28 Patient Reported Outcomes and Quality of Life

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Introduction

Pancreatic cancer is known to be one of the most aggressive malignancies, with a cumulative 5-year overall survival (OS) of around 9% [1]. Moreover, the incidence and mortality of pancreatic cancer is expected to increase in coming years and pancreatic cancer will become the second most common cause of cancer death in the USA in 2040 [2]. Most cancer trials focus primarily on an OS endpoint to determine the true efficacy of a specific intervention, be it for systemic or local therapeutic modalities. Given the diversity of patient presentations with pancreatic ductal adenocarcinoma (PDAC), primarily focusing on an OS benefit may fail to capture other benefits that therapies may provide—such as quality of life (QoL) and symptom improvement, which would be meaningful in patients who present with a poor performance status (PS) and advanced disease that carries a limited chance of a cure [3]. While extending OS should be a primary focus of any intervention, it is imperative to maximize QoL and minimize treatment-related toxicity and cancer-related symptoms. The experience of patients with PDAC should not be understated as they often experience substantial disease related morbidity that is compounded by treatment-related toxicity especially in elderly patients or those with advanced disease. To date, the benefits of any therapy on OS for PDAC have been comparatively modest. Given the overall poor prognosis for patients with PDAC and the fact that mortality is not expected to significantly improve in the near future, treatments that can improve QoL or symptom burden will be especially meaningful in this patient population.

Even with the improvements in the side effect profile of aggressive systemic therapeutic regimens and technological advancements with local

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therapeutic modalities, QoL outcomes for PDAC remain unacceptably low. A population-matched analysis of PDAC patients with an age-matched healthy patient cohort demonstrated a 98% loss of healthy life and a loss of 610,000–915,000 quality-adjusted life-years (QALYs) annually [4]. PDAC patients also had significantly lower scores on validated health-related quality of life instruments versus population norms [5].

Precedence for the use of QoL metrics has been established for investigating the benefit of various therapeutic modalities such as surgery, systemic therapy, and radiation for pancreatic cancer. For example, a randomized trial in the 1990s used a composite endpoint, termed "clinical benefit" of pain, Karnofsky performance status (KPS) after treatment, and weight to investigate the efficacy of gemcitabine in patients with advanced stage PDAC [6]. Although there was a significant but only modest median OS benefit with gemcitabine, the "clinical benefit" with gemcitabine was 23.8% versus only 4.8% with 5-fluorouracil chemotherapy [6]. However, these metrics remain largely underutilized in PDAC and significant heterogeneity remains in how they are used to capture the patient experience and define the benefit of various therapeutic modalities [7].

Going forward, increased emphasis should be placed in future studies and trials on metrics that can accurately capture the patient experience and define the QoL benefit when evaluating new therapies and interventions for pancreatic cancer.

Definitions of Quality of Life

Historically, physician-graded measures, such as performance status (PS), have been used to measure a patient's QoL in the form of disease burden [8]. The most common metrics used to define PS in PDAC include Karnofsky Performance Status (KPS) and the scoring system described by the European Cancer Oncology Group (ECOG) [4, 9]. KPS describes a patient's functional status as a comprehensive 11-point scale correlating to percentage values ranging from 100% (no evidence of disease, no symptoms) to 0% (death) [4]. The ECOG system was derived from KPS and utilizes a simpler scoring system from 0 to 5 with zero being in excellent health and five signifying death [4]. Although PS scores can be prognostic for survival and provide a consistent way to determine if a patient will be eligible for various therapeutic modalities, they often lack the granularity to drive specific treatment decisions [8]. Nevertheless, most clinical trials include ECOG or KPS as part of the inclusion criteria. Moreover, PS scores like other physician-graded measures, such as the Common Terminology Criteria for Adverse Events (CTCAE) criteria, are subjective and determined by healthcare providers as opposed to being self-reported by the patient. For example, in a multidisciplinary setting it is not uncommon for multiple providers to give different ratings of performance status and Common Terminology Criteria for Adverse Events (CTCAE) criteria for the same patient. This could be addressed by having all data points collected in aggregate, ideally in a dashboard within an electronic health record. This way decisions can be made when there are discrepancies, however, there may still be some incongruence between physician-graded measures and patient reported assessments. In addition, physician-graded measures may not fully capture the range of patient concerns with treatment and disease burden such as maintaining sexual intimacy [7].

Conversely, healthcare related quality of life (HrQoL) assessments are completed by patients, caregivers, and/or with the assistance of the healthcare team. HrQoL evaluations are structured assessments that use data provided by patients and/or family members but are processed with a specific methodology to produce a score or measure that can be used to assess a patient's baseline status or evaluate how a specific treatment regimen alters their current state (positively or negatively). It may cover direct experience of disease or treatment but will also include specific questions which are important to the condition experienced by the patients. The general or global component often includes physical, social, or psychological parameters. The broader term Quality of Life (QoL) will also include factors beyond healthcare and will try to include all aspects of a patient's life. Historically, when QoL was included as part of a clinical trial, HrQoL evaluations were often done on paper and stored away until the completion of the clinical trial. The responses from these HrQoL questionnaires

were not usually incorporated into the routine management of patient care and therefore did not address the acute needs that patients may have.

Patient reported outcomes (PROs) are reports of a patient's status on a specific issue or health condition that comes directly from the patient, without interpretation by a clinician or anyone else [10]. Patient Reported Outcome Measures (PROMs) describe how a patient functions or feels in regard to a condition or therapy, and includes a variety of constructs and methodologies. PROMs can encompass concepts from specific physical symptoms to overall physical function, well-being, and social involvement. HrQoL assessments are a type of PROM that are multi-dimensional, focusing on the patient's overall perception of the effect of their illness and treatment. PROMs can provide an assessment of symptom burden during treatment and are often utilized to provide real-time supportive care and or change management such as adjusting chemotherapy dose or switching to other regimens. The Food and Drug administration (FDA) now takes into consideration patient-reported outcomes for approval of new therapeutic interventions [10], and recognition by the FDA has led to PROMs being more frequently utilized as a surrogate endpoint in clinical trials [11].

QoL can also be captured with objective measures such as evaluation of body composition and mobile-device controlled actigraphy monitoring. Furthermore, with the advent of smartphones and watches, researchers now also have the ability to track patient well-being and or toxicity throughout the trajectory of care. The ability to intervene in "real time," such as by integrating novel interventions like virtual mentoring coupled with virtual reality, may well drastically change how QoL metrics are defined and utilized during treatment. While the focus of the chapter is on QoL, it is important to note that other objective measures of the patient's status exist such as lab values (e.g., albumin, tumor biomarkers), imaging (e.g., sarcopenia, radiomics), vitals, and body mass index (BMI). A holistic approach to patient care with true integration of QoL metrics and the aforementioned objective measures will help better characterize the needs and burden of patients leading to improved overall care of the patient, and potentially translate into improved outcomes (Fig. 28.1).

