.2–2.5)	0.261
Healthcare satisfaction	–0.7 (–7.3–5.9)	0.828
Altered bowel habit	–0.1 (–6.4–6.1)	0.970
Sexuality	–3.0 (–10.3–4.3)	0.421

B = beta regression coefficient, CI = confidence interval, HRQoL = health-related quality of life, EORTC = european organization for research and treatment of cancer, QLQ = quality of life questionnaire. Bold indicates statistical significance.
[a] Reference = control (i.e. no treatment) group (vs. intervention (i.e. treatment) group). Random intercept on patient level included. Adjusted for the baseline HRQoL score.

opioids to treat the pain, while still experiencing more pain than patients with cancer treatment. Still, these associations may also be related to a type I error. Therefore, future studies should be performed to either confirm or contradict these associations.

The summary score was evaluated additionally as a reflection of global HRQoL as it is a combination of 13 of the 15 scales of the EORTC QLQ-C30 questionnaire.[15] For the cancer treatment group, the summary score did not change from baseline to three months follow-up, as most of the separate scales remained similar over time. For the no cancer treatment group, however, the summary score improved with a clinically relevant difference of $\geq$10 points, perhaps because they received good supportive care. Still, in the multivariable mixed model analysis, the patient group (treatment vs. no treatment) was not associated with the follow-up summary score. This is probably due to the lower baseline summary score in the no treatment than in the treatment group, while it was higher at the three months follow-up measurement.

So far, studies often investigate the relation between cancer treatment and HRQoL,[5,8,19] and data are scarce on HRQoL of patients without cancer treatment. Therefore, it is of interest to investigate how HRQoL scores develop over a period of time longer than three months in both patient groups. Unfortunately, not enough data were available in our cohort at six months follow up (or at a later time point) to examine longer term follow-up HRQoL scores. This is amongst other things related to the median OS of 6 months of patients without cancer treatment. While it will therefore remain challenging, future studies are needed that investigate differences in HRQoL between the patient groups with and without cancer treatment at follow-up exceeding three months from baseline closer to patients' death. Possibly after three months follow-up, HRQoL of patients without cancer treatment may deteriorate faster than of patients with treatment due to earlier disease progression and accompanying complaints. Earlier disease progression likely occurred in the no treatment group, because their median survival time is substantially shorter than in the cancer treatment group (6 vs. 15 months). This may additionally result in faster deterioration of HRQoL (e.g. due to worsening of symptoms) and selective dropout of patients.

In some of the subscales, patients receiving cancer treatment reported better HRQoL at follow-up compared to baseline, such as (pancreatic) pain, insomnia, and hepatic symptoms. Our results therefore confirm the results of previous studies, which also found that HRQoL improved after palliative chemotherapy.[5,6] Pain and hepatic symptoms may be reduced after treatment due to alleviation of mechanical complaints or reduction of tumor load, while insomnia may be reduced due to less worries regarding the disease itself or its progression. Nevertheless, most of the HRQoL subscale scores remained similar over time in the treated patient group. Patients were possibly still recovering from surgery or receiving chemotherapy at the time of the three months follow-up questionnaire. This is in line with a review that showed that HRQoL recovered to baseline scores three to six months after a pancreatoduodenectomy for malignancies.[4] Interestingly, in the no treatment group, almost all HRQoL subscale scores were lower at baseline but improved clinically relevantly at three months follow-up. We cannot exclude the possibility of a regression to the mean effect. However, part of this improvement may also reflect adequate palliative care with symptom targeted therapies such as biliary drainage or celiac blockade without additional side effects related to chemotherapy.

In this study, patients with pancreatic and periampullary cancer were included. We cannot exclude the possibility of differences in outcomes between these groups, as different treatment strategies may be offered. However, the limited sample size per tumor type hampered subgroup analyses.

The results of this study should be interpreted in light of several limitations. First, while the patient groups were better balanced after propensity score matching, confounding by indication may still be of influence, as for example performance status was unknown in nearly a quarter of the patients. Second, selection bias may have occurred in this cohort in comparison with the total patient population in the Netherlands. This is illustrated by the higher resection (28% vs. up to 20%) and chemotherapy rate (61% vs. around 30%), and corresponding median OS compared to results from other Dutch population-based studies.[20,21] Possibly, fitter patients are more willing to complete HRQoL questionnaires and physicians could more often be inclined to include these patients in studies. In addition, selective dropout may have occurred as patients who filled out the 3-months questionnaire had slightly better tumor stage and underwent resection more often than patients who did not. Third, approximately 40% of the baseline questionnaires were not completed prior to the start of cancer treatment and were therefore either not used or treated as follow-up questionnaires. This resulted in missing data. Even though this was partly taken into account by performing mixed model analysis with a longitudinal dataset, data of some patients needed to be deleted from the analyses. Fourth, in 12% of patients, the three-months questionnaire was missing, while the baseline questionnaire was completed after (the median of) start of cancer treatment, which was therefore used as follow-up questionnaire. Therefore, in these cases, the follow-up HRQoL outcomes may be more influenced by the diagnosis or treatment, because the time interval was shorter. Fifth, inherent to HRQoL studies, multiple testing effects may have occurred, due to the large number of subscales per questionnaire. In this case, 23 outcomes were assessed. We have therefore used a cut-off of clinically relevant difference of 10%. In addition, this cohort is relatively small by which the risk of type II errors is higher. The main strengths and unique features of this study are that patients without cancer treatment were included and were matched with patients who received cancer treatment. Even within nationwide cohorts it is difficult to include enough of these patients.

In conclusion, a propensity score-matched cohort of patients with pancreatic or periampullary cancer who did not receive cancer treatment reported similar or worse HRQoL scores at three months follow-up compared to patients with cancer treatment, while their survival was worse. These outcomes may be taken into account in shared-decision making in daily clinical practice. Future studies are needed that take up the challenge to investigate the course of HRQoL of patients with and without cancer treatment on the longer term, closer to death.

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Conflicts of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2021.09.003.