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Meeting Report

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Results from a 1-day workshop on the assessment of quality of life in cancer patients: a joint initiative of the Japan Clinical Oncology Group and the European Organisation for Research and Treatment of Cancer

Mitsumi Terada[1,2,*], Kenichi Nakamura[2,3], Francesca Martinelli[4], Madeline Pe[4], Junki Mizusawa[2,3], Junko Eba[2,3], Haruhiko Fukuda[2,3], Naomi Kiyota[5], Laureline Gatellier[6,7], Yoshiyuki Majima[8], Galina Velikova[9], and Andrew Bottomley[4]

[1]Medical Department, European Organisation for Research and Treatment of Cancer (EORTC) Headquarters, Brussels, Belgium, [2]Clinical Research Support Office, National Cancer Center Hospital, Tokyo, Japan, [3]Japan Clinical Oncology Group (JCOG), Data Center/Operations Office, Tokyo, Japan, [4]Quality of Life Department, European Organisation for Research and Treatment of Cancer (EORTC) Headquarters, Brussels, Belgium, [5]Department of Medical Oncology and Hematology, Kobe Univeersity Hospital Cancer Center, Kobe, Japan, [6]Japan Brain Tumor Alliance, Yokohama, Japan, [7]Rare Cancers Japan, Tokyo, Japan, [8]PanCAN Japan, Tokyo, Japan, and [9]Leeds Institute of Medical Research at St James's University of Leeds, Leeds, UK

*For reprints and all correspondence: Mitsumi Terada, Clinical Research Support Office, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: mitterad@ncc.go.jp

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Abstract

This report summarizes the presentations and discussion in the first Japan Clinical Oncology Group-European Organisation for Research and Treatment of Cancer Quality of Life/Patient-Reported Outcome workshop funded by the National Cancer Center Hospital that was held on Saturday, 1 September 2018 in Tokyo, Japan. The infrastructure and understanding regarding the Quality of Life/Patient-Reported Outcome assessment of cancer patients in Japan is still immature, in spite of the increased demand for oncological Patient-Reported Outcome research felt not only by researchers but also by patients or other stakeholders of cancer drug development. The workshop aimed to share each perspective, common issues to be considered and future perspectives regarding the strong alliance between the European Organisation for Research and Treatment of Cancer Quality of Life Group and the Japan Clinical Oncology Group for Quality of Life/Patient-Reported Outcome research as well as explore the possibility of conducting collaborative research. European Organisation for Research and Treatment of Cancer is a leading international cancer clinical trials organization, and its Quality of Life Group is a global leader in the implementation of Quality of Life research in cancer patients. The three invited speakers from the European Organisation for Research and Treatment of Cancer Quality of Life Group presented their perspective, latest methodology and ongoing projects. The three speakers from the Japan Clinical Oncology Group presented their current status, experience and some issues regarding data management or interpretation of the Patient-Reported Outcome data. The two

patient advocates also shared their expectations in terms of advances in cancer research based on the Patient-Reported Outcome assessment. As the next steps after this workshop, the Japan Clinical Oncology Group and European Organisation for Research and Treatment of Cancer have decided to cooperate more closely to facilitate Patient-Reported Outcome research in both the groups, and the Japan Clinical Oncology Group has approved the establishment of a new committee for Quality of Life/Patient-Reported Outcome research in Japan.

Key words: quality of life, patient-reported outcome measures, international cooperation, surveys and questionnaires

Overview

Global developments in novel cancer treatments have progressed rapidly. Objective endpoints, such as overall survival and rate of adverse events, have been used for evaluating the efficacy and safety of new treatments in cancer clinical trials, supporting the practice of evidence-based medicine. In contrast, the concept that the experiences and opinions of cancer patients undergoing treatment should be better reflected in the process of treatment development (patient-centered medicine) is prevalent in Western countries. In 2009, the Food and Drug Administration (FDA) published guidelines on the use of patient-reported outcome (PRO) measures in medical product development (1), and the European Medicines Agency has developed guidelines for the use of PRO measures in oncology studies (2). However, the infrastructure for the assessment and interpretation of PRO data in cancer trials in Japan is underdeveloped and is still immature. The Japan Clinical Oncology Group (JCOG) is the leading multicenter clinical study group in Japan that has conducted nationwide clinical trials to establish effective standard treatments for various types of malignant tumors. However, the JCOG has maintained a cautious approach toward the implementation of quality of life (QOL) assessment of cancer patients in their trials with concerns about the subjectivity of the QOL data, the complexity of the interpretation as well as the patient and administrative burden for QOL data collection.