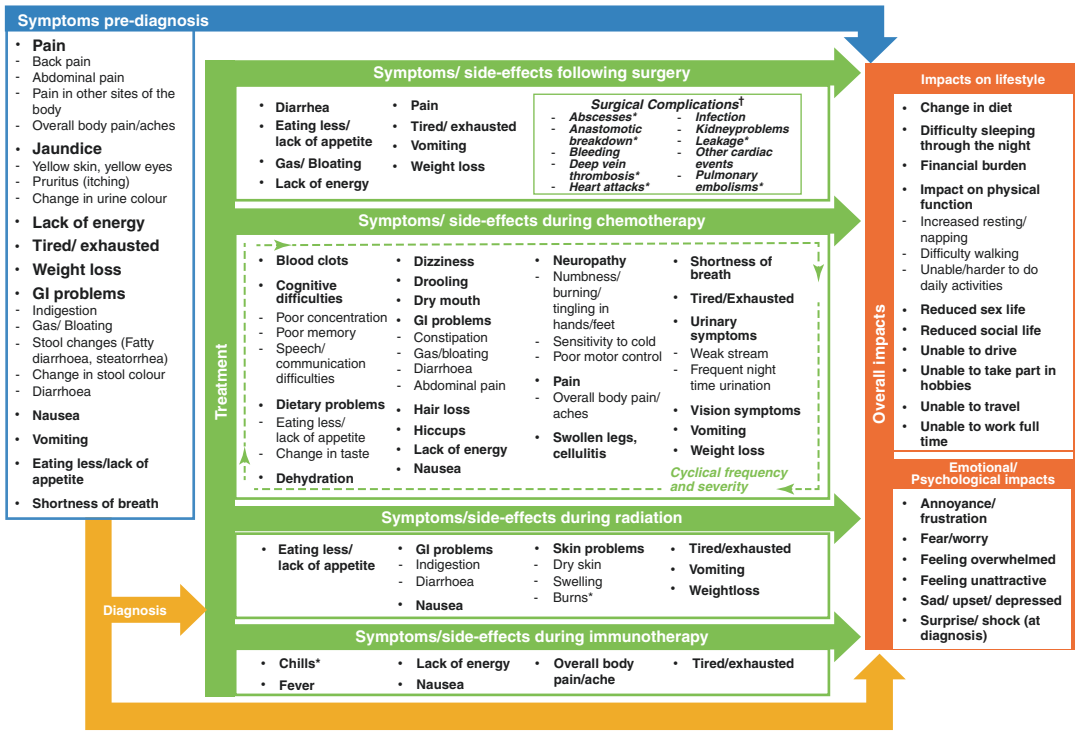


Fig. 28.1 Conceptual model of patient's experience of pancreatic cancer diagnosis and treatment [12]

Potential QoL Tools That Can Be Optimally Implemented for Patients with PDAC

The choice of which QoL tools or PROMs to administer in a study or utilize for patient care should be well thought out and with the patient at the center (Fig. 28.2). These measures should be used to assess the severity of patients' symptoms, monitor global QoL, and composite clinical benefit scores while managing patients' symptoms in real time. There are many factors that may influence the reliability of the information gathered through such assessments, including education and literacy level, preferred language of the patient, how it is administered (paper or online); and the environment in which it is administered (clinic or at home). Moreover, although there are many such tools, only a few have been externally validated. Although non-validated tools may be easier to administer and complete for patients, they should not be used as a primary endpoint in a trial as the significance of results acquired by non-validated tools remain unclear. The value to patients with non-validated tools has yet to be fully characterized.

An example of a HrQoL tool that has been commonly used for various diseases is the National Institute of Health's Patient-Reported Outcome Measurement Information System (PROMIS) tool [14]. Examples of common validated HrQOL tools specific to cancer include the European Organization for Research and Treatment Quality-of-Life Core Questionnaire (EORTC QLQ-C30) and its site-specific subset for the pancreas (PAN26), and the Functional Assessment of Chronic Illness Therapy-Treatment Satisfaction-General (FACIT-TS-G) [15–17]. These tools have also been validated in various settings for PDAC. For example, PROMIS and the EORTC QLQ-C30 have been previously validated in patients with metastatic PDAC [18, 19]. FACIT-TS-G scores have also been used as endpoints in trials for metastatic PDAC [20]. The QLQ-C30 (global) and QLQ-PAN26 (site specific) have been used in the unresectable setting in a multicenter stereotactic body radiation therapy (SBRT) study [7, 21]. In early stage PDAC treated with adjuvant or neoadjuvant chemotherapy, the most common tools utilized were the EORTC QLQ-C30 and PAN26 [22].

It can be challenging to know which QoL tool is ideal for a specific need, and which PROM selection for study design will be ideal in its ability to capture the intended changes in the specific patient population. For example, Herman et al. used both generic and PDAC-specific HrQoL tools (i.e., EORTC-QLQ-C30 and PAN26) to demonstrate that the addition of stereotactic body radiation therapy (SBRT) to pancreatic cancer did not change patients' global QoL while also improving their pain [21]. We therefore reviewed the most commonly utilized QoL tools and PROMs in PDAC and provide an overview of the ones felt to provide the most clinical utility for PDAC patients as summarized in Table 28.1. For research protocols, we recommend that investigators consider using these QoL tools in Table 28.1 for patient and caregiver evaluation at baseline, at specified time points during treatment, and at each follow-up. Ideally, the FH&RF questionnaire could be given at baseline and the FACIT-TS-G can be given at 4 and 12 months. Of note, caregiver reports should be tracked and deemed acceptable as an alternative for PROMs if the patient cannot self-complete the surveys. Additionally, a comprehensive family history questionnaire and Daily Status Log are other PROMs that can be used to further characterize the patient experience.

These tools should be used by investigators to better capture the patient perspective in characterizing the safety and effectiveness of various treatment regimens for PDAC, and to use as a guide for consideration of what modifications may be needed in the future. In addition, utilization of these tools in the clinic should improve symptom management and lessen any stresses and anxieties that pancreatic cancer patients experience as a result of illness and treatment. Consideration should be given to capturing responses on mobile devices or computers so that the responses are available in real time for pro-

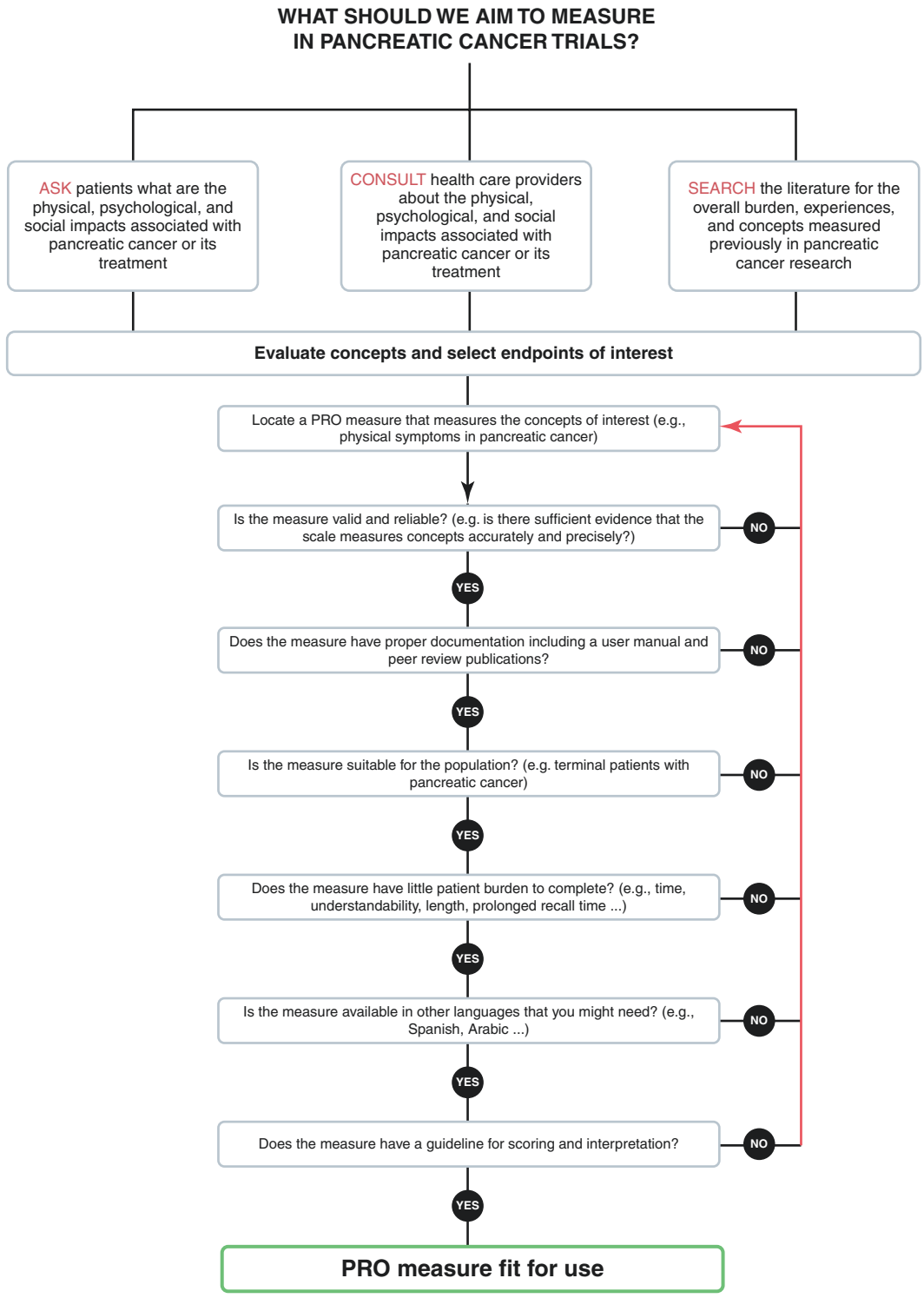


Fig. 28.2 Patient-reported outcome (PRO) measure selection [13]

