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Core Set of Patient-reported Outcomes in Pancreatic Cancer (COPRAC): An International Delphi Study Among Patients and Health Care Providers

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Core Set of Patient-reported Outcomes in Pancreatic Cancer (COPRAC)

An International Delphi Study Among Patients and Health Care Providers

Lennart B. van Rijssen, MD,* Arja Gerritsen, MD, PhD,*† Inge Henselmans, PhD,‡
 Mirjam A. Sprangers, PhD,‡ Marc Jacobs, PhD,‡ Claudio Bassi, MD, FRCS, FACS,§
 Olivier R. Busch, MD, PhD,* Carlos Fernández-Del Castillo, MD, PhD,¶ Zhi Ven Fong, MD, MPH,¶
 Jin He, MD, PhD,|| Jin-Young Jang, MD, PhD,** Ammar A. Javed, MD,|| Sun-Whe Kim, MD, PhD,**
 Laura Maggino, MD,§ Abhishek Mitra, MS, DNB,†† Vikas Ostwal, MD,‡‡ Silvia Pellegrini, MSc,§§
 Shailesh V. Shrikhande, MS, FRCS, (Hon.),†† Johanna W. Wilmink, MD, PhD,¶¶
 Christopher L. Wolfgang, MD, PhD,|| Hanneke W. van Laarhoven, MD, PhD, PhD,¶¶
 and Marc G. Besselink, MD, PhD*, for the COPRAC study group

Objective: To establish an international core set of patient-reported outcomes (PROs) selected by both patients and healthcare providers (HCPs) from the United States (US), Europe, and Asia.

Summary Background Data: PROs are increasingly recognized in pancreatic cancer studies. There is no consensus on which of the many available PROs are most important.

Methods: A multicenter Delphi study among patients with pancreatic cancer (curative- and palliative-setting) and HCPs in 6 pancreatic centers in the US (Baltimore, Boston), Europe (Amsterdam, Verona), and Asia (Mumbai, Seoul) was performed. In round 1, participants rated the importance of 56 PROs on a 1 to 9 Likert scale. PROs rated as very important (scores 7–9) by the majority ($\geq 80\%$) of curative- and/or palliative-patients as well as HCPs were included in the core set. PROs not fulfilling these criteria were presented again in round 2, together with feedback on individual and group ratings. Remaining PROs were ranked based on the importance ratings.

Results: In total 731 patients and HCPs were invited, 501 completed round 1, and 420 completed both rounds. This included 204 patients in curative-setting, 74 patients in palliative-setting, and 142 HCPs. After 2 rounds, 8 PROs were included in the core set: general quality of life, general health, physical ability, ability to work/do usual activities, fear of recurrence, satisfaction with services/care organization, abdominal complaints, and relationship with partner/family.

Conclusions: This international Delphi study among patients and HCPs established a core set of PROs in pancreatic cancer, which should facilitate the design of future pancreatic cancer trials and outcomes research.

Keywords: Delphi, pancreatic cancer, patient-reported outcome, PRO, quality of life

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While trials have traditionally focused on clinical outcomes, patient-reported outcomes (PROs) are increasingly regarded equally important.^{1,2} PROs are of particular interest in oncology, due to the often limited survival after morbid and complex treatments requiring careful appraisal and shared decision-making. Future trials and outcomes research programs should therefore not only focus on survival but specifically also study effects on quality of life.³

Pancreatic cancer is one of the most lethal cancers with a high disease burden and its systemic and surgical treatments are associated with high complication rates.^{4,5} Resected pancreatic cancer is associated with a 5-year survival of around 20%.⁶ Median survival in the 80% of patients with nonresectable pancreatic cancer is approximately 6 months, despite new systemic therapies.^{4,7,8} It is estimated that by 2030, pancreatic cancer will be the second most common cause of cancer-related death in the United States (US).⁹ The impact of both pancreatic cancer and its treatment on quality of life is enormous. A recent systematic review demonstrated a 98% loss of healthy life in affected individuals.¹⁰ Given this grim outlook, large-scale randomized controlled trials assessing new treatment strategies and high-quality outcomes research programs for pancreatic cancer are urgently needed. Given the morbid nature of most new treatment strategies, such trials should also include PROs to assess quality of life.

