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Landscape of Health-Related Quality of Life in Patients With Early-Stage Pancreatic Cancer Receiving Adjuvant or Neoadjuvant Chemotherapy

A Systematic Literature Review

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Objectives: Pancreatic resection is associated with postoperative morbidity and reduced quality of life (QoL). A systematic literature review was conducted to understand the patient-reported outcome measure (PROM) landscape in early-stage pancreatic cancer (PC).

Methods: Databases/registries (through January 24, 2019) and conference abstracts (2014–2017) were searched. Study quality was assessed using the Newcastle-Ottawa Scale/Cochrane risk-of-bias tool. Searches were for general (resectable PC, adjuvant/neoadjuvant, QoL) and supplemental studies (resectable PC, European Organisation for Research and Treatment of Cancer QoL Questionnaire [QLQ] – Pancreatic Cancer [PAN26]).

Results: Of 750 studies identified, 39 (general, 22; supplemental, 17) were eligible: 32 used QLQ Core 30 (C30) and/or QLQ-PAN26, and 15 used other PROMs. Baseline QLQ-C30 global health status/QoL scores in early-stage PC were similar to all-stage PC reference values but lower than all-stage–all-cancer values. The QoL declined after surgery, recovered to baseline in 3 to 6 months, and then generally stabilized. A minimally important difference (MID) of 10 was commonly used for QLQ-C30 but was not established for QLQ-PAN26.

Conclusions: In early-stage PC, QLQ-C30 and QLQ-PAN26 are the most commonly used PROMs. Baseline QLQ-C30 global health status/QoL scores suggested a high humanistic burden. Immediately after surgery, QoL declined but seemed stable over the longer term. The QLQ-C30 MID may elucidate the clinical impact of treatment on QoL; MID for QLQ-PAN26 needs to be established.

Key Words: health-related quality of life, minimally important difference, pancreatic cancer, pancreatic resection, patient-reported outcome measures

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Surgical resection is the only potentially curative option for pancreatic cancer (PC).[1,2] However, pancreatic resection is associated with significant postoperative morbidity and reduced quality of life (QoL).[3–5] In early-stage PC, adjuvant chemotherapy may significantly improve survival outcomes compared with surgery alone,[6,7] and recent trials of combination chemotherapy are changing the treatment landscape.[8–10] Current guidelines of the National Comprehensive Cancer Network, American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO) recommend adjuvant chemotherapy as a standard of care for patients with resected PC.[1,2,11] In addition, some studies have documented conversion of locally advanced, unresectable PC to resectable status with neoadjuvant chemotherapy, and the postsurgical survival rates in these patients were comparable to those observed in patients with resectable disease.[12–14] It is not completely clear how recent advances have influenced QoL in patients with early-stage PC who have undergone surgery and received chemotherapy. Therefore, it is important to understand the landscape of patient-reported outcome measures (PROMs) that can quantify and track QoL in these patients.

In advanced PC, tools such as the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30), the EORTC Quality of Life Questionnaire Pancreatic Cancer Module (QLQ-PAN26), and the EuroQoL 5-Dimension Questionnaire (EQ-5D) have been used to assess the effect of therapy on QoL.[15–17] However, in early-stage PC, it is unclear from the few available studies of QoL which PROMs are most commonly used and appropriate. A more thorough understanding

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of QoL in early-stage PC, including how it changes over time after surgery as well as the PROMs most commonly used to measure QoL, may help identify specific areas that have not been fully examined and help clinicians use appropriate symptom management and adjuvant strategies in this patient population.

To address this need, we conducted a systematic literature review (according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines) of studies evaluating QoL in patients with early-stage PC who underwent resection to (1) assess the landscape of the QoL PROMs used, (2) understand how QoL changes over time after surgical resection, and (3) assess which specific thresholds have been used to define a minimally important difference (MID) in QoL.

MATERIALS AND METHODS

Search Strategy and Study Selection

A team composed of medical oncologists, health economics and outcomes research scientists, and a statistician formed a panel to develop the search, selection, and review strategies. Databases (Medline, Embase [via ProQuest], Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials) and registries (ClinicalTrials.gov and International Clinical Trials Registry Platform) were searched through January 24, 2019. In addition, congress abstracts and presentations (ASCO, ASCO Gastrointestinal Cancers Symposium, and ESMO World Congress of Gastrointestinal Cancer) from 2014 to 2017 were searched. Studies were included in accordance with the PRISMA statement.[18] Search terms were designed to include specific populations (resectable or borderline-resectable PC), interventions (adjuvant or neoadjuvant chemotherapy), and outcomes (QoL as assessed by PROMs; Supplemental Table 1 http://links.lww.com/MPA/A776). Any of the following study designs were permitted: randomized, controlled trials (phase 2, 3, or 4); single-arm trials; observational studies; prospective studies; and protocols (for the MID and PROM identification objectives). Only studies published in English were considered. The original search did not identify any study reporting MID results for the EORTC QLQ-PAN26 PROM; therefore, a supplemental search with expanded search terms (resectable or borderline-resectable PC; EORTC QLQ-PAN26) was conducted to identify studies that assessed MID for EORTC QLQ-PAN26 (Table, Supplemental Digital Content 1 http://links.lww.com/MPA/A776). Studies of advanced PC, case series, case reports, nonsystematic literature reviews, nonhuman studies, and studies with no abstract were excluded. Duplicates were removed, and only the most up-to-date reports of research were included (eg, congress presentations were removed if a peer-viewed article was identified).

Data Extraction

Two reviewers independently screened all titles and abstracts to develop a list of reports for full-text review. Any discrepancies were adjudicated by a third reviewer. Reports selected for full-text review were screened by 1 reviewer for data extraction and qualitative synthesis. Data on population characteristics (eg, location, time frame, sample size, and demographic characteristics), interventions (eg, adjuvant or neoadjuvant chemotherapy), and outcomes (eg, PROMs used, survival data, QoL [including longitudinal data, when available], and MID) were extracted from the included studies into a database.