Table 28.1 Description of potential PRO questionnaires for PDAC

PRO questionnaire	Description	Measure	Why chosen, significance
European Organization of Research and Treatment of Cancer (EORTC) QLQ-C30 [15]	30-item rating scale including nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale	Patient QOL, toxicity, symptom distress	• Very meaningful to our PRPs • Previous collaborative experience using these at JHU, Stanford, and MSKCC • Widely used to evaluate QOL in cancers and well-liked • Used in previous SBRT and FOLFIRINOX studies [16–18]
European Organization of Research and Treatment of Cancer (EORTC) QLQ-PAN26 [17]	26-item rating scale related to disease symptoms, treatment side effects, and emotional issues specific to PDAC	Patient QOL, toxicity, symptom distress	• Very meaningful to our PRPs • Individual questions can be used to determine stage and outcomes • Previous collaborative experience using these at JHU, Stanford, and MSKCC • Used in previous SBRT and FOLFIRINOX studies [16–18]
Patient-reported outcomes measurement information system (PROMIS) 29 [16]	29-item rating scale of 7 core domains (physical function, anxiety, depression, fatigue, sleep disturbance, satisfaction with social role, pain interference) as well as one 11-point rating scale for pain intensity	Patient QOL, toxicity, symptom distress	• Key factors to optimizing care per our PRPs (pain, anxiety, depression especially) • Widely used in other PCORI and oncology studies, external validation
Brief assessment scale for caregivers (BASC) of the medically ill [23]	14-item rating scale measuring burden and QOL, plus 8-item subscale measuring negative personal impact	Caregiver QOL, symptom distress	• Very important to and selected by our team of PRPs • Limited data on this topic for PDAC
Functional assessment of chronic illness therapy-treatment satisfaction—general (FACIT-TS-G) [24]	8-item rating scale measuring overall evaluation of current treatment and patient experience	Treatment satisfaction	• Important given poor PS and short life expectancy • Contributes to improving patient-centered care • Can be used to make modifications to future regimens
Family history and risk factors (FH&RF) questionnaire	9-item questionnaire designed to evaluate family history and predisposing risk factors	Family history, risk factors	• Insightful into future methods to detect PDAC earlier • Can combine these measures with biomarker profile to predict outcome • Can relieve stress of patient and family members
Daily status log	Personalized tool designed to monitor daily status and progress (i.e., weight, troubling symptoms, energy level, physical activity level, and comments)	Patient QOL, symptom distress	• Designed by our team of PRPs • Personalized to patient-specific needs • Can help patient, caregiver, and clinical team

viders to review. This can lead to improved patient-physician communication and providers can address any concerns and manage symptoms more efficiently and effectively.

Associated Tools to Collect Patient Reported Outcomes

Actigraphy (wearables) has become a promising method for obtaining and measuring patient-reported outcomes in clinical cancer research. Many clinical trials have utilized wearable activity trackers to collect data in real time and assess a patient's quality of life throughout their course of treatment. Data obtained from wearable devices can be used to predict clinical outcomes by monitoring different activity patterns simultaneously, including sleep parameters [25, 26], heart rate [27], and steps per day [27–29]. These devices provide patients an avenue to track their own health and can encourage them to engage in physical activity through regular prompts and feedback [29, 30]. Although wearable activity devices present a greater upfront and long-term cost than other quality of life measures, such as patient reported outcome questionnaires and surveys, these devices provide a method for objective data collection that is not influenced by a patient's expectations, recall bias or memory impairments.

The use of wearable devices, such as the physical activity monitors made by Fitbit, have been correlated with improvements in quality-of-life measures for cancer patients [29, 30]. In addition to improving objective data collection, wearable devices have helped reduce health care costs by reducing odds for adverse events and hospitalizations in advanced cancer patients [28]. While there are no currently published actigraphy studies for pancreatic cancer patients in particular, the efficacy of wearable devices in other cancer trials suggest similar benefits may be seen in the pancreatic cancer patient population [31]. Difficulty getting patients to consistently wear activity trackers and tracker accuracy are other areas of concern, although device accuracy has been steadily improving over time [32, 33]. Ultimately, wearable activity trackers may be most useful as a supplement to other quality of life measurement tools, rather than a standalone method of data collection for cancer patients.

Challenges in Implementing QoL Measures Into Clinical Trials

There are several challenges that researchers face in implementing an effective QoL element in their research or clinical trial. In a systematic review of available PRO studies (not specific to cancer), challenges included the fact that (1) PRO-specific guidance is difficult to access in real time, (2) QoL measures lack consistency and are often unwieldy, (3) results and interpretations are not standardized, and (4) statistical interpretations are varied and missing data is common [34]. Like other endpoints such as survival, we recommend that the methodology of analyzing data with PRO should be determined a priori and included in the protocol and manuscript. The methodology should include how missing data will be handled, which is a common phenomenon in PDAC given the risk of early patient progression. The lack of standardization with PROM with variations in scale, measurement, and interpretation can make it difficult to reach conclusions when results from clinical trials are evaluated. For example, some metrics can indicate favorable results with higher values whereas others may indicate favorable results with lower values. The determination of appropriate time points to assess clinically meaningful changes with QoL tools can be difficult. Furthermore, for pancreatic cancer, it is therefore extremely challenging to implement PROs into daily practice because studies are often small and not powered to demonstrate statistically meaningful differences.

Both the European Medicines Agency (EMA) and the FDA have attempted to address these issues in guidance provided to researchers [31, 35]. The focus of this guidance is primarily on the registration process of new drugs and pharmaceuticals. The 2005 EMA paper recommends that clinical trials have dual HrQoL evaluation and efficacy endpoints. The FDA guidance also highlights the importance of incorporating PRO measures into trials to help improve the validity and relevance of the results to the patients enrolled in the study. In the last 20 years, QoL research has progressed significantly since the EMA and FDA papers (2005 and 2009, respectively). However, the core criticisms indicated above remain largely unaddressed.

Statistical Challenges and Opportunities Related to QoL Analyses

Longitudinal and Cross-Sectional Studies

When reviewing clinical reports, it is important to recognize if the QoL tool was administered at one cross-sectional time point or over multiple longitudinal time points. If longitudinal, a generalized estimating equation (GEE) or random effects model should be used for the analysis.