Standardization of measurement, analysis, and reporting of PROs is desired.^{3,11,12} Surprisingly, little research has been done on PROs in pancreatic cancer, while it is especially important for this specific disease due to high disease burden, invasive treatments, and

From the *Department of Surgery, Cancer Center Amsterdam, Academic Medical Center, Amsterdam, The Netherlands; †Department of Surgery, Gelre Hospital, Apeldoorn, The Netherlands; ‡Department of Medical Psychology, Cancer Center Amsterdam, Academic Medical Center, Amsterdam, The Netherlands; §General and Pancreatic Surgery, The Pancreas Institute, University of Verona Hospital Trust, Verona, Italy; ¶Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA; ||Department of Surgery, Johns Hopkins Medical Institutions, Baltimore, MD; **Department of Surgery, Seoul National University Hospital, Seoul, Korea; ††GI and HPB Service, Department of Surgical Oncology, Tata Memorial Hospital, Mumbai, India; ‡‡Department of Medical Oncology, Tata Memorial Hospital, Mumbai, India; §§Department of Medical Psychology, University of Verona Hospital Trust, Verona, Italy; and ¶¶Department of Medical Oncology, Cancer Center Amsterdam Academic Medical Center, Amsterdam, The Netherlands.

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LBvR and AG share first authorship.

HWvL and MGB share senior authorship.

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Reprints: Marc G. Besselink, MD, PhD, Department of Surgery, Office G4-146.1, Cancer Center Amsterdam, Academic Medical Center, PO Box 22660, 1100DD Amsterdam, The Netherlands.

E-mail: m.g.besselink@amc.nl.

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limited survival.^{9,10} Current investigations of PROs are typically based on input from physicians only, stem from teleconferences or open meetings with limited scientific methodology, or originate from single countries limiting international generalizability. Numerous PROs exist and opinions on the relevance of each PRO may differ between patients and health care professionals (HCPs). Many patients may not experience each PRO (eg, pain, fatigue), whereas HCPs with considerable experience in the field of pancreatic cancer will be able to make a generalized impression of which domains are important for patients with pancreatic cancer. Identifying a core set of PROs in pancreatic cancer should therefore involve both patients and HCPs. Such a core set would support current efforts toward patient-centered healthcare, and can enable future trials and outcomes research programs.¹³ The aim of this study was to establish an international core set of PROs in pancreatic cancer, with consensus among both patients and HCPs. We performed a multicenter Delphi study involving both patients and HCPs from the United States (US), Europe, and Asia.¹⁴

METHODS

Participants

Eligible adult patients with pancreatic or periampullary cancer diagnosed between January 2012 and September 2016, and HCPs were included from 6 centers in 5 countries: Johns Hopkins Hospital, Baltimore, US; Massachusetts General Hospital, Boston, US; University of Verona Hospital Trust, Verona, Italy; Academic Medical Center, Amsterdam, The Netherlands; Tata Memorial Centre, Mumbai, India; and the Seoul National University Hospital, Seoul, South Korea. These centers were selected for their known specific interest, experience, and research in pancreatic cancer. Patients with a life expectancy under 3 months (determined at the discretion of the local investigator) were excluded to maximize the odds of completing both rounds. HCPs (surgeons, medical-oncologists, gastroenterologists, radiotherapists, nurses, and dieticians) were currently active in the treatment of patients with pancreatic or periampullary cancer and working in the participating centers. Institutional Review Board waiver for informed consent procedure was obtained in all centers. Eligible patients and HCPs received an electronic invitation to participate in the survey.

PRO Selection

A list of 56 PROs was composed, based on a previous study by the Dutch Pancreatic Cancer Group (eSupplement 1, <http://links.lww.com/SLA/B358>).¹⁵ In that study, all randomized controlled trials on pancreatic cancer published between 2004 and 2014 and included in the patient-reported outcomes measurements over time in oncology registry were screened, to identify PROs used in pancreatic cancer research.¹⁶ Additionally, patient reported outcome measures that measured PROs in a (yet unpublished) systematic review on quality of life in pancreatic cancer were analyzed. The individual PROs from each patient-reported outcome measure were extracted. This resulted in a list of 53 PROs. Three additional PROs were added, based on the results of the open text field of the first round in the Dutch study.¹⁵