Assessment of Study Quality

The study quality was assessed independently by 2 reviewers, and a third reviewer resolved any disagreements. Nonrandomized observational studies were assessed using the Newcastle-Ottawa Scale (NOS),[19] and randomized controlled trials were assessed using the Cochrane risk-of-bias tool.[20] The NOS assesses study quality in 3 domains—selection, comparability, and outcome—and assigns scores of ≤4, 2, and 3 points, respectively, yielding a total maximum score of 9. A study was considered to be of high quality if the total NOS score was ≥7.[21,22] The Cochrane risk-of-bias tool assesses study quality in 6 bias domains: selection (sequence generation and allocation concealment), performance (blinding of participants and personnel), detection (blinding of outcome assessments), attrition (incomplete outcome data assessment), reporting (selective reporting), and other (any important concern not covered in the other domains). The Cochrane tool assigns a risk of bias—low, high, or unclear—for each category.

Result Synthesis

In a narrative synthesis, the EORTC QLQ-C30 global health status (GHS)/QoL scale scores were compared with EORTC QLQ-C30 reference norms[23] and assessed longitudinally when possible. The MID estimates for the most frequently used PROMs were assessed.

RESULTS

Study Selection and Data Extraction

Of the 750 records identified initially, 660 were captured from the general search; the supplemental search produced 90 additional records (Fig. 1). After removing duplicates and excluding records during initial screening, 95 studies were assessed in full; of these, 56 studies did not meet the eligibility criteria and were excluded. Overall, 39 studies (22 captured from the general search and 17 from the supplemental search) were included in the final qualitative synthesis (Fig. 1); of these, 28 were observational studies and 11 were randomized, controlled trials (Table 1).

Study and Population Characteristics

The key characteristics of the included studies and their respective populations are shown in Table 1. The sources for 3 studies were conference abstracts,[32,46,47] and the remaining 36 were full journal articles, including 3 study protocols.[31,57,58] The studied populations included patients in North America, Europe, and Asia who typically received neoadjuvant and/or adjuvant chemotherapy and were assessed for QoL for a variable period (a few months to several years).

Using NOS, 11 of the 28 observational studies were assigned a score of ≥7 (high quality), 13 received a score of 5 or 6 (moderate quality; primarily due to comparability and outcome biases), and 4 received a score of 3 or 4 (low quality due to biases in all 3 domains; Table 2). The risks of bias in the 11 randomized, controlled trials as assessed by the Cochrane tool are shown in Figures 2A and B.

QoL PROMs Landscape in Early-Stage PC

Among the 22 studies included from the original general search, EORTC QLQ-C30 and QLQ-PAN26 were the most commonly used PROMs (15 [68%] studies); among all 39 studies included from the original and supplemental searches, 32 (82%) used EORTC QLQ-C30 and/or QLQ-PAN26 (Table 1). Overall, 15 studies (nonexclusive) used other PROMs: Functional Assessment of Cancer Therapy (FACT; n = 5), 36-item Short Form Survey (SF-36; n = 4), Center for Epidemiologic Studies Depression Scale (n = 2), Audit of Diabetes Dependent QoL (n = 2), EQ-5D (n = 1), Karnofsky performance status (n = 1), visual analog scale (VAS) for pain (n = 1), and Spitzer QoL Index (n = 1; Table 1).

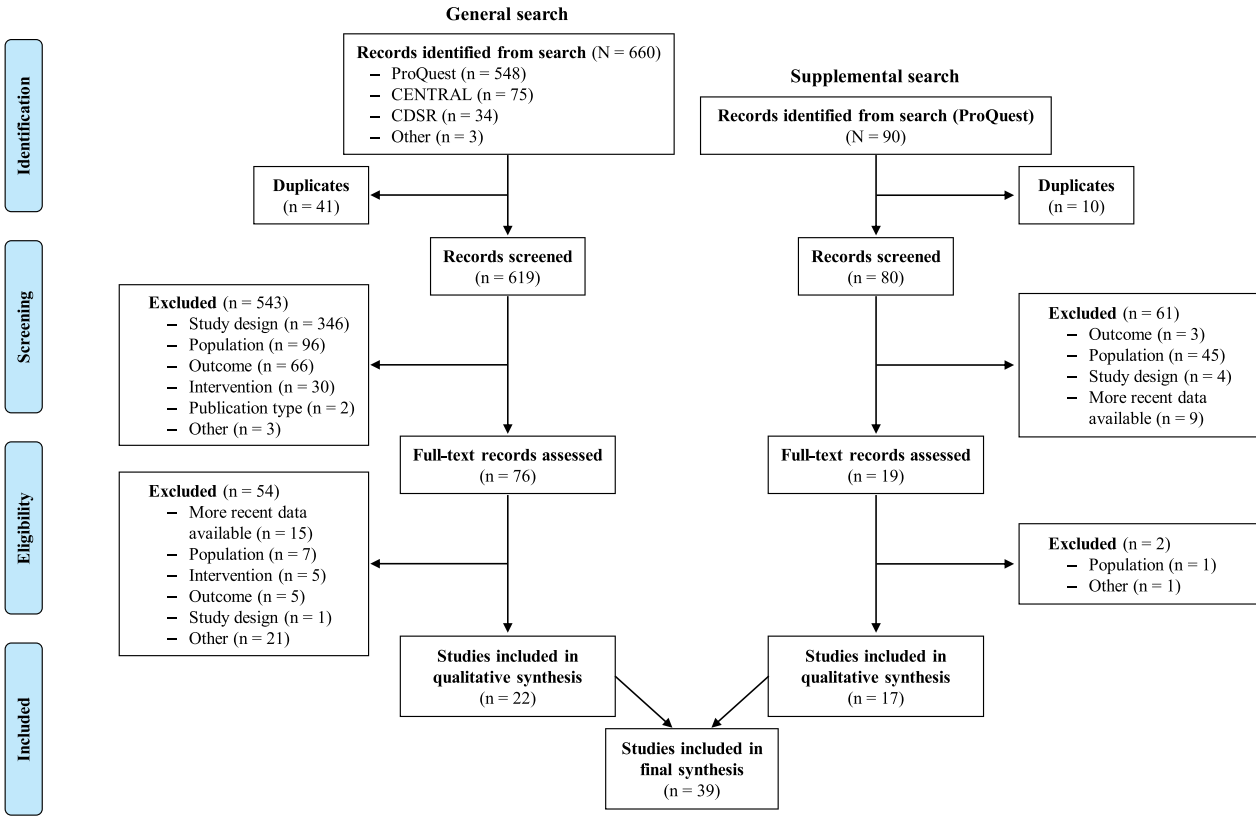

FIGURE 1. Flow diagram based on PRISMA. CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials.