Using QoL Studies to Compare Arms

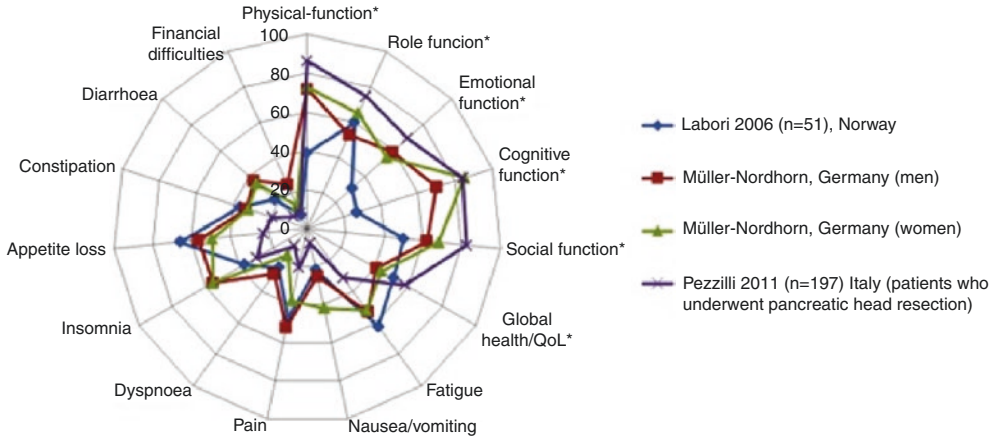
Finding a statistically significant difference using QoL tools can be difficult given smaller sample sizes common in PDAC studies. That is why a "clinical significance" cut-off is often defined prior to the study to identify an "important" clinical/meaningful difference (positive or negative) of an intervention or comparison of interventions. Another approach used by Anota et al. was the HrQoL deterioration-free survival (QFS), defined as the time from randomization to a first significant deterioration as compared to baseline score with no further significant improvement or death [36]. To help balance groups, propensity scores can be used, and multivariate cox regression analyses can identify independent factors influencing QFS [36].

Statistical Presentation

In addition to standard tables outlining QoL and PRO responses, spider plots can be very helpful in understanding how a specific treatment (before, during, and after) influences QoL as well as comparing QoL between treatment arms. For example, Carrato et al. [5] summarized five studies using a spider plot based on reported HrQoL data as demonstrated in Fig. 28.3 [37–41].

Options to Address Missing Data

Unfortunately, missing data is common in pancreatic cancer studies because a large proportion



Note: In the first 6 function scales a high score = better level of functioning, whereas a high score on symptom scale/single item = worse symptoms

Fig. 28.3 Example of spider plot of QoL symptoms [5]

of patients become ill or die earlier than anticipated thus preventing them from completing the forms longitudinally [42]. Researchers should partner with statisticians to incorporate validated methods to account for missing data that can result in statistical uncertainty. One approach is to use multiple imputation as described in Rubin or a rank-based approach [43]. A sensitivity analysis can also be helpful when there is missing data [44]. This is where different missing data imputation techniques can be employed and the results of each can be qualitatively compared. If results differ significantly based on the type of missing data, imputation techniques are used, and additional analyses or comparisons may be needed to explain the cause(s).

The use of the propensity score in conjunction with the time until definitive deterioration (TUDD) method can reduce the bias due to the occurrence of missing data depending on patients' characteristics during follow-up [45]. Multiple imputations on the HrQoL scores could also be performed but this method requires a larger sample and can only include one or two factors associated with missing data [38], but more variables can be retained in the propensity score. This approach could be considered for use in trials with limited sample sizes. Contrary to the pattern mixture models, the inverse probability of treatment weighting (IPTW) method in conjunction with the TUDD approach is optimal for oncology clinical trials, for which a lot of HrQoL measures are done. In fact, the number of possible patterns increases with the number of HrQoL measures. Austin et al. recommended use of IPTW for time to event data [46]. Finally, the IPTW method is easy to understand (weighting observations according to the presence or absence of missing data) [46].

QoL Clinical Studies

In patients with PDAC, QoL, PS, and pain should be assessed at baseline to better understand whether any intervention provides benefit or harm. Subsequent clinical visits should document whether these measures changed over time, ideally in a structured way. In a clinical trial this is often done as part of the study and at specific intervals centered around re-staging. Outside of a clinical trial quality of life is often less structured and more challenging to ascertain a change from baseline. Using structured notes in an EMR can help remind healthcare teams to reassess performance status, pain, and quality of life but missing data are still common. Using apps and/or questionnaires that can be administered electronically can minimize missing data and lead to more complete and often accurate information. However, electronic forms can sometimes be more challenging for elderly patients or those who are less educated.

A comprehensive systematic review of QoL in adults with PDAC and their caregivers was recently conducted and, again, showed significantly poorer HrQoL scores for PDAC patients compared to population norms and a loss of 610,000–915,000 QALY annually with PDAC [5]. This was confirmed in another systematic review of the literature where PDAC patients were also compared with healthy adults or population norms: adults with pancreatic cancer had worse QoL across most domains [47]. In addition, compared with other cancer types, patients with PDAC also reported worse psychological symptoms [47]. This is likely due to the poor prognosis of PDAC and its known association with depression. Physical and social QoL symptoms are either similar or even more compromised than in patients with other cancers. QoL studies related to sexual, spiritual, and caregiver QoL are limited and desperately needed. In fact, depression and anxiety are common in patients with advanced PDAC [37–39]. In a Norwegian population, 42% of patients had moderate or severe anxiety and depression [40]. In a German study, the number of patients experiencing anxiety/depression was approximately tenfold higher than the normal population [38]. Moningi et al. looked at how clinical factors correlated with quality of life (QoL) questionnaires administered to patients presenting to the Johns Hopkins Pancreas Multidisciplinary Clinic (PMDC) with various stages of disease [7]. The study examined associations between disease status, PFS, and QoL responses in order to identify patient subgroups

that were most at risk for reduced QoL using the QLQ-PAN26 questionnaire [7]. They found that patients with a worse performance status, defined as ECOG > 1, were significantly more likely to report symptomatic pancreatic pain ($P > 0.001$), digestive symptoms ($P > 0.017$), cachexia ($P > 0.004$), and ascites ($P > 0.001$) compared with patients with a performance status of 0 [7]. The majority (92%) of patients reported a significant fear of future health problems, regardless of disease status or performance status [7]. A summary of the key randomized trials in PDAC that incorporate PRO as an endpoint is presented in Table 28.2.

Table 28.2 Key randomized studies that incorporate QoL as an outcome in pancreatic adenocarcinoma

Author, year, journal	Stage, comparison of arms	Type of QoL measure and frequency	Findings	Other
Polistina, 2010, Ann Surg Oncol [48]	23 patients with LAPC undergoing SBRT, assessing treatment response, local control, pain, and QoL	SF-36	No QoL differences between pretreatment, 3-month, or 6-month follow-ups	
Quan, 2018, Pract Radiat Oncol [49]	Phase 2 clinical trial with 35 patients with either BRPC or LAPC assessing induction chemo followed by SABR	FACT-G	No QoL differences between pretreatment, post-chemo, SABR, or surgery	
Krempien, 2005, BMC Cancer [50]	Phase 2 clinical trial with 66 patients LAPC evaluating Cetuximab and IMRT	QLQ-C30, QLQ-PAN26	N/A	
Morak, 2010, Cancer [51]	Prospective study comparing QoL between 120 patients with or without adjuvant CRT	QLQ-C30	Better QoL scores for patients with neoadjuvant CRT versus control	
Knaebel, 2005, BMC Cancer [52]	Phase 3 clinical trial with 110 patients comparing adjuvant 5-fluorouracil, cisplatin, interferon alpha and radiation versus folinic acid and 5-fluorouracil	QLQ-C30, QLQ-PAN26, CES-D	N/A	
Herman, 2015, Cancer [21]	Phase 2 clinical trial with 49 patients with LAPC evaluating Gemcitabine and SBRT	QLQ-C30, QLQ-PAN26	Stable QoL scores from baseline to post-SBRT, improvement in pain scores post-SBRT	
Serrano, 2014, Int J Radiat Oncol Biol Phys [53]	Phase 2 clinical trial with 55 patients with PDAC evaluating QoL during and after neoadjuvant CRT and surgery	QLQ-C30, QLQ-PAN26, FACT-Hep	Temporary increase in GI symptoms and decrease in physical functioning after neoadjuvant CRT. QoL returned to baseline after surgery	
Short, 2013, Int J Radiat Oncol Biol Phys [54]	Phase 2 clinical trial with 63 patients with PDAC evaluating QoL using 3D conformal CRT sandwich technique	QLQ-C30, QLQ-PAN26	Stable QoL, improvement in local symptoms for CRT	
Katz, 2017, BMC Cancer [55]	Phase 2 clinical trial with 134 patients with PDAC comparing mFOLFIRINOX versus mFOLFIRINOX with SBRT	PRO-CTCAE	N/A	
Haddock, 2007, J Clin Oncol [56]	Phase 2 clinical trial evaluated QoL differences for 48 patients with LAPC who received Gem-CRT or Gemcitabine alone	SDS LASA	No QoL difference between baseline and final measurement, however certain measures improved (outlook, insomnia, pain)	