Delphi Survey

The Delphi methodology is the preferred method to systematically gather input from relevant stakeholders on a topic.¹⁷ In a Delphi survey, a panel of stakeholders is asked for their opinion on a question and subsequently repolled with controlled feedback regarding the polled opinions, to encourage consensus between the involved experts.¹⁸

Questionnaires were made available electronically and translated from Dutch into English, and subsequently from English into

Hindi, Italian, Korean, and Marathi. For each language, 1 translator, a HCP familiar with the medical terminology, translated the document into the required language (forward translation). Thereafter, for each language, a second translator, without specific medical knowledge, translated the document back to English (backward translation). Discrepancies between the forward and backward translations were addressed by discussion and consensus between the 2 translators, and in case of any doubt resolved through discussion with additional members of the study team (LBvR, J-YJ, LM, AM).

The Delphi survey consisted of 2 rounds. Participants received the questionnaires through email with a web link to the online questionnaire and were instructed to complete the questionnaire within 2 weeks. Nonrespondents received up to 3 reminders. The questionnaire of the first round consisted of 3 parts. In the first part, patients were asked to provide sociodemographic and clinical information. HCPs were asked to provide sociodemographic and professional information. In the second part, participants were asked to rate the importance of the predefined list of PROs on a 1 to 9 Likert scale (1 equaling not important and 9 equaling very important) with the following introduction: "Please indicate how important you think it is that these topics are addressed in questionnaires for patients with pancreatic cancer." The third part consisted of a free text field for suggestions on additional important PROs.

The invitation to the second questionnaire was sent to all respondents 8 weeks after the completion of the first round. The questionnaire for round 2 comprised the same list of PROs as in round 1, excluding those PROs for which consensus was already reached. Additional PROs that were mentioned in the first round were categorized by 2 authors independently (LBvR and AG), and checked by additional members of the study team (IH, HWVL, MGB). Topics that were not represented by any of the PROs in the original list were added to the list for the second round. The questionnaire included feedback on the median score of curative and/or palliative patients (depending on the patient's group) and HCPs, as well as the participant's own score in round 1. HCPs received feedback on each patient group separately, additional to the median score of HCPs and the HCP's own score in round 1.

In the absence of a formal guideline,¹⁹ consensus was considered obtained when the majority (80%) of curative and/or palliative patients and HCPs rated the topic as either "not important" (scores 1–3) or "very important" (scores 7–9), unless $\geq 15\%$ of curative or palliative patients or HCPs rated the PRO as "not important" (scores 1–3). Furthermore, all PROs were ranked in order of decreasing importance; $\geq 80\%$ of curative and/or palliative patients and HCPs rated the topic as "very important" (scores 7–9), $\geq 70\%$ of curative and/or palliative patients and HCPs rated the topic as "very important" (scores 7–9), $\geq 60\%$ of curative and/or palliative patients and HCPs, $\geq 50\%$, etc.

Statistical Analysis

Data were analyzed using SPSS for Windows version 21.0 (SPSS Inc, Chicago, IL). Continuous variables were expressed as median (interquartile range) and categorical variables were expressed as frequencies (percentage) unless specified otherwise. Missing data were handled by complete case analysis as no more than 1% of data per PRO was missing. No sample size guidelines exist for Delphi surveys.¹⁴ To ensure a heterogeneous and representative study population of patients and HCPs, we aimed to include per center 40 to 80 patients treated in a curative setting, 20 to 40 patients treated in a palliative setting, and 20 to 40 HCPs with at least 3 HCPs from each of the following specialties: surgery, medical-oncology, gastroenterology, radiotherapy, nursing, and dietician. Subanalyses were performed to determine which PROs reached consensus in patients and HCPs separately, and to determine differences of 20% or more in the number of HCPs or patients rating a

TABLE 1. Characteristics of 334 Patients Who Completed the First Delphi Round on Patient-reported Outcomes in Pancreatic Cancer