The study that used Karnofsky performance status to assess QoL collected self-reported assessments via mail-in or telephone interview.[24]

QoL Outcomes

The EORTC QLQ-C30 GHS/QoL scores at baseline were compared with previously reported data for PC or all cancers. The baseline QoL was defined using presurgical data (n = 6) or the first postsurgical data (n = 5). The baseline EORTC QLQ-C30 GHS/QoL scores in early-stage PC (median [interquartile range], 61 [59–64]) seemed similar to reference norms reported for PC (all stages and including liver and biliary cancers; 58 [42–75]; n = 750) but lower than those reported for all cancers (all stages; 67 [50–83]; n = 23,553).[23]

Overall, 13 studies reported longitudinal QoL data; of these, 11 studies reported longitudinal EORTC QLQ-C30 GHS/QoL data (Table 3). Most of these studies used chemotherapy (with or without radiation) in the adjuvant setting (Table 3). Chemotherapy included gemcitabine, FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin), mitoxantrone, fluorouracil, cisplatin, carboplatin, oxaliplatin, capecitabine, paclitaxel, and pasireotide. In addition to the EORTC QLQ-C30, 6 studies used EORTC QLQ-PAN26 and 5 studies used other PROMs (SF-36, EQ-5D, Pain VAS, and FACT-General/FACT-Hepatobiliary Cancer Subscale) to report longitudinal QoL data. As expected, the number of patients who completed the QoL questionnaires decreased over time in most studies (Table 3).

Two of the 11 studies that reported longitudinal EORTC QLQ-C30 GHS/QoL data reported change over time but did not report absolute scores; the remaining 9 studies reported GHS/QoL scores in 11 settings at baseline and at multiple postsurgical time points (Fig. 3). Some of these studies reported a transient decline immediately after surgery in GHS/QoL scores, which recovered to baseline levels in 3 to 6 months (Fig. 3, Table 3). In one study, a significant decrease was reported in GHS/QoL scores at 2 weeks ($P < 0.01$) and 2 months ($P = 0.03$) in postsurgical versus presurgical scores.[55] In another study, the overall QoL scores were significantly lower in patients receiving chemotherapy (5-fluorouracil plus leucovorin [$P = 0.03$] or gemcitabine [$P = 0.001$]) versus observation at 3 months after surgery, but the scores were similar at 12 months after surgery (Table 3).[53] Collectively, these studies demonstrated a trend of decline in GHS/QoL scores during the first few months after surgery with recovery of GHS/QoL scores over time. Consistent with this observation, Park et al[34] reported numerically higher GHS/QoL scores at 12 months after surgery versus before surgery, and Pezzilli et al[29] reported a significant increase in QoL for 24 months after surgery ($P < 0.001$). Most studies (7/10) reported no statistically significant change in GHS/QoL scores over the follow-up period (Table 3). Changes in the EORTC QLQ-C30 functionality and symptoms scales were generally similar to those in the GHS/QoL scale, and no specific patterns were observed in individual scales across studies (data not shown). In the 6 studies that used EORTC QLQ-PAN26, changes in specific subscales varied but were generally consistent with those in QLQ-C30 scales (data not shown).

MID Outcomes

Six studies used specific thresholds to define clinically important differences in EORTC QLQ-C30 GHS/QoL scores within or between groups (Table 4). Four of these studies used a cutoff of 10 points in QoL scores to define an MID, including 1 study that additionally

TABLE 1. Study Population Characteristics

Study	Study Design	Populations: Country/ Region	N	Age, Median, y	Disease Type	CT Setting	QoL Assessment: PROM Used	Follow-Up Period	Schedule
Observational studies									
Kokoska et al[24]	Multicenter, prospective	United States	781	63*	PC, including colloid, giant and small cell, squamous, acinar, and papillary tumors	Adj	KPS	NR	At least once a year
Billings et al[25†]	Chart review with cross-sectional QoL follow-up	United States	99	61*	PDAC: 33; chronic pancreatitis: 20; IPMN with CIS or invasive adenocarcinoma: 17; IPMN: 9; islet cell neoplasm: 6; periampullary adenocarcinoma: 5; cystic neoplasm of pancreas: 3; other malignancy: 6	NR	QLQ-PAN26; SF-36; ADDQoL	7.5 y[‡]	NR
Kostro and Sledzinski[26†]	Single center, prospective	Poland	54	60	PC	NR	QLQ-C30; QLQ-PAN26	6 mo	1–4 d presurgery; 1, 2, 3, and 6 mo postsurgery or until death
Ocuin et al[27†]	Chart review with cross-sectional QoL follow-up	United States	31	55, 54[§]	PC with lesions confined to neck or proximal body	NR	QLQ-C30; QLQ-PAN26	29 mo[‖]	NR
Katz et al[28]	Phase 2	United States	28	60	PDAC of pancreatic head	Adj	QLQ-C30; QLQ-PAN26; CES-D	5 y	At enrollment; weeks 3 and 6; before each systemic 5-FU; at each surveillance evaluation
Pezzilli et al[29]	Multicenter, prospective	Italy	197	62*	PC: 145 (ductal carcinoma, 97; IPMN, 35; nonfunctioning endocrine tumor, 7; serous cystadenoma, 4; renal cancer or multiple myeloma metastasis, 2); cancer of papilla of Vater: 33 (adenocarcinoma, 31; adenoma, 2); chronic pancreatitis: 8; other periampullary neoplasia: 11 (duodenal, 5; common bile duct, 5; duodenal endocrine tumor, 1)	Neoadj or adj	QLQ-C30; VAS	24 mo	Presurgery; 6, 12, 18, and 24 mo after discharge
Mbah et al[30]	Prospective	NR	34	65	PC (PDAC, 23; other, 11)	Adj	QLQ-C30; FACT-An	6 mo	Presurgery; 2, 3 and 6 wk; 3 and 6 mo postsurgery