Table 28.2 (continued)

Author, year, journal	Stage, comparison of arms	Type of QoL measure and frequency	Findings	Other
Heras, 2009, Am J Ther [57]	Prospective study comparing QoL differences for 30 patients with unresectable PDAC who received RT with 5-FU or RT with gemcitabine	QLQ-C30	Overall QoL improved for both groups with RT	
Hurt, 2015, Int J Radiat Oncol Biol Phys [58]	Phase 2 clinical trial evaluated QoL differences for 114 patients with LAPC who received gemcitabine plus capecitabine and either Gem-CRT or Cap-CRT	QLQ-C30, QLQ-PAN26	Initial QoL improvement at start of CRT, decline during CRT, and return to baseline post-CRT	
Loehrer, 2011, J Clin Oncol [59]	ECOG clinical trial with 74 patients with unresectable PDAC evaluating QoL differences between Gem-CRT versus Gemcitabine alone	FACT-Hep	No QoL difference between groups, both groups showed decline in QoL over treatment period	
Moore, 2007, J Clin Oncol Off J Am Soc Clin Oncol [60]	Phase 3 clinical trial comparing 569 PDAC patients with either erlotinib plus gemcitabine or gemcitabine alone	QLQ-C30	No QoL difference between groups (except worse diarrhea in Gem+Erlotinib group)	
Neoptolemos, 2001, Lancet [61]	Randomized control trial with 541 patients with resectable PDAC evaluating adjuvant CRT and chemotherapy	ESPAC-1 QoL	Improved QoL for adjuvant CRT and Chemo versus control	
Neoptolemos, 2017, Lancet [62]	Phase 3 clinical trial comparing 732 patients with resected pancreatic cancer who received either gemcitabine plus capecitabine or gemcitabine alone	QLQ-C30	No effect on QoL by treatment group	
Oettle, JAMA, 2007 [63]	Randomized control trial evaluating role of adjuvant gemcitabine for 368 patients with resected pancreatic cancer	Spitzer QL-Index	QoL improvement for both groups, no difference between groups	
Conroy, NEJM, 2018 [64]	Phase 2 and Phase 3 clinical trial comparing 493 patients with resected pancreatic cancer who received FOLFIRINOX and gemcitabine	QLQ-C30	No QoL differences between 5-FU and gemcitabine groups	
Deng, 2018, Euro J Cancer [65]	Hospital-based cohort of racially/ethnically diverse patients with PDAC	Short-form 12, including PCS and MCS	Hispanics at significantly higher risk of lower PCS and MCS compared to non-Hispanic whites; stage III and IV patients with lower PCS than stage I patients	
Crippa, 2008, J Gastrointest Surg [66]	92 patients with different stages of PDAC who underwent surgical and/or medical intervention	Functional assessment of cancer therapy questionnaire	Surgery favorably impacts quality of life (patients who underwent surgical resection had improved QOL), whereas chemotherapy/chemoradiation did not significantly modify QOL	

(continued)

Table 28.2 (continued)

Author, year, journal	Stage, comparison of arms	Type of QoL measure and frequency	Findings	Other
Al-Batran, 2021, Int J Cancer [67]	601 patients treated with Nab-paclitaxel/gemcitabine	QoL/global health score	Patients improved or maintained QoL after 3 and 6 months, and QoL is predictor of outcome	
Mackay, 2020, JNCCN [68]	100 patients with newly diagnosed pancreatic or periampullary cancer	IN-PATSAT32 and QLQ-C30	Satisfaction with care, but not QoL, decreases after treatment. QoL factors not independently associated with patient satisfaction	
Gourgou, 2012, J Clinical Oncology [19]	342 patients assigned to take FOLFIRINOX or gemcitabine	QLQ-C30	FOLFIRINOX significantly reduces QoL impairment compared to gemcitabine for metastatic pancreatic cancer patients	
Troger, 2014, Deutsches Arzteblatt International [69]	220 patients with locally advanced or metastatic pancreatic cancer who were only receiving supportive care, divided into groups that received mistletoe extract or not	QLO-C30	Mistletoe extract significantly improved QoL compared to supportive care alone	
Bernhard, 2009, J Clinical Oncology [70]	Patients assigned to receive GemCap or Gem	CBR criteria and Karnofsky performance status	No difference in CBR or QoL between GemCap and Gem	
Wong, 2004, JAMA [71]	100 patients with unresectable pancreatic cancer with pain assigned to neurolytic celiac plexus block vs. opioids alone	Pain intensity (0–10), QoL scores	NCPB improves pain relief but does not affect QoL	

QoL Studies in Resectable Disease and Prior to Surgery

Surgery studies incorporating QoL in general tend to be cross sectional instead of longitudinal which is a significant limitation [72, 73] because it does not allow us to gather sufficient information about the temporality of the observed phenomena. This precludes us from proposing causal pathways between psychological predictors of QoL and psychological distress. Future research should use a longitudinal design to (1) identify other important psycho-logical predictors of preoperative and postoperative psychological distress and QoL and (2) distinguish the proper effect of surgery from the psychobiological effect of pancreatic cancer on depression.

In a review of nine studies with QOL and other psychological factors post-pancreatectomy, the authors showed that although quality of life initially declined postoperatively, it significantly improved 3–6 months after surgery [74]. Regarding the postoperative experience, one study reported that there was a high fear of cancer recurrence [74]. One study explained how the ability to adapt to the diagnosis of PDAC was mainly influenced by the age and the subjective experience of the patients [74]. Interestingly, depression did not appear to affect survival rate after surgery [74]. Only a few studies have characterized the psychological experience of patients as it relates to surgery and there remains a need for more studies to describe and characterize the patients' psychological characteristics in this setting.

In patients with resectable pancreatic cancer, QoL studies can help in determining if patients are good surgical candidates and/or identify areas that may need attention perioperatively. Ngo-Huang et al. at MD Anderson Cancer Center investigated relationships among physical activity, physical function, and QoL among patients with patients with resectable PDAC enrolled in a home-based exercise rehabilitation program [75]. Patients with resectable PDAC receiving preoperative chemotherapy and/or chemoradiation were advised to perform ≥60 min each of moderate-intensity aerobic exercise and strengthening exercise weekly. Increased weekly light physical activity was associated with increased HrQoL [75]. Patients with potentially resectable pancreatic cancer exhibited meaningful improvement in physical function with rehabilitation, and, in turn, physical activity was associated with improved physical function and HrQoL [75]. This data highlights the importance of physical activity during treatment for pancreatic cancer and its potential benefit in improving QoL.

QoL in Adjuvant Therapy Studies

Results from one of the seminal trials in the adjuvant setting, the European Study Group for Pancreatic Cancer-1 Trial (ESPAC-1), which compared adjuvant chemotherapy to chemoradiation (CRT), demonstrated that the potentially negative effects on QoL with therapy should be considered in addition to any improvement in survival to get a more comprehensive picture of the efficacy of the intervention [62, 76]. Interestingly, in the subset of patients (n = 316) who were followed longitudinally for QoL outcomes with the EORTC-QLQ-C30, when survival was integrated with QoL the Quality Adjusted Life Months at 2 years (QALM-24) post-surgical resection was lower for both chemotherapy (17.3 vs. 9.6 months) and CRT (15.5 vs. 7.1 months) compared to 2-year survival without integration of QoL [62, 76]. Ultimately, however, the difference in QoL outcomes between the chemotherapy and CRT arms were not significant. It should be noted that this trial used inferior chemotherapy regimens (i.e., single agent 5-Fluorouracil), and antiquated radiation techniques with a split course regimen and prescribed doses that are now known to be inadequate for disease control.