	Treatment With Curative Intent n = 237	Treatment With Palliative Intent n = 97
Male	136 (57)	53 (55)
Age [yrs; mean (SD)]	61 (11)	62 (11)
Geographic location		
United States	41 (17)	1 (1)
Europe	105 (44)	56 (58)
Asia	91 (38)	40 (41)
Educational level		
None/primary	40 (17)	18 (19)
Secondary	80 (34)	34 (35)
Postsecondary nonuniversity/university	102 (43)	43 (44)
Other	15 (6)	2 (2)
Employment status		
Working	83 (35)	29 (30)
Not working	58 (25)	19 (20)
Retired	85 (36)	36 (37)
Other	11 (5)	13 (13)
Married/in a relationship	202 (85)	81 (84)
Living with partner/family	211 (89)	85 (88)
Months after diagnosis [median (range)]	13 (1–76)	5 (1–37)
Underwent surgery	237 (100)	29 (30)
Months after surgery [median (range)]	9 (1–66)	4 (0–30)
Metastatic disease	44 (19)	25 (26)
Experienced recurrence	41 (17)	N/a
Current therapy		
None	141 (60)	32 (33)
Chemotherapy	64 (27)	56 (58)
Radiotherapy	3 (1)	2 (2)
Other	29 (12)	7 (7)

Data are expressed as n (%) unless otherwise specified. SD indicates standard deviation; N/a, not applicable.

PRO as “very important.” Additional subanalyses were performed to determine scores in each continent separately.

RESULTS

Participants

A total of 731 participants received an electronic invitation to participate. This included 502 patients (339 in curative-intent and 163 in palliative setting), and 229 HCPs. Questionnaires were returned by 501 participants, including 334 (66%) patients (237 in curative-intent and 97 in palliative setting) and 167 (73%) HCPs in round 1. Characteristics of the participants are shown in Table 1 for patients and Table 2 for HCPs. Characteristics of the participants per continent are available in eSupplement 2, <http://links.lww.com/SLA/B358>. Round 2 was completed by 204 patients (86% of patients in round 1, 60% overall) in curative setting and 74 patients (76% of patients in round 1, 45% overall) in palliative setting. Only 1 patient in the US treated with palliative intent completed both rounds and was therefore excluded as this would otherwise lead to an underrepresentation of this treatment group from the US. A total of 142 HCPs completed round 2 (85% of HCPs in round 1, 62% overall).

First Round

After the first round, no consensus was reached for any single PRO, that is, none of the 56 PROs was rated as “very important”

TABLE 2. Characteristics of 167 Health Care Practitioners Who Completed the First Delphi Round on Patient-reported Outcomes in Pancreatic Cancer

	Total n = 167
Male sex	82 (49)
Age [yrs; mean (SD)]	39 (10)
Geographic location	
United States	25 (15)
Europe	87 (52)
Asia	55 (33)
Specialty	
Surgeon	57 (34)
Gastroenterologist	24 (14)
Medical oncologist	20 (12)
Radiotherapist	16 (10)
Nurse	35 (21)
Dietitian	15 (9)
Working experience	
<5 yrs	43 (26)
5–10 yrs	56 (34)
>10 yrs	68 (41)
Experience in pancreatic cancer care	
<5 yrs	64 (38)
5–10 yrs	52 (31)
>10 yrs	51 (31)

Data are expressed as n (%) unless otherwise specified. SD indicates standard deviation.

(scores 7–9) or “not important” (scores 1–3) by 80% of the curative or palliative patients or HCPs. One additional PRO was identified in the first round and added to the questionnaire of the second round: *concerns about hereditary cancer*.

Second Round

After the second round, 8 PROs fulfilled the criteria for inclusion in the core set. Six were rated as “very important” by patients (both curative and palliative setting) and HCPs: general quality of life, general health, physical ability, ability to work/do usual activities, fear of recurrence, and satisfaction with services/care organization. Two PROs were rated as “very important” by patients in the palliative setting and HCPs: abdominal complaints (pain/discomfort), and relationship with partner/family. None of these PROs was rated as “not important” by $\geq 15\%$ of curative or palliative patients or HCPs. Results of the 2-round Delphi survey are summarized in Figure 1. The final list of PROs included in the core set is listed in Table 3. Ranking of all PROs based on the number of curative and/or palliative patients and HCPs rating each topic as “very important” is shown in eSupplement 3, <http://links.lww.com/SLA/B358>.