The European Organisation for Research and Treatment of Cancer (EORTC) is an independent, nonprofit international cancer research organization that coordinates and conducts clinical trials for improving the standard of care for cancer patients. In 1980, the EORTC Quality of Life Group (EORTC QLG) was created to advise the EORTC headquarters and the various cooperative groups on the design, implementation and analysis of QOL studies within selected phase III clinical trials. At the time of writing this report, there are 397 QOL researchers who are members of the EORTC QLG and attend the meetings regularly, according to the QLG newsletter (3) provided by the current secretary of the EORTC QLG, Karin Kuljanic. The EORTC QLG has developed and refined questionnaires for assessing health-related QOL (HRQL) for use in oncology clinical trials (e.g. EORTC QLQ-C30), and these well-validated questionnaires have been globally used in clinical trials and clinical practice. From 2003 to 2017, 53 EORTC trials included QOL assessment (Tables 1a and 1b), and there are ongoing projects that aim to understand the effects of cancer and its treatment on the QOL of diverse populations of cancer patients across different cultures.

Recently, the JCOG and the EORTC strengthened their ties to facilitate intercontinental collaborations through conducting collaborative trials and projects (e.g. EORTC-1527-GITCG-IG: DREAM—Diffusion-Weighted Magnetic Resonance Imaging Assessment of Liver Metastasis to Improve Surgical Planning, and the first JCOG-EORTC scientific symposium took place in December 2017 in Tokyo) (4,5). For further cooperation, the gap in the stance about QOL research between EORTC and JCOG should be bridged.

The JCOG has organized this first-ever workshop on QOL/PRO research for cancer in collaboration with the EORTC. The workshop aimed to share the approaches and policies on QOL research of both organizations, discuss current global issues and focus on future perspective on collaborative QOL projects across the EORTC and the JCOG.

Part 1: the EORTC Quality of Life Group's perspective

Quality assurance of QOL: how to develop ways to ensure robustness in QOL assessment and tools as well as in the creation of policies and standards of practice in instrument validation

FM (Specialist in Quality of Life, EORTC, Brussels, Belgium) first presented an overview on the history of QOL research and terminology/concept, highlighting the difference between the HRQL and PRO. HRQL is a multi-domain concept that represents the patient's general perception of the effect of illness and treatment on the physical, psychological and social aspects of life. PRO is a measurement based on a report that comes directly from the patient about the status of his/her health condition without amendment or interpretation of the patient's response by a clinician or anyone else. Thereafter, she discussed the procedure to develop a questionnaire or a module for HRQL assessment according to the EORTC Quality of Life Group (QLG) guidelines (6) with some examples. The term 'questionnaire' is used in reference to a stand-alone instrument, while the term 'module' refers to an instrument that needs to be administered in conjunction with a questionnaire.

The QLG started working on the development of the first questionnaire to measure the QOL in cancer patients as a self-reported outcome in 1980. The result of this work was the creation of a core questionnaire, the QLQ-C30 (7), that has been translated into over 110 languages and has been used, in the current version, since 1993.

Other instruments have been developed thereafter; these are not disease-specific, and organizations other than the QLG have developed them. Research organizations worldwide have developed tools to assess the specific aspects of the QOL in different subgroups of cancer patients.

FM showed the practical steps to develop a well-designed questionnaire or a module as per the QLG guidelines (8), including the several phases (phase 1–4), starting from conception to the development and validation of the desired instrument. This part of the talk focused on the conceptual work and the practical details, with examples and hints regarding the importance of cross-cultural validation as well as static (non-customizable) and dynamic (customizable) questionnaires (9).