Roeder et al[31]	Single center, single arm, phase 1/2	Germany	NR	NR	PC of pancreatic head	Neoadj	QLQ-C30; QLQ-PAN26	5 y	NR
Ryska et al[32]	Multicenter, prospective	NR	151	NR	PDAC	Adj	SF-36	3 mo	Before and 3 mo after treatment
Zabernigg et al[33]	Single center cohort	Austria	23	67*	PC: 18; gallbladder cancer: 5	Adj	QLQ-C30	NR	At diagnosis; when possible, during each CT cycle
Park et al[34]	Prospective	Korea	136	59*	PC: 83 (ductal, 31; ampulla of Vater, 25; common bile duct, 18; IPMN, 5; duodenal, 2; NET, 1; renal cancer metastasis, 1); benign disease: 53 (solid pseudopapillary, 8; IPMN, 8; MCN, 7; chronic pancreatitis, 7; NET, 4; SCN, 4; ampulla of Vater adenoma, 4; duodenal stromal, 1)	Adj	QLQ-C30	1 y	Presurgery; 1 and 2 wk and 3, 6, and 12 mo postsurgery
Short et al[35†]	Prospective, longitudinal	Australia	22	56*	PDAC of head or body	Adj	QLQ-C30, QLQ-PAN26	NR	<14 d before initiating gem; time points 1 (end of induction of gem and before RT/5-FU), 2 (end of final week of RT/5-FU, 3 (4 wk after RT/5-FU), and 4 (end of study)
Toyama et al[36]	Phase 1	Japan	94	68, 69¶	PC (adenocarcinoma, 87; other, 7)	Adj	QLQ-C30; QLQ-PAN26	NR	At each outpatient appointment
Epelboym et al[37†]	Chart review with cross-sectional QoL follow-up	United States	77	NR	PC: 57 (PDAC, including IPMN, 50; endocrine, 4; mucinous cystadenocarcinoma, 2; renal cancer metastasis, 1); benign disease: 20 (diffuse IPMN, 15; pancreatitis, 4; serous cystadenoma, 1)	NR	QLQ-C30; QLQ-PAN26	45 mo‖	45 mo postsurgery
Roberts et al[38†]	Case-matched analysis	United Kingdom	23	63	Chronic pancreatitis: 9; IPMN: 5; renal cancer metastasis: 3; NET: 3; POPF/sepsis, 3; adenocarcinoma: 2, necrotizing pancreatitis: 1; solid pseudopapillary: 1; microcystic adenoma: 1#	NR	QLQ-C30; QLQ-PAN26	9.9 y**	NR
Serrano et al[39]	Multicenter, prospective, phase 2	NR	55	64	PDAC	Neoadj and adj	QLQ-C30; QLQ-PAN26; FACT-G; FACT-Hep	2 y	Presurgery (at baseline and after cycle 2 of neoadj therapy); postsurgery month 3 (preadjuvant), 6 mo after treatment initiation and at 6-mo intervals for 24 mo

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TABLE 1. *(Continued)*

Study	Study Design	Populations				CT Setting	QoL Assessment		
		Country/ Region	N	Age, Median, y	Disease Type		PROM Used	Follow-Up Period	Schedule
Aguilar et al[40]	Dose escalation	United States	14	67	PC	Adj	FACT-Hep	NR	At baseline and follow-up visits
Arvaniti et al[41†]	Prospective	Greece	20	66*	PC of pancreatic head: 17; duodenal cancer: 3; gallbladder cancer: 1; chronic pancreatitis: 1	Adj	QLQ-C30; QLQ-PAN26	6 mo	Presurgery; 1, 3, and 6 mo postsurgery
Hartwig et al[42†]	Prospective, database	Germany	434	64	PDAC: 289; IPMN: 75; NET: 28; other adenocarcinoma: 18; adenosquamous carcinoma: 8; SCN: 4; acinar cell cancer: 4; other: 8	Adj	QLQ-C30; QLQ-PAN26	21.5 mo	At 3-, 6-, and 12-mo intervals
Moningi et al[43†]	Prospective, cross-sectional cohort	United States	26	67, 63*,††	Majority had PDAC, but patients with IPMN and NET were included	NR	QLQ-PAN26	Once	At initial presentation
Baekelandt et al[44†]	Prospective	Norway	44	68	PDAC	Adj	QLQ-C30; QLQ-PAN26	39 mo	At diagnosis (≤1 mo presurgery)
Wu et al[45†]	Prospective, database	United States	186	62	PC: 134 (PDAC, 106; NET, 19; renal cancer metastasis, 8; other periampullary, 1); benign disease: 52 (noninvasive IPMN, 20; chronic pancreatitis, 19; MCN/SCN, 4; other, 9)	NR	QLQ-PAN26; SF-36; ADDQoL	5.9 y‖	NR
Zonderhuis et al[46†]	Cross-sectional survey	NR	77	NR	NR	NR	QLQ-C30; QLQ-PAN26	18 mo‖	18 mo postsurgery
Abdel-Rahman et al[47]	Single center, cohort	Canada	167	63	PC, with 68% having adenocarcinoma and 53% having pancreatic-head tumors	Adj‡‡	QLQ-C30; QLQ-PAN26	NR	Presurgery; postsurgery
Laitinen et al[48†]	Prospective, longitudinal	Finland	47	66	PDAC	Adj§§	QLQ-C30; QLQ-PAN26	2 y	Presurgery; 3, 6, 12, 18, and 24 mo postsurgery
Okada et al[49]	Single center, prospective, phase 1	Japan	10	70*	Adenocarcinoma or adenosquamous carcinoma	Neoadj	FACT/GOG-NTX subscale	NR	NR
Arvaniti et al[50†]	Singe center, prospective, longitudinal	Greece	40	66*	PC of pancreatic head: 37; duodenal cancer, 3; PC of pancreatic body, 1, lower bile duct cancer, 1; chronic pancreatitis: 1	NR	QLQ-C30; QLQ-PAN26;	6 mo	Presurgery; 1, 3, and 6 mo postsurgery