The PRO “appetite” reached the 80% consensus cut-off in round 2 by curative patients, but not by HCPs or palliative patients. The PROs vomiting, jaundice, pain, and diabetes reached the 80% cut-off in round 2 by HCPs, but not by patients. PROs that were regarded substantially (difference $\geq 20\%$) more important by HCPs compared with patients included fever/chills, nausea, enteral nutrition, itching, pain, vomiting, jaundice, and diabetes. PROs that were regarded substantially (difference $\geq 20\%$) less important by HCPs compared with patients included eye problems, skin problems, cognition, change in taste of food, and dry mouth. There were no substantial differences between patients treated with curative intent and patients treated with palliative intent.

When analyzing each continent (US, Europe, Asia) separately, the criteria for inclusion in the core set was reached for all 8 PROs in

Europe. There were 3 PROs which additionally reached the inclusion criteria for consensus in Europe but not in the US and Asia: weight changes, appetite and fatigue. In the US (including only curative patients and HCPs), criteria for consensus were not reached for fear of recurrence and relationship with partner/family (consensus in 70%–80% range). There was 1 PRO which additionally reached the inclusion criteria for consensus in the US by curative patients and HCPs: pancreatic enzyme replacement therapy. There were no PROs which reached the inclusion criteria for consensus in Asia but the core set PROs were the highest scoring PROs in Asia with a $\geq 70\%$

rating curative and/or palliative patients and HCPs (except the ability to do work/usual activities).

DISCUSSION

This study provides the first international core set of PROs in pancreatic cancer selected by 333 pancreatic cancer patients and 167 HCPs through a Delphi process: general quality of life, general health, physical ability, ability to work/do usual activities, fear of recurrence, satisfaction with services/care organization, abdominal complaints (pain/discomfort), and relationship with partner/family.