In addition, QoL measures have been used to assess the therapeutic benefit and safety of chemotherapy in the adjuvant setting. One example is a phase 2 prospective study evaluating the addition of erlotinib in combination with adjuvant chemoradiation and chemotherapy for resected PDAC [77]. In this study 48 patients received adjuvant erlotinib and capecitabine twice daily concurrently with intensity modulated radiation therapy (IMRT) to 50.4 Gy in 28 fractions followed by four cycles of gemcitabine and erlotinib. QoL was assessed with the EORTC QLQ-C30 and the QLQ-PAN26 just before CRT initiation or during the first week of its administration, between completion of CRT and starting maintenance chemotherapy, and within 3 months after completion of maintenance chemotherapy [77]. The mean global QoL scores remained stable throughout both phases of treatment, and there were no significant changes in 4 of the 5 functional QoL scales (role, cognition, emotional, and social), although physical function score declined slightly (by 6.2 points) during CRT. Symptoms of pain, fatigue, nausea/vomiting, dyspnea, insomnia, and constipation did not change significantly from baseline [77]

Neoadjuvant and Definitive Therapy: Resectable, Borderline Resectable, and Locally Advanced Pancreatic Cancer

Most reports describing the tolerability of radiation in pancreas cancer are derived from physician-assessed toxicities using RT techniques that are either outdated or expose greater volumes of normal tissue to radiation with limited supportive care. These older studies often combine RT with more aggressive chemothera-

pies including bolus 5-FU or higher doses of concurrent gemcitabine, thus increasing treatment related toxicities (often GI) and decreasing quality of life. For example, in ECOG 4201, patients with LAPC were randomized to full dose gemcitabine (1000 mg/m^2) alone or chemoradiation with a lower dose of gemcitabine (600 mg/m^2) combined with standard fractionated radiation (50.4 Gy over 5.5 weeks) [59]. Although the study was closed prior to reaching its planned accrual, there was a significant improvement in survival in patients receiving combined gemcitabine and radiation [59]. Although there was an improvement in survival with CRT, patients who received combined chemoradiation had substantially more grade 4 toxicity (41.2 vs. 5.7%; $p < 0.000$) compared to those who were treated with gemcitabine alone [59].

Since the ECOG 4201 study, reported rates of RT associated grade 3–4 toxicity have declined in part due to improvements in RT planning (IMRT), decrease in target volumes, avoidance of organs at risk (OAR) using a planning OAR volume (PRV), image guidance (CT on rails, MRI), advancements in nutrition (enzymes), and proactive supportive care. A more recent trial in the LAPC setting, the LAP07 trial (gemcitabine and CRT vs. gemcitabine alone), used 3D-CRT (tumor plus a margin but no elective nodal coverage) with concurrent capecitabine, grade 3+ toxicity was similar to the group that received chemotherapy alone (20%) [78]. Recent trials in the resectable and borderline resectable pancreatic cancer (BRPC) setting, such as the PREOPANC-1 trial which compared upfront surgery vs. neoadjuvant CRT, showed improved survival outcomes in the CRT arm without any significant increase in grade 3+ toxicity [55]. The Alliance trial A021101 prospectively treated BRPC patients with CRT (tumor plus margin, not covering ENI) but with more aggressive systemic therapy with FOLFIRINOX (FFX) at several high-volume centers [79]. Although grade 3+ toxicity was 43%, most toxicity was thought to be attributed to FFX chemotherapy as opposed to the radiation [79]

However, to date, most trials have not consistently reported on QoL metrics in the neoadjuvant or definitive settings. Breen et al. reported on a multi-center prospective registry evaluating the effect of CRT on patient-reported QoL for patients with intact and localized PDAC [80]. QoL was assessed pre-CRT (immediately before CRT and after neoadjuvant chemotherapy) as well as at the completion of CRT with FACT-Hep and its component parts: FACT-General (FACT-G) and hepatobiliary cancer subscore (HCS) [80]. A minimally important difference from pre-CRT was defined as $\geq$ 6, 5, and 8 points for FACT-G, HCS, and FACT-Hep, respectively [80]. Approximately 40% of patients had BRPC whereas 57% had LAPC [80]. FFX (75%) or gemcitabine and nab-paclitaxel (GnP, 42%) were given for a median of six cycles (range, 0–42) before CRT [80]. Radiation therapy techniques included 3-dimensional conformal (22%), intensity modulated photon (55%), and intensity modulated proton (23%) radiation therapy to a median dose of 50 Gy (range, 36–62.5) [80]. Concurrent chemotherapy was most commonly capecitabine (82%) [80]. Sixty-three patients (63%) had surgery after CRT [80]. The mean decline in FACT-G, HCS subscale, and FACT-Hep from pre- to post-CRT was 3.5 (standard deviation [SD], 13.7), 1.7 (SD 7.8), and 5.2 (SD 19.4), respectively [80]. Each of these changes were statistically significant, but did not meet the minimally important difference threshold [80]. Pancreatic head tumor location was associated with decline in FACT-Hep on MVA [80]. Nausea was the toxicity with the greatest increase from pre- to post-CRT by both physician-assessment and patient-reported QoL [80]. Interestingly, type of radiation modality did not significantly alter the QoL changes, but the numbers were small [80].

One of the concerns of long course CRT is that patients are not receiving full dose systemic therapy and therefore may be at an increased risk of metastatic spread. A prospective, phase 2 multi-institutional trial evaluated a regimen using full dose chemotherapy (gemcitabine and oxaliplatin) with a more focused and lower dose RT

(tumor plus a 1–1.5 cm margin, 30 Gy in 15 fractions) given concurrently with the first cycle of chemotherapy in patients with mostly resectable and BRPC [81]. Patients completed the EORTC-QLQ C30, EORTC-PAN 26, and FACT-Hep at baseline, after two cycles of neoadjuvant therapy, after surgery, at 6 months from initiation of therapy, and at 6-month intervals for 2 years [81]. A change >10% in mean score compared to baseline was considered a minimal clinically important difference [81]. The EORTC-QLQ C30 global QoL did not significantly decline after neoadjuvant CRT with full dose chemotherapy, whereas the Functional Assessment of Cancer Therapy global health measure showed a statistically, but not clinically significant decline (−8, P = 0.02) [81]. This was in parallel with deterioration in physical functioning (−14.1, P = 0.001), increase in diarrhea (+16.7, P = 0.044), and an improvement in pancreatic pain (−13, P = 0.01) as per EORTC-PAN 26 [81]. Because of poor patient compliance in the nonsurgical group (no longer followed after progression), long-term analysis was performed only on surgically resected participants (n = 36) [81]. The authors found that the first 2 months of systemic therapy was completed without a clinically significant QoL deterioration [81]. A transient increase in gastrointestinal symptoms and a decrease in physical functioning were seen after neoadjuvant chemoradiation [81]. In those patients who underwent surgical resection, most domains returned back to baseline levels by 6 months [81]. The study also highlighted the challenge of missing data in these studies, especially when patients progress and come off study. Using smaller volumes with modern technology that limits the dose of RT to the bowel complemented by more aggressive management of symptoms can improve QoL while receiving aggressive multimodality treatment. There also appears to be a good correlation with GI toxicity and a decline in QoL with both the EORTC and FACT questionnaires.

Other approaches are also currently being investigated for the potential to improve QoL such as (1) decreasing the size of the radiation treatment volume by using motion management (breath-hold, tracking), (2) increasing visualization (MRI/fiducials), (3) decreasing the number of fractions a patient receives (1–5 vs. 25–30). More sophisticated radiation techniques have the potential to improve QoL metrics as well. Bittner et al. found that IMRT was associated with lower rates of grade 3+ acute nausea ± vomiting, diarrhea, and late GI AEs [82]. This suggests that limiting dose to bowel correlates with less toxicity and improved QoL. Jethwa et al. reported on their initial experience with intensity modulated proton therapy (IMPT) for intact pancreas cancer [83]. Although a small study (N = 13), patients completed the FACT-Hep questionnaire prior to CRT and at the end of CRT. The FACT-Hep score dropped by a median of −7.5 (P = 0.18) [83]. The FACT-Gen dropped by a mean difference of −6.3 (P = 0.09). The authors concluded that there were low rates of acute GI AEs and no significant change of PROs from baseline suggesting further exploration of IMPT in localized PDAC [83].