Heerkens et al[5†]	Prospective, cohort	The Netherlands	137	67	Adenocarcinoma: 77; papillary carcinoma: 17; IPMN: 17; cholangiocarcinoma: 9; NET: 7; duodenal carcinoma: 4; Hamoudi tumor: 2; acinar cell carcinoma: 1; mucinous cystadenoma: 1; solitary fibrous tumor: 1; metastasis: 1	Adj[‖‖]	QLQ-C30; QLQ-PAN26; SF-36	12 mo	1, 3, 6, and 12 mo postsurgery until loss to follow-up or death
Randomized controlled trials									
Oettle et al[6]	Open label, multicenter, phase 3	Germany, Austria	179	62	Adenocarcinoma: 175; other: 4	Adj	Spitzer QoL Index	2 y	Every 4 weeks postsurgery
Carter et al[51]	Longitudinal QoL study in a subset of ESPAC-1 patients	Europe	316	60	PDAC	Adj	QLQ-C30	24 mo	Postsurgery and before randomization; 3-mo intervals thereafter
Morak et al[52]	Prospective	NR	59	62	Adenocarcinoma (pancreatic head, 31; periampullary, 28)	Adj	QLQ-C30	24 mo	Every 3 mo after randomization
Neoptolemos et al[53]	Open label, phase 3	Europe, Australia, Japan, Canada	284	61, 63[¶¶]	Periampullary cancer of pancreatic head (ampullary, 192; bile duct, 65; other, 27)	Adj	QLQ-C30	5 y	Baseline; 3 mo; 6 mo; and then yearly
Schmidt et al[54]	Open label, multicenter, phase 3	Germany	110	60*	Pancreatic adenocarcinoma	Adj	QLQ-C30; QLQ-PAN26; CES-D	5 y	Baseline; every 3 mo in years 1 and 2; every 4 mo in year 3; every 6 mo in years 4 and 5
Eaton et al[55] and Allen et al[56]	Double blind, placebo controlled, phase 3	United States	300	64*	Adenocarcinoma: 188 (pancreatic, 154; ampullary, 23; bile duct, 6; duodenal, 5); intraductal papillary mucinous neoplasm: 35; NET: 28; serous cystadenoma: 17; acinar cell carcinoma: 6; other, 26	Adj[###]	QLQ-C30; QLQ-PAN26	60 d	Presurgery; 14 and 60 d postsurgery
Richter et al[57†]	Prospective	Germany	NR	NR	PC; bile duct carcinoma; NET; periampullary carcinoma; duodenal carcinoma; IPMN	Adj	QLQ-C30; QLQ-PAN26	12 mo	2 d presurgery; 5 d and 3, 6, and 12 mo postsurgery
Müller et al[58]	Single center	Switzerland	140***	NR	PC	Adj	QLQ-C30; QLQ-PAN26	60 mo	Screening; discharge; 1, 3, 6, 12, and 60 mo postsurgery
Neoptolemos et al[8]	Open label, multicenter, 2 arms, phase 3	Europe	730	65	PDAC	Adj	QLQ-C30	43.2 mo[‖]	Baseline; 3, 6, and 12 mo
Burrell et al[59,60]	Nested, longitudinal	United States	143	67*	PDAC	Adj[†††]	FACT-Hep	9 mo	Presurgery; 3, 6, and 9 mo postsurgery

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TABLE 1. *(Continued)*

Study	Study Design	Populations: Country/ Region	N	Age, Median, y	Disease Type	CT Setting	QoL Assessment: PROM Used	Follow-Up Period	Schedule
Hagiwara et al[61]	Open label, multicenter, noninferiority, phase 3	Japan	354	66	Tubular adenocarcinoma: 317; other, 37	Adj	EQ-5D	2 y	Baseline (postsurgery, before randomization); 3, 6, 12, 18, and 24 mo after initiating adjuvant therapy

*Mean age.

†Study captured in supplemental search.

‡Reported as mean.

§Mean age for patients with central and extended lateral pancreatectomy, respectively.

‖Reported as median.

¶In patients who received gem and 5-FU–based CT, respectively.

#Numbers add up to 28; 5 patients (unclear which ones) were excluded from analysis due to mismatch with the control group.

**Reported as median potential follow-up period.

††In resectable and resected, respectively.

‡‡In 75% of patients.

§§In 41 patients; 6 received no chemotherapy.

‖‖In 49 patients; 86 received no adjuvant therapy, and 2 were lost to follow-up.

¶¶In patients who received gem and FU + leucovorin, respectively.

##Given twice daily starting on the morning of surgery and continuing for 7 days.

***Estimated.

†††In 117 patients.

5-FU indicates fluorouracil; ADDQoL, Audit of Diabetes Dependent QoL; adj, adjuvant; CES-D, Center for Epidemiologic Studies Depression Scale; CIS, carcinoma in situ; CT, chemotherapy; FACT-An, FACT-Anemia; FACT-G, FACT-General; FACT/GOG-NTX, FACT/Gynecologic Oncology Group–Neurotoxicity; FACT-Hep, FACT–Hepatobiliary Cancer; FU, fluorouracil; gem, gemcitabine; IPMN, intraductal papillary mucinous neoplasms; KPS, Karnofsky performance status; MCN, mucinous cystic neoplasm; neoadj, neoadjuvant; NET, neuroendocrine tumor; NR, not reported; PDAC, pancreatic ductal adenocarcinoma; POPF; postoperative pancreatic fistula; RT, radiation therapy; SCN, serous cystic neoplasm.

TABLE 2. Quality of Nonrandomized Observational Studies as Assessed by Scores on the NOS*

Study	Selection (Out of 4)	Comparability (Out of 2)	Outcome (Out of 3)	Total (Out of 9)
Kokoska et al[24]	4	1	0	5
Billings et al[25†]	3	1	2	6
Kostro and Sledzinski[26†]	4	1	2	7
Ocuin et al[27†]	3	1	0	4
Katz et al[28]	3	2	1	6
Pezzilli et al[29]	4	1	2	7
Mbah et al[30]	4	1	2	7
Roeder et al[31]	4	1	2	7
Ryska et al[32]	4	1	0	5
Zabernigg et al[33]	2	1	1	4
Park et al[34]	4	2	2	8
Short et al[35†]	3	1	1	5
Toyama et al[36]	4	0	1	5
Epelboym et al[37†]	4	1	1	6
Roberts et al[38†]	4	1	1	6
Serrano et al[39]	4	2	2	8
Aguilar et al[40]	4	2	2	8
Arvaniti et al[41†]	3	1	2	6
Hartwig et al[42†]	3	1	2	6
Moningi et al[43†]	2	1	0	3
Baekelandt et al[44†]	4	2	1	7
Wu et al[45†]	4	1	0	5
Zonderhuis et al[46†]	3	1	1	5
Abdel-Rahman et al[47]	4	1	0	5
Laitinen et al[48†]	4	1	2	7
Okada et al[49]	3	0	0	3
Arvaniti et al[50†]	4	1	2	7
Heerkens et al[5†]	4	1	2	7

*The NOS assigns a maximum score of 4, 2, and 3 for selection, comparability, and outcome parameters, respectively, for a maximum total score of 9.
†Study captured in supplemental search.

defined smaller (5–10 points) and larger (>20 points) cutoffs. Two studies used 0.5 × baseline standard deviation (SD) as the cutoff.