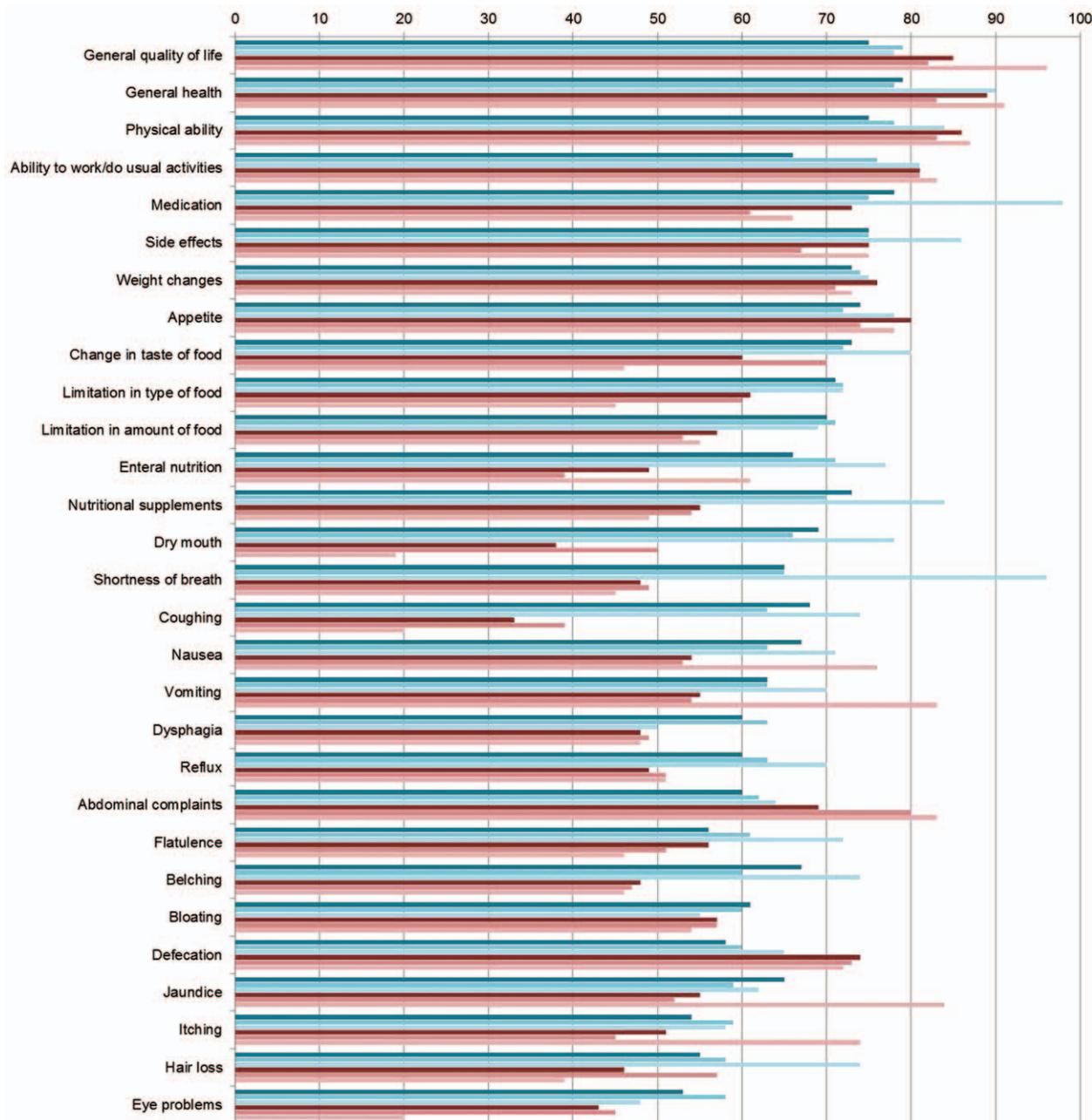


FIGURE 1. A, B, Results of the 2-round Delphi survey. The bars represent the percentage of participants (curative patients, palliative patients, and HCPs) rating the PRO as “very important” (scores 7–9) in rounds 1 (blue) and 2 (red). The 80% line represents the level of agreement for consensus to be included.