Table 1a. Number of EORTC trials as per the publication year (2003–2017)

Year	CTs with NO QOL	CTs with QOL	TOTAL	% CTs with QOL
2003	14	3	17	18%
2004	17	2	19	11%
2005	6	2	8	25%
2006	10	3	13	23%
2007	9	2	11	18%
2008	5	4	9	44%
2009	5	3	8	38%
2010	4	2	6	33%
2011	2	6	8	75%
2012	6	1	7	14%
2013	6	5	11	45%
2014	9	2	11	18%
2015	12	6	18	33%
2016	8	4	12	33%
2017	8	8	16	50%
Total	121	53	174	30%

EORTC, European Organisation for Research and Treatment of Cancer; CTs, clinical trials; QOL, quality of life.

Table 1b. Number of trials as per the EORTC Group (2003–2017)

EORTC group	CTs with NO QOL	CTs with QOL	Total	% CTs with QOL
BTG	10	11	21	52%
STBSG	13	6	19	32%
ROG	3	3	6	50%
LCG	15	3	18	17%
GITCG	15	4	19	21%
Melanoma group	4	2	6	33%
GUCG	5	5	10	50%
BCG	12	9	21	43%
GCG	3	4	7	57%
HNCG	5	1	6	17%
Leukemia group	6	1	7	14%
CLG	2	2	4	50%
Elderly task force	1	1	2	50%
Other groups	28	0	28	0%
Total	121	53	174	30%

BTG, brain tumor group; STBSG, soft tissue and bone sarcoma group; ROG, radiation oncology group; LCG, lung cancer group; GITCG, gastrointestinal tract cancer group; GUCG: genito-urinary cancer group; BCG, breast cancer group; GCG, gynecological cancer group; HNCG, head and neck cancer group; CLG, children's leukemia group.

FM also provided guidance on a common question: 'How to choose a good tool?'. Given the multidimensional nature of QOL, the measurement requires a valid and reliable instrument that is able to assess the target parameters accurately and to provide an answer to the research question. Preference should always be given to validated instruments.

Once the tool is chosen and data are collected, it is time for the analyses. While talking about the analyses techniques, FM pointed out the importance of the interpretation of PRO/HRQL data. While analyzing the QOL data, researchers should consider not only the statistical significance but also the clinical interpretation. In other words: 'A difference is a difference when it makes a difference'. Without clinical significance, a number is just a number; however, with the correct interpretation, the same number can become an important source of clinically relevant information.

Design and analysis of PROs and HRQL endpoints in randomized controlled trials on cancer patients

MP (Specialist in QOL, EORTC, Brussels, Belgium) presented on the current trends regarding the increase in the number of trials that have assessed PRO and HRQL data; further, many stakeholders are interested in the assessment of PROs that can be used to integrate patient perspective into the drug development process. However, MP also mentioned the lack of set standards on how to analyze PRO data statistically, a factor that could hamper the interpretation of PRO findings.

An example was provided. Two trials with the same population, trial design, and treatment arms showed discrepant conclusions regarding HRQL outcomes (10,11). The discrepancy could mislead people to regard PRO and HRQOL assessment in cancer trials as not being useful. However, in the light of PRO research, the different

design and statistical analysis decisions could lead to different results. MP presented the importance of standardizing the statistical analyses of PRO and HRQL data to resolve the inherent issues of PRO data that are mentioned above. She has been in charge of the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data for Cancer Clinical Trials (SISAQOL) project (12) that aims to provide recommendations on the methods of standardizing the analysis of HRQL and other PRO data in cancer randomized trials. She stressed that more specific hypothesis, research questions, and objectives are needed and that 'to evaluate if QOL is improved' is insufficient as a research objective. Finally, she presented how to classify and handle missing data (13). Statistical methods that can handle the missing data were also presented. Issues in the use of statistical methods were discussed, with a focus on demonstrating the importance of identifying the reasons for missing PRO assessments. Finally, missing data is almost inevitable in cancer randomised controlled trials (RCTs); therefore, the importance of sensitivity analysis to test the different assumptions about missing data was emphasized to ensure the robustness of the PRO findings. More information about the recommendations from the SISAQOL initiative has recently been published (14).