Four studies used specific thresholds to define clinically important differences in EORTC QLQ-PAN26 scores within or between groups (Table 4); of these, 2 studies used 10 points, 1 used 0.5 × baseline SD, and 1 used a specific absolute score to define a clinically important change in QoL. The reported MIDs for EORTC QLQ-C30 and QLQ-PAN26 were used in various ways, including to interpret differences in mean scores between groups, mean changes over time within groups, individual patient scores at

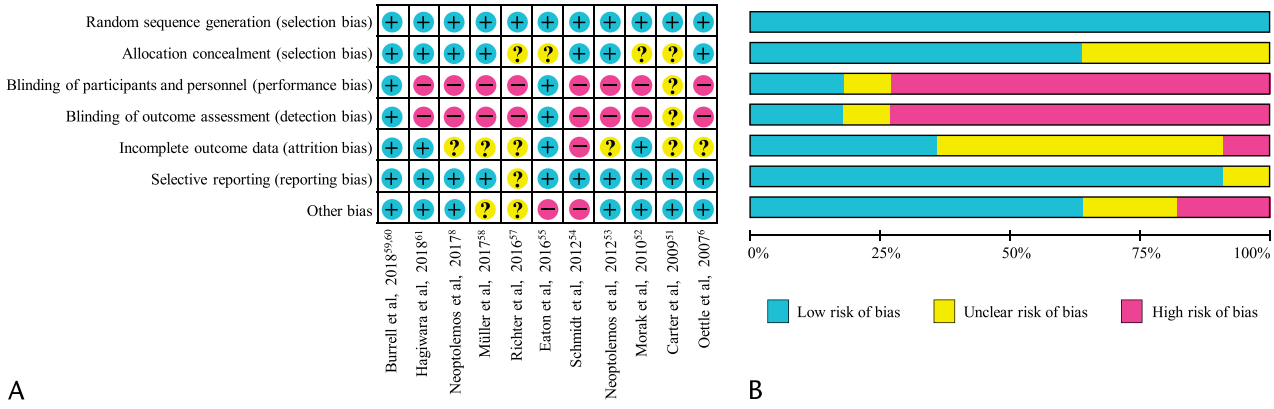

FIGURE 2. Quality of randomized, controlled trials as assessed by the Cochrane risk-of-bias tool. A, Assessments by study and category. B, Proportion of studies with low, unclear, and high risk of bias in each category.

TABLE 3. QoL Outcomes Over Time

Study	CT Setting	PROMs	QoL Follow-Up Schedule (N)*	Change in GHS/QoL From Baseline† (*P*)	Relevant Remarks
Observational studies					
Pezzilli et al[29]	Neoadjuvant or adjuvant	QLQ-C30; VAS	Presurgery (197); postsurgery months 6 (174), 12 (148), 18 (127), and 24 (102)	↑ (<0.001)	At the end of study, the GHS/QoL score was similar to norms, except for emotional and cognitive functioning scores—which were higher than norms—and symptoms scores for pain, fatigue, insomnia, and dyspnea—which were lower than norms.
Park et al[34]	Adjuvant	QLQ-C30 (GHS and functionality scales)	Presurgery (136); postsurgery week 1–2 (136), months 3 (136), 6 (136), and 12 (136)	↑ (NR)	GHS/QoL and functionality scores decreased after surgery but recovered to preoperative levels by 3 mo ($P < 0.001$). The scores were similar to those in the general population. At 12 mo, GHS/QoL score was higher than the presurgery score (P = NR), which may be due to higher emotional and social scores.
Short et al‡[35]	Adjuvant	QLQ-C30; QLQ-PAN26	Postsurgery baseline (≈6 wk), after first chemotherapy cycle (≈10 wk), after chemoradiation (≈16 wk), before 2nd chemotherapy cycle (≈20 wk), and at the end of treatment (≈32 wk; NR)	↔ at ≈10 wk and ≈16 wk (>0.05); ↑ at ≈20 wk (0.03); ↔ at ≈2 wk (>0.05)	After a nonsignificant decline from baseline (≈6 wk) to time point 1 (≈10 wk), GHS/QoL progressively increased to become significantly higher at time point 3 (≈20 wk), both statistically ($P = 0.03$) and clinically (increase of 15.3%); it remained high and clinically significant at the end of study (≈32 wk) but was not statistically significant.
Serrano et al[39]	Neoadjuvant + adjuvant	QLQ-C30; QLQ-PAN26; FACT-G; FACT-Hep HCS	Presurgery baseline (53) and at completion of cycle 2 (39); postsurgery months 3 (23), 6 (21), 12 (19), 18 (13), and 24 (10)	↔ (0.0987) for neoadjuvant; NR for neoadjuvant and adjuvant	GHS/QoL score showed tendency to decrease, and physical functioning decreased significantly ($P = 0.0014$) during neoadjuvant therapy; GHS/QoL and physical and emotional functioning scores showed tendency to increase after surgery.
Arvaniti et al‡[41]	Adjuvant	QLQ-C30; QLQ-PAN26	Presurgery (20); postsurgery months 1 (18), 3 (17), and 6 (16)	↔ (0.467)	Improvement in most of the assessed parameters suggests that surgical resection may have a favorable impact on QoL.
Arvaniti et al‡[50]	NA	QLQ-C30; QLQ-PAN26	Presurgery (40); postsurgery months 1 (40), 3 (39), and 6 (37)	↔ (0.089)	Fatigue, loss of appetite, diarrhea, and financial difficulty worsened; pain and constipation decreased; and dyspnea and insomnia remained unaltered over time. Nausea/vomiting increased initially and decreased to presurgery levels by 6 mo. Physical, role, and social functioning worsened, and emotional and cognitive functioning did not significantly change over time. Scores on GHS, diarrhea, and social functioning scales improved slightly from months 3–6.
Heerkens et al‡[5]	Adjuvant	QLQ-C30; QLQ-PAN26; SF-36	Presurgery (137); postsurgery months 1 (118), 3 (95), 6 (85), and 12 (58)	↔ (NR)	General health in patients with or without severe postoperative complications was similarly stable during first year after surgery. For most items, QoL decreased in first months and recovered to baseline by 3–6 mo.