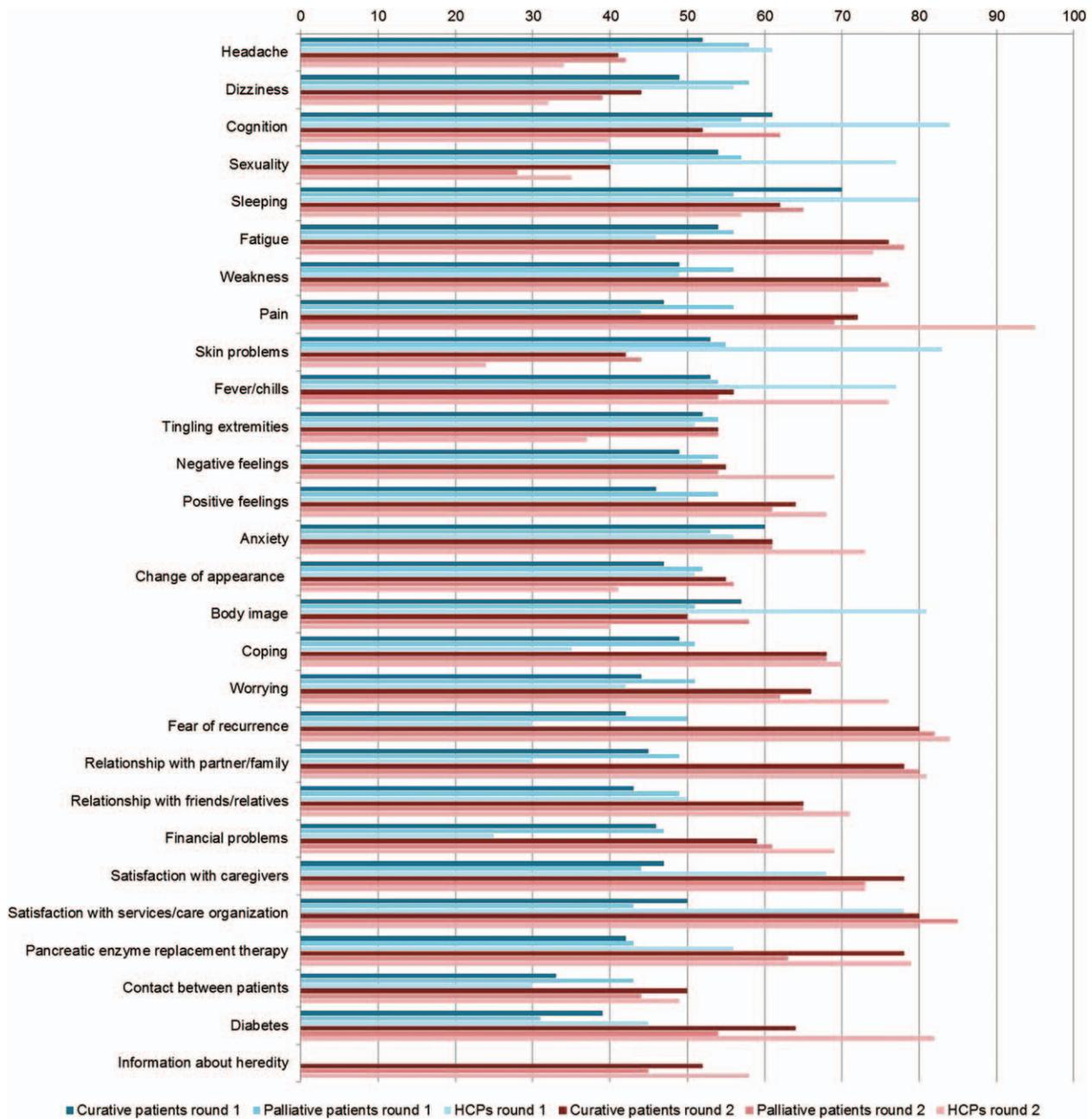


FIGURE 1. Continued

The intercontinental core set can facilitate the design of future pancreatic cancer trials and outcomes research programs.

The Delphi process is the preferred method to systematically gather input from relevant stakeholders on a topic.^{17,18} Most consensus statements often omit the patient’s perspective.¹⁴ To our knowledge, there have been very few other Delphi approaches with patient involvement to identify core PROs in oncology. These studies were performed with a low (er) number of participants (range 16–208 participants completing 2 Delphi rounds, compared with 420 in this study), and were performed in a single or 2 countries.^{15,20,21} The current study is one of the first identifying core PROs in oncology through a scientific approach, with a large number of participating

centers, and including a large amount of patient input. It is the first with an intercontinental design.

A previous Dutch multicenter Delphi study among 150 patients (curative and palliative setting) with pancreatic cancer and 78 HCPs identified a core set of 17 PROs, selected out of the identical 56 PROs as used in the current study.¹⁵ Due to social-cultural differences, priorities and expectations of patients may differ between various regions and this might influence the selection of PROs.^{22,23} This is illustrated by the lack of consensus on any PRO in the first Delphi round of the present study. These findings also support the international design of the present study.

TABLE 3. International Core-set of Patient-reported Outcomes in Pancreatic Cancer

	Median (IQR) Rating		
	Curative Patients	Palliative Patients	HCPs
Completed either first or second round:	n = 237	n = 97	n = 167
General quality of life	8 (2)	8 (2)	8 (1)
General health	8 (2)	8 (2)	8 (1)
Physical ability	8 (1)	8 (2)	7 (1)
Ability to work/do usual activities	8 (1)	8 (1)	8 (1)
Fear of recurrence	8 (2)	8 (2)	8 (2)
Satisfaction with services/care organization	8 (2)	8 (2)	7 (1)
Abdominal complaints (pain/discomfort)	7 (1)	7 (1)	7 (1)
Relationship with partner/family	8 (1)	8 (1)	8 (1)

Items in bold reached consensus to be included (more than 80% of participants in the group rates 7–9 on the Likert scale). IQR indicates interquartile range.

The 8 core PROs identified in the current study include the general domains of quality of life and health. It seems reasonable that consensus was reached on these PROs as they describe a comprehensive sense of general wellbeing, which is appealing and desirable for all stakeholders. Three core PROs included psychosocial domains: fear of recurrence, satisfaction with services/care organization, and the relationship with partner and family. This highlights the importance that should be placed on the psychosocial aspect of pancreatic cancer care, which has traditionally been an understudied domain.²⁴ Research on pancreatic cancer has mainly focused on physical PROs such as disease-related symptoms, while patients and HCPs consider psychosocial PROs of equal importance.^{20,25} Importantly, validated questionnaires to measure both psychosocial domains^{26–28} and physical domains (ie, the ability to work/do usual activities and abdominal complaints)^{29–31} are available. Physical ability describes a general sense of wellbeing and the ability to do work/usual activities is closely related, but highlights the patients' desire to resume normal life.