The role of PRO and QOL measures in trials and clinical practice

GV (Professor of Medical Oncology, University of Leeds and Leeds Cancer Centre, Leeds, United Kingdom) first presented on the role of PRO/HRQL assessment in cancer clinical trials. Conventional clinical methods can be supplemented by PRO measures. The potential role of PROs is recognized and endorsed by national and international practice guidelines. For example, the UK TACT2 trial (15) was a phase III randomized controlled trial with 2 × 2 factorial design that aimed to test two hypotheses for breast cancer: whether the use of accelerated epirubicin was able to improve overall survival as compared to standard epirubicin and whether the use of oral capecitabine instead of standard combination chemotherapy (CMF) would be comparable in terms of overall survival, cause less toxicity and improve the QOL. The conclusion was that accelerated epirubicin did not offer greater efficacy; however, the PRO data showed worse symptoms, functioning and HRQOL scores with accelerated epirubicin than with standard epirubicin. Therefore, accelerated epirubicin could not be recommended as an alternative to epirubicin for moderate–risk, early-breast cancer patients. For the second hypothesis, capecitabine was as efficacious as CMF when following anthracycline chemotherapy; however, patients assigned to the CMF arm reported significantly more serious adverse effects that influenced their functioning and HRQL, with differences persisting for 12 and 24 months after the treatment. Based on both the overall survival and HRQOL results, the TACT2 trial recommends against the use of accelerated epirubicin for moderate–risk, early-breast cancer and confirms that oral capecitabine is as efficient but less toxic than standard CMF. Thus, the HRQOL data provided important information for clinicians and patients to support their treatment decisions.

Second, GV presented novel PRO concepts for cancer clinical trials. Conventionally, the tolerability of cancer treatment has been assessed mainly based on the clinician's safety data (e.g. CTCAE or other adverse events); however, several studies showed discrepancies between the adverse events or symptoms reported by clinicians and patients. The use of PRO data could be potentially beneficial to stakeholders engaged in drug development (Table 2). Regulatory agencies, such as the FDA, recommend the use of well-validated and reliable PRO measurements, such as the NCI PRO-CTCAE (16) and the EORTC item libraries (17), to complement existing clinical safety assessments and assess cancer treatment tolerability. Some investigators may not be confident about implementing PRO assessment in clinical trials, and some studies are ongoing to check the feasibility of collecting PRO data in multicenter cancer clinical trials (18).

Table 2. Potential beneficiaries of patient-reported adverse symptoms in cancer treatment trials

Stakeholder	Potential benefits
Clinical trial participants	Earlier detection of toxic effects through improved communication with clinical staff
Investigators and/or sponsors	More complete adverse event data during drug development
Regulatory agency reviewers	Additional toxicity data to balance safety with efficacy during regulatory review
Clinicians	Improved information about prior patients' experiences with treatments, for use when counseling future patients or assessing adverse reactions
Future patients	Access to information about prior patients' experiences with particular treatments, to inform therapy decisions

The third part of her presentation focused on the use of PROs in clinical practice to monitor symptoms and adverse effects during cancer treatment. There is increasing research evidence showing that the use of PROs in individual patient care in oncology is beneficial to patients, supports communication, achieves better symptom control and results in higher survival rates (19–21). A brief overview of this evidence was provided, followed by an example of her experience, in Leeds, UK, of online monitoring of toxicity during cancer chemotherapy using data on patient-reported adverse effects integrated with the electronic patient records (electronic patient self-reporting of adverse events: Patient Information and aDvice—electronic patient self-Reporting of Adverse-events: Patient Information and aDvice (eRAPID) research program funded by the National Institute for Health Research) (Fig. 1) (22,23). The values and challenges involved in integrating PRO data into routine oncology practice were also presented.

Part 2: current status of PRO and QOL assessment in Japan

Summary of QOL/PRO in the JCOG studies

JM (Coordinating Statistician, JCOG Data Center, Tokyo, Japan) presented the timeline of QOL/PRO research in the JCOG and the current issues to be solved for further implementation of HRQL assessment in clinical trials.

The timeline was split into the following two time frames: (i) 1990–2004 and (ii) 2005–2017.

1990–2004: before the establishment of the JCOG QOL policy. In this period, 19 of the 44 randomized phase III trials and 5 of the 72 nonrandomized and/or phase I and II trials included QOL assessment as their endpoints (Table 3a). The proportion of completed QOL