SBRT is another technological advancement in radiation technique that has significantly decreased acute side effects when compared to CRT. SBRT is given over 1–5 treatments, covers smaller volumes (typically gross tumor volume plus 3–5 mm margin) and is typically delivered without concurrent chemotherapy. Koong et al. was the first investigator to evaluate single-fraction SBRT in the treatment of LAPC [84]. A single dose of 25 Gy effectively palliated symptoms with nearly 100% local progression-free survival (LPFS) at 1 year [84]. While acute GI toxicity was acceptable, late GI toxicity was high (~40%) [85]. To improve patient OS while limiting toxicity Herman et al. conducted a multicenter phase II study to test the safety and efficacy of adding fractionated SBRT (6.6 Gy × 5) to full-dose gemcitabine (SBRT given after 1–3 doses) in patients with LAPC [21]. This prospective study enrolled 49 LAPC patients with KPS >70 and a median age of 67.9 years [21]. One- and two-year OS was 61% and 18%, respectively, while mOS was 13.9 mos [21]. Four patients

(8.2%) with LAPC underwent margin- and node-negative resections following gemcitabine (GEM) +SBRT [21]. Rates of acute and late grade ≥2 gastritis, enteritis, or ulcer toxicities were 2% and 11%, respectively [21]. Acute toxicity included: grade 2 anorexia (37%), fatigue (28%), nausea (22%), abdominal pain (19%), weight loss (9%), diarrhea (3%); grade 3 nausea (9%); and grade 4 nausea (6%) [21]. Late grade ≥3 GI toxicity appeared to have improved at 9% with fractionated SBRT compared to historical outcomes [21]. Mean QoL score 4 weeks post-SBRT was similar to baseline ($p = 0.38$) [21]. In fact, at 6 months there was a trend towards improved QoL ($p = 0.07$) [21]. Overall, fractionated SBRT coupled with GEM achieved high rates of LPFS and tumor response. Minimal grade ≥3 acute and late toxicity was observed. It was determined that a combination of SBRT with more aggressive chemotherapy may further improve outcomes.

This led to a prospective non-randomized controlled phase II trial that investigated whether fractionated SBRT could be safely and effectively delivered in the setting of aggressive multi-agent chemotherapy (MA-CTX) [86]. This enrolled 48 patients between 2012 and 2015. The median follow-up after SBRT was 60 months among three patients still alive. Patients received MA-CTX with modified FOLFIRINOX (mFFX) or GnP followed by four fractions of SBRT (median 33 Gy). The primary outcome was the rate of late grade ≥2 gastrointestinal toxicity attributable to SBRT. Only one patient (2%) had late ≥ grade 2 gastrointestinal toxicity attributable to SBRT [86]. Neoadjuvant CTX duration was ≥4 months in 24 patients and 28 patients received mFFX [86]. Of 44 LAPC patients, 17 (39%) were surgically explored, and 12 (75%) achieved a margin-negative resection [86]. For all patients, the median overall survival (OS) was 21.6 months from diagnosis and 14.6 mo. from SBRT [86]. The 1- and 2-year OS from SBRT was 58% and 28%, respectively [86]. The study also evaluated the impact of fractionated stereotactic body radiation therapy (SBRT) on patient-reported quality of life (QoL) and physician-reported toxicity in patients with recurrent or locally advanced pancreatic cancer (PDAC) was prospectively evaluated. 42 PDAC patients had patient-and physician-reported outcomes prior to SBRT and 4–6 weeks post-SBRT [86]. Outcomes were consistently evaluated among both groups—performance status, fatigue, pain, anorexia, nausea, vomiting, constipation, and diarrhea. Patient-reported QoL metrics were assessed using a 4-point Likert scale on the EORTC QLQ-C30 and QLQ-PAN26, while physician-reported toxicities were graded using the NCI CTCAE version 4.0. Comparisons between those with paired patient-and physician-reported outcomes collected prior to and 4–6 weeks after SBRT were made using the Wilcoxon signed-rank test. A total of 29 had both patient- and physician-reported outcomes collected prior to and 4–6 weeks after SBRT. There was no significant impairment of any of the 8 physician-reported toxicities, nor were significant changes observed in patient-reported overall health ($p = 0.66$) or QoL ($p = 0.18$) scores following SBRT [86]. Patients felt less worried about their future health (mean change [mΔ] = −0.45, $p = 0.02$), and an improvement in feeling less attractive as a result of disease and treatment reached borderline significance (mΔ = 0.31, $p = 0.09$) [86]. However, patients felt limited in planning activities in advance (mΔ = 0.45, $p = 0.02$) and were more constipated (mΔ = 0.38, $p = 0.01$) 4–6 weeks post-SBRT [86]. Although the numbers are small, patients with unresectable or locally recurrent PDAC do not appear to suffer any detriment of overall health or QoL after receiving a 5-day course of SBRT. Moreover, this regimen may lead to a more optimistic point of view on future health and/or level of physical attraction.

Metastatic Disease

Several reports describe that QoL, toxicity, and symptom control all play a significant role in the well-being of patients with PDAC. This is especially important in patients with metastatic disease where the likelihood of cure is lower, and patients and caregivers want to balance quality and quantity of life. In the RESPONSE trial, an

important secondary endpoint was a composite score of "clinical benefit" as defined by Burris et al. [6]. This was one of the first studies to obtain FDA approval for a drug based on a non-survival endpoint. The PRODIGE 4 study, which evaluated FOLFIRINOX versus gemcitabine in the first-line metastatic setting, showed that FOLFIRINOX improved OS and HRQOL, despite the having worse toxicity than gemcitabine [64]. There were two earlier interventional studies in other chemotherapy combinations in the second-line setting, however, either did not report HRQOL (CONKO-003) or found no significant change between treatment arms (PANCREOX) [63, 87].

Anota et al. reported on sequential FOLFIRI.3 plus gemcitabine compared to gemcitabine alone in the first line metastatic setting [36]. They used the EORTC QLQ-C30 at baseline and every two months until end of study or death. The authors used the deterioration-free survival (QFS) propensity score analyses to balance arms, and MVA to look at other factors that may influence QFS. Specifically, the study used the IPTW propensity scoring method which is preferred when there is missing data. Regarding the weighted analyses, the treatment arm (gemcitabine + FOLFIRI.3) and the number of metastatic sites (one site) seemed to be independently associated with longer QFS of physical functioning [36]. The number of metastatic sites (more than one vs. one) were associated with a shorter QFS of GHS (global health status), fatigue and pain [36]. In multivariate analyses, treatment arm (gemcitabine + FOLFIRI.3) and number of metastatic sites (one site) tended to be associated with longer QFS of physical functioning in the weighted analysis [36]. In conclusion, analyses of QFS in this study demonstrated that FOLFIRI.3 and gemcitabine in patients in first line metastatic PDAC is feasible and, despite more toxicities, delayed the HrQoL deterioration [36]. Moreover, using the propensity score methods controlled for the imbalance of informative missing data between the two arms and provided more precise estimation of the true benefit of the treatment [36].