The topics with the lowest priority PROs (rated as “very important” by less than 40%) of patients and HCPs included mainly highly specific physical domains which may be less often experienced or considered less relevant. In patients, this included coughing, dry mouth, sexuality, dizziness, and enteral nutrition. HCPs considered eye problems, skin problems, headache, tingling of extremities, and hair loss as low priority.

Some PROs with diagnostic and treatment-related importance such as vomiting, jaundice, and pain reached the criteria for inclusion by HCPs, but not by patients. We found a surprising amount of overlap in PROs rated as very important between patients treated with curative intent and patients treated with palliative intent. Most curative patients will at some point become palliative patients, which also makes the use of 1 core set more feasible. The PROs abdominal complaints and relationship with partner/family were considered as very important by the majority of HCPs and palliative patients, but not curative patients. Patients treated with palliative intent may give priority to physical discomfort and relationships due to a shorter survival time. Alternatively, these “symptoms” may be more frequent in patients treated with palliative intent.

Our aim was to establish an international consensus based on a majority of votes from patients and HCPs from different continents, but we also explored each continent (USA, Europe, Asia) separately. Although some additional PROs reached consensus in Europe (weight changes, appetite, fatigue) and the US (pancreatic enzyme replacement therapy), few differences were found. In the US, the importance of pancreatic enzyme replacement therapy could be explained by the high costs of pancreatic enzymes.³² Interestingly,

in Asia consensus was not reached on any PRO. Overall scores were lower, but the overall variance in Asia did not differ from other continents, and mean ratings for PROs included in the final consensus were not different between India and South Korea (data not shown). PROs included in the core set were, however, the highest scoring PROs in Asia and 7 out of 8 were scored as “very important” by $\geq 70\%$ of all groups. Therefore, these PROs also seem the most relevant to the Asian population.

Another application of PROs is their routine, longitudinal measurement in clinical practice, which may benefit both patient-centered care (patient-provider communication, monitoring of treatment response, and detection of unrecognized problems) and general quality of care (patient management, health outcomes, transparency, accountability, and public reporting).^{1,33} Clinicians or researchers wanting to initiate a routine collection of PROs in pancreatic cancer patients may want to include more than 8 PROs. Therefore, we created a list (eSupplement 3, <http://links.lww.com/SLA/B358>) ranked in order of decreasing importance of all 57 PROs based on the number of curative and/or palliative patients and HCPs rating each topic as “very important.”

Our study should be interpreted in the context of its design. The Delphi survey consisted of 2 rounds. With more rounds, the chance of more PROs reaching consensus increases. However, no guidelines on the optimal number of rounds exist and since pancreatic cancer patients have a limited survival, increasing the length of the study would increase dropout and consequently result in lower response rates. Total response rate in this study was 84% of the respondents in round 1 which means consensus was not reached by attrition but in the way intended by the Delphi method. We observed some intra- and intercontinental heterogeneity regarding baseline characteristics of patients and HCPs (eSupplement 2, <http://links.lww.com/SLA/B358>). The intercontinental differences may be regarded as a strength because the aim of this study was to establish an internationally valid consensus, despite such differences. Finally, in the US we included less patients and HCPs than anticipated (35% and 63% of target number of patients and HCPs, respectively). Furthermore, only 1 patient in the US treated with palliative intent completed both rounds and was therefore excluded. Therefore, we cannot claim that the consensus also counts for patients from the US treated with palliative intent. The lower number of inclusions from the US and the resulting underrepresentation of American participants may have introduced cultural bias. However, all PROs included in the core set reached a score $>70\%$ by curative patients in the US.

In conclusion, this study identified an international core set of 8 PROs in pancreatic cancer selected by 333 patients treated in both

curative- and palliative setting, and 167 HCPs from 5 countries in 3 continents. These PROs are recommended to be used when designing trials in pancreatic cancer and in outcomes research programs.

Collaborators

Nita Nandkumar Chavan, RGNM; Suriya Umesh Dalvi, MA; Both Tata Memorial Hospital, Mumbai, India.

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