(Continued on next page)

TABLE 3. *(Continued)*

Study	CT Setting	PROMs	QoL Follow-Up Schedule (N)*	Change in GHS/QoL From Baseline† (*P*)	Relevant Remarks
Randomized controlled trials					
Morak et al[52]	Adjuvant	QLQ-C30	Postsurgery months 3 (baseline; 46), 6 (45), 9 (33), 12 (16), 15 (17), 18 (14), 21 (15), and 24 (9)	↔ (0.08)§	Mean functionality and symptoms scores improved after therapy, but changes were not statistically significant, except for pain and nausea/vomiting symptoms, which reduced significantly. Effect of therapy was most apparent during 12–24 mo.
Neoptolemos et al[53]	Adjuvant	QLQ-C30	Postsurgery baseline (246), months 3 (170) and 6 (153), and then yearly for 5 y (129 at 12 mo)‖	↓ at mo 3 (<0.05); ↔ at mo 12 (NR)¶	Nausea/vomiting and diarrhea scores were higher at month 3 ($P = 0.050$), and loss of appetite score was higher at months 3 and 6 ($P = 0.030$), with therapy vs observation; the scores were similar in the 2 groups at mo 12 (P = NR).
Eaton et al‡[55]	Adjuvant#	QLQ-C30; QLQ-PAN26	Presurgery (299); postsurgery days 14 (273) and 60 (265)	Baseline to day 14: ↓ (<0.01); baseline to day 60: ↓ (0.03)	Patients undergoing pancreatic resection were treated with pasireotide or placebo; since the results were similar, the data were pooled for the 2 groups.
Neoptolemos et al[8]	Adjuvant	QLQ-C30	Postsurgery baseline (665), months 3 (496), 6 (452), and 12 (388)	↔ (0.3)**	QoL was assessed as a longitudinal covariate modeled jointly with OS. No significant effect was observed in the longitudinal QoL estimate by treatment group (HR, −0.10; 95% CI, −0.29 to 0.09; $P = 0.3$).

*Number of patients who completed QoL questionnaires.

†Baseline was defined as first presurgery score for 6 studies and first postsurgery score for 4 studies.

‡Study captured in supplemental search.

§Change and *P* value reported for therapy versus observation for 24 months.

‖Data were presented only for 12 months after surgery.

¶Change and *P* value reported for therapy versus observation arms.

#Given twice daily starting on the morning of surgery and continuing for 7 days.

**Change and *P* value reported for joint model with OS that included treatment group but not time-by-treatment interaction.

↔, no significant change; ↑, significant increase; ↓, significant decrease.

CA indicates celiac axis; CI, confidence interval; CT, chemotherapy; FACT-G, FACT-General; FACT-Hep HCS, FACT-Hepatobiliary Cancer, Hepatobiliary Cancer Subscale; GHS, HR, hazard ratio; NA, not applicable; NR, not reported; OS, overall survival.

a single time point, and individual patient changes over time (ie, to define which patients had clinically important changes; Table 4).

DISCUSSION

In this systematic literature review assessing QoL PROMs in early-stage PC, EORTC QLQ-C30 and QLQ-PAN26 were identified as the most commonly used QoL PROMs. The EORTC QLQ-C30 GHS/QoL scores at baseline were consistent with reference norms for PC but lower than those for all cancers collectively, supporting the high humanistic burden (ie, challenges faced by patients and their families/caregivers) and unmet need for these patients. The present systematic literature review is one of the few that comprehensively assessed longitudinal QoL data before and after pancreatic resection. The change in QoL over time after surgery varied across the 11 studies that reported these data, but the overarching observation was that QoL initially declined after surgery as observed previously,[53,55] recovered in approximately 3 to 6 months after surgery, and remained generally stable for the rest of the follow-up period. The QoL dynamics reported here are generally consistent with those from a recent systematic literature review that assessed the effect of pancreatoduodenectomy on QoL (17 studies published up to June 2016; 1240 patients), which showed no change in global health and overall QoL during 12 postoperative months in 6 of the 12 studies; the remaining 6 studies reported a postoperative decline in QoL that recovered after 3 to 6 months.[62] Similar trends were seen in physical and social functioning domains and in pain, fatigue, and diarrhea symptoms scales.[62] The initial decline in QoL is consistent with a delayed initiation of adjuvant chemotherapy in a considerable proportion of patients with resected PC,[63,64] and the recovery and stability suggest that QoL may not be negatively affected by chemotherapy, at least in the longer term. Additional research is needed to understand the effect on QoL of other important factors, such as use of neoadjuvant chemotherapy and intensity of adjuvant chemotherapy.

The MID for EORTC QLQ-C30 and QLQ-PAN26 may be useful in understanding the clinically relevant impact on QoL of treating early-stage PC. An MID of 10% (equivalent to a score of 10 points) change in mean QLQ-C30 scores was considered to be clinically important in most studies. This was generally consistent with the previously reported mean differences between groups (range on different subscales, 4–11) or those over time

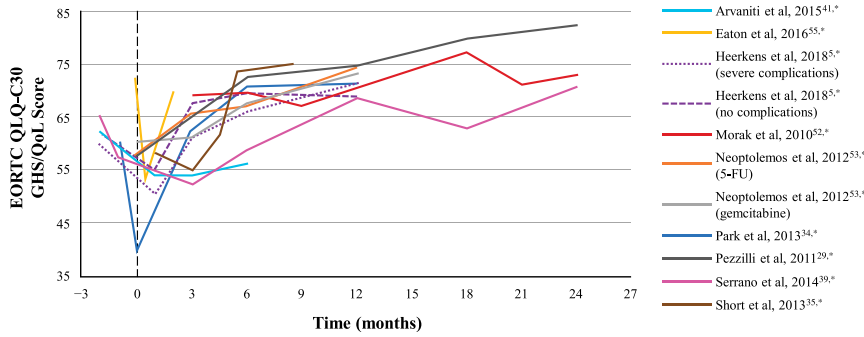

FIGURE 3. Longitudinal GHS/QoL scores before and after surgery. Dashed vertical line represents the time of surgery. *Study captured in supplemental search. 5-FU, 5-fluorouracil.