The NAPOLI-1 study was a global phase III, randomized, open-label, multicenter trial (NCT01494506) that tested liposomal irinotecan (nal-IRI; Onivyde®; MM-398) with or without 5-fluorouracil/leucovorin (nal-IRI+5-FU/LV) for patients with PDAC who had progressed following gemcitabine-based therapy [43]. The nal-IRI+5-FU/LV regimen led to significant improvements in median overall survival (OS; an increase by 45% [6.1 months vs. 4.2 months]; hazard ratio 0.67; 95% CI 0.49–0.92; $P = 0.01$]). This regimen also significantly improved a number of secondary endpoints, including progression-free survival [42]. A recently updated analysis confirmed this survival benefit. Side effects reported for the nal-IRI+5-FU/LV combination were manageable and typically reversible; the most frequent grade ≥3 adverse events included neutropenia, diarrhea, and vomiting [42]. HrQoL was a secondary endpoint in the NAPOLI-1 study. The EORTC QLQ-C30 was administered at baseline (within 7 days of starting treatment), every 6 weeks thereafter, and 30 days after discontinuation of study treatment, and a ten-point change in the EORTC QLQ-C30 was considered clinically meaningful [85, 88]. For global health subscales and functional subscales, patients were categorized as improved (≥10% improvement *vs.* baseline and remaining improved over baseline for ≥6 weeks), worsened (either died or had scores that worsened by 10% vs. baseline), or stable (did not meet criteria for improved or worsened). Duration of improvement was the interval between the first date when the score improved ≥10% and the date when the score returned to baseline or lower. This analysis shows that patients had no substantial deterioration from baseline in most HrQoL subscales [42]. The only differences from baseline between the nal-IRI+5-FU/LV combination and 5-FU/LV control therapy were a lower physical functioning score (−6.7) and a higher fatigue score (+11.1) with nal-IRI+5-FU/LV [42]. Patients subjectively assessed these changes as "minor" for physical function and "moderate" for fatigue [85]. In a post hoc analysis of the NAPOLI-1 study, using the quality-adjusted time without

symptoms or toxicity (Q-TWiST) methodology, nal-IRI+5-FU/LV provided a relative gain of 24% compared with 5-FU/LV [89], exceeding the 15% difference threshold considered clinically meaningful [3].

The HrQoL findings from NAPOLI-1 are supported by Q-TWiST and complement previously reported survival benefit [42, 89], suggesting that nal-IRI+5-FU/LV also maintains HRQOL in patients whose disease has progressed on a prior gemcitabine-based regimen, despite the addition of an active chemotherapy agent. Generally, HrQoL assessments have seldom been reported in pancreatic cancer trials, both in first-line or second-line settings [19, 63, 87]. This may be because poorly controlled metastatic PDAC (mPDAC) has a high symptom burden. In the NAPOLI-1 trial, the EORTC QLQ-C30 questionnaire compliance rate was high until week 12 of treatment, after which the frequency of missing or incomplete data increased [42]. The vast majority of missing data were explained by terminal missingness, the most frequent reason being progressive disease [42]. This is consistent with other reports in mPDAC and reflects patient attrition typically observed in end-stage cancer studies [87, 90, 91]. As patients discontinued the study, EORTC QLQ-C30 compliance decreased. A more frequent HrQoL assessment may have increased data capture. It is unclear whether the improvements in HrQoL at week 12 were due to selection of patients with better HrQoL via attrition of patients with worsened QoL at week 6. It would be expected for this to be noted particularly with 5-FU/LV alone, as treatment discontinuation and progression were observed earlier in this arm [42]. Another reason could be general amelioration of side effects over time [91]. HRQOL improvements could also be due to adequate dose reductions and supportive measurements, improvement of disease symptoms via treatment of side effects, or a combination of all these factors. Other study limitations include a potential reporting bias because of the open-label design of the NAPOLI-1 study and a limited power to detect significant HrQoL differences between the two treatment arms. Additionally, the EORTC QLQ-C30 is a general questionnaire and may have failed to capture all nuances of mPDAC. Despite these limitations, this study provides randomized trial data on HrQoL, an important clinical insight.

Elderly and Poor Performance Status Patients

As described earlier, performance status is often a key factor in evaluating the appropriateness of therapy. It is a subjective composite measure used by clinicians to measure functional capacity and the likelihood of adverse events, QoL, and OS after treatment. Single agent systemic therapy such as gemcitabine in patients with advanced PS has historically been the favored approach although optimal treatment remains controversial in this setting due to lack of evidence [92]. Furthermore, there are no clear guidelines on how PDAC patients with poor PS such as ECOG 2 or worse or KPS of 70% or worse should be managed. However, clinical trials in metastatic patients with poorer PS who received multi-agent therapy with GnP had a greater reduction in the risk of death in comparison with GEM alone (79.3% vs. 90.7%) [93]. In a phase II trial of ECOG 2 patients, GnP was well tolerated and demonstrated acceptable efficacy [94]. Single-agent GEM + SBRT has also shown efficacy in non-metastatic PDAC with power performance status [21].

Similar to patients with poor PS, elderly patients are often excluded from clinical trials for PDAC. However, limited clinical trial data and several series have explored the potential benefits and downsides of surgical resection, chemotherapy, and radiation in the localized and metastatic settings [95]. The optimal treatment decision making remains challenging in these patients, but age should not be the primary determining factor for treatment decisions. A holistic approach to decision making would benefit these patients with consideration given to incorporating PRO and HrQoL measures for treatment selection.

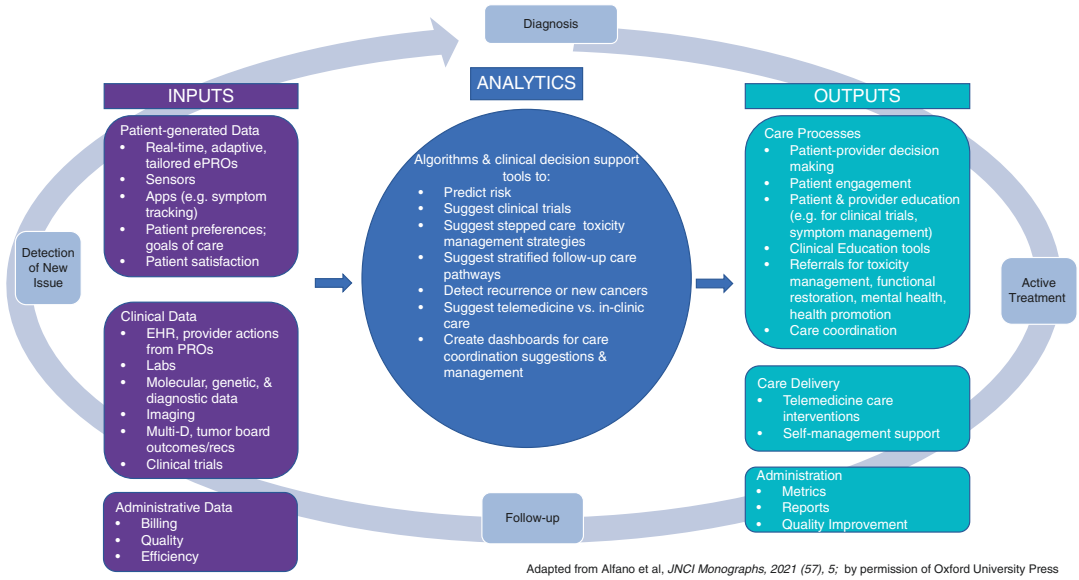


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Fig. 28.4 Draft of technical requirements for a cancer data ecosystem inclusive of patient reported outcomes

Future Directions

Integrating PROs via patient online portals may increase PRO compliance, decrease missing data and correlate more reliably with clinical outcomes. Instead of simply monitoring QoL it may be helpful to include mind and body supportive services such as yoga and aerobic exercise. These services have been shown to improve QoL in breast cancer patients [96]. Moving forward, PDAC clinical trials should include PROs that encompass physical and social well-being (nutrition, pain and symptom management, family support), emotional and spiritual well-being (anxiety, depression, spirituality, etc.), advanced directives, and planning for the future throughout the entire trajectory of care [97]. An example framework for this approach at Northwell Health Cancer Institute is outlined in Fig. 28.4. Future trials should consider incorporating PRO questionnaires for patients and caregivers, predisposing risk factors, and family history, due to the evidence found in multiple studies emphasizing the importance of treatment satisfaction and logging daily progress (Table 28.1). While the patient QoL questionnaires target physical, mental, and emotional well-being, the other questionnaires are to learn about all other aspects of the treatment process: the impact on the caregiver, the overall treatment experience, and behavioral and genetic risk factors that may predispose an individual for PDAC.

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