(improvement, 4–8 points; deterioration, 5–13 points).[65,66] Two studies also used the same threshold for EORTC QLQ-PAN26 scales, but overall, the MID data for this PROM were limited. Two studies for EORTC QLQ-C30 and 1 for EORTC QLQ-PAN26 used 0.5 × baseline SD as a threshold for identifying clinically important change in QoL. For EORTC QLQ-C30, this threshold seems equivalent to a change of approximately 8 to 10 points in mean scores[52,55]; for EORTC QLQ-PAN26, this threshold may be slightly higher (approximately 10–15 points).[55] A recent study underscored the unavailability of reference values for EORTC QLQ-PAN26 in the United States,[45] further suggesting that MID has not been assessed comprehensively and that there is a need to fully establish the reference values for this PROM. The systematic literature review by van Dijk et al[62] did not assess MID values.

Both EORTC QLQ-C30 and QLQ-PAN26 seem to be useful PROMs in assessing QoL in early-stage PC. However, because EORTC QLQ-PAN26 is specifically designed to assess QoL in patients with PC, it may provide more relevant data to help physicians effectively manage symptoms and make treatment decisions

TABLE 4. Reported MID Outcomes for EORTC QLQ-C30 and QLQ-PAN26 PROMs

Study	Reported MID	MID Context*
EORTC QLQ-C30		
Morak et al[52]	0.5 × SD of any QoL tool, usually equivalent to a score of 8–10	MID used to interpret differences in mean scores between groups
Zabernigg et al[33]	Small clinical difference: change in score of 5–10 points Moderate clinical difference: change in score of 10–20 points Large clinical difference: change in score of >20 points	MID used to interpret mean changes within groups
Short et al[35†]	>10% change in mean QoL in an individual scale was considered clinically important (assumed to be equivalent to a score of 10 points based on context)	MID used to interpret mean changes within groups
Serrano et al[39]	10% change in QoL, equivalent to a score of 10 points	MID used to interpret mean changes within groups
Eaton et al[55†]	Moderate or larger clinically important difference in QoL: ≥0.5 × baseline SD	MID used in a responder definition (to define clinically important worsening for an individual patient)
Heerkens et al[5†]	10 points on a 0–100 scale	MID used to interpret differences in mean scores between groups
EORTC QLQ-PAN26		
Short et al[35†]	>10% change in mean QoL in an individual scale was considered clinically important (assumed equivalent to a score of 10 points based on context)	MID used to interpret mean changes within groups
Moningi et al[43†]	Symptom score of 50% (ie, score of 50 points) or higher was considered symptomatic with moderate to severe impairment of QoL	MID used as a diagnostic threshold to define a clinically important score for individual patients
Eaton et al[55†]	Moderate or larger clinically important difference in QoL: ≥0.5 × baseline SD	MID used in a responder definition (to define clinically important worsening for an individual patient)
Heerkens et al[5†]	10 points on a 0–100 scale	MID used to interpret differences in mean scores between groups

*For the purpose of this research, we did not distinguish between MID and responder definition; text in the right column provides additional relevant details.
†Study captured in supplemental search.

in this patient population. Additional research is needed to further validate the EORTC QLQ-PAN26 PROM and establish the MID for adjuvant and neoadjuvant chemotherapy in early-stage PC.

Understanding QoL in patients with early-stage PC may help improve management strategies after pancreatic resection. Adjuvant chemotherapy improves survival outcomes and is recommended by the National Comprehensive Cancer Network, ASCO, and ESMO guidelines as a standard of care[1,2,6–11]; however, only approximately 50% of all patients undergoing pancreatic resection receive adjuvant therapy.[63,64] Pancreatic resection is associated with significant postsurgical morbidity and impaired QoL,[3–5] and postsurgical complications are associated with significantly lower rates and delayed administration of adjuvant therapy.[63,64] Hence, there may be reluctance among physicians and patients toward adjuvant chemotherapy, which could prompt considerations of neoadjuvant or perioperative treatment. A recent study showed that patients with PC who were undergoing resection experienced high levels of depression before surgery through 6 months after surgery; the study suggested that managing physical symptoms and providing psychological support before surgery may improve QoL outcomes in these patients.[67] Results from this systematic literature review may guide more efficient management of patients with early-stage PC who are receiving adjuvant chemotherapy and thus improve the overall outcomes in these patients.

Study Limitations

The studies included in this analysis were heterogeneous in terms of study design (populations and interventions [including the type of chemotherapy]) and QoL assessments (frequency, follow-up duration, and schedule). The reference norms with which the early-stage PC QoL outcomes from this study were compared are approximately a decade old and include all stages of cancer, but these types of data are generally limited in availability, and the norms used here are, to our knowledge, the only such currently available. As a result of disease recurrence, treatment withdrawal, or death, longitudinal QoL assessments do not include the entire initial patient population; therefore, improvement in QoL observed in some studies may reflect survivor selection bias. The changes in QoL over time are presented here in terms of statistical significance, which may not always align with changes of clinical significance. Some did not assess QoL before surgery, which makes it difficult to assess the extent of QoL recovery to the presurgical levels. To partially address this limitation, the graphs across studies were normalized to the time of surgery, which helped to standardize and clarify the trajectory of scores over time. The quality of included studies, as assessed by the NOS and Cochrane risk-of-bias tools, was generally low; however, their collective use in this analysis allowed for a comprehensive assessment of QoL to address an important question for early-stage PC.

CONCLUSIONS AND CLINICAL IMPLICATIONS

In conclusion, EORTC QLQ-C30 and QLQ-PAN26 are the most commonly used PROMs for assessing QoL in patients with early-stage PC who are undergoing surgery. The poor EORTC QLQ-C30 GHS/QoL scores in PC compared with scores in all cancers indicate a high unmet need in this patient population. Although the aforementioned limitations, especially survival bias, should be considered, QoL declined immediately after surgery, recovered in approximately 3 to 6 months, and remained generally stable for the rest of the follow-up period. The MID values for QLQ-C30 may help elucidate the clinically relevant impact on QoL of treating early-stage PC. Future research should establish the MID for EORTC QLQ-PAN26 in this patient population.

The results of this and other studies reveal QoL patterns in patients with early-stage PC who underwent surgical resection. With this knowledge, physicians might be able to identify points of intervention through several approaches: symptom(s) management, psychological and social support, neoadjuvant therapy, and adjuvant therapy initiation as early as possible depending on the individual patient situation and opinion of the treating physician. Collectively, a holistic approach to QoL management may help further refine the treatment guidelines in this patient population.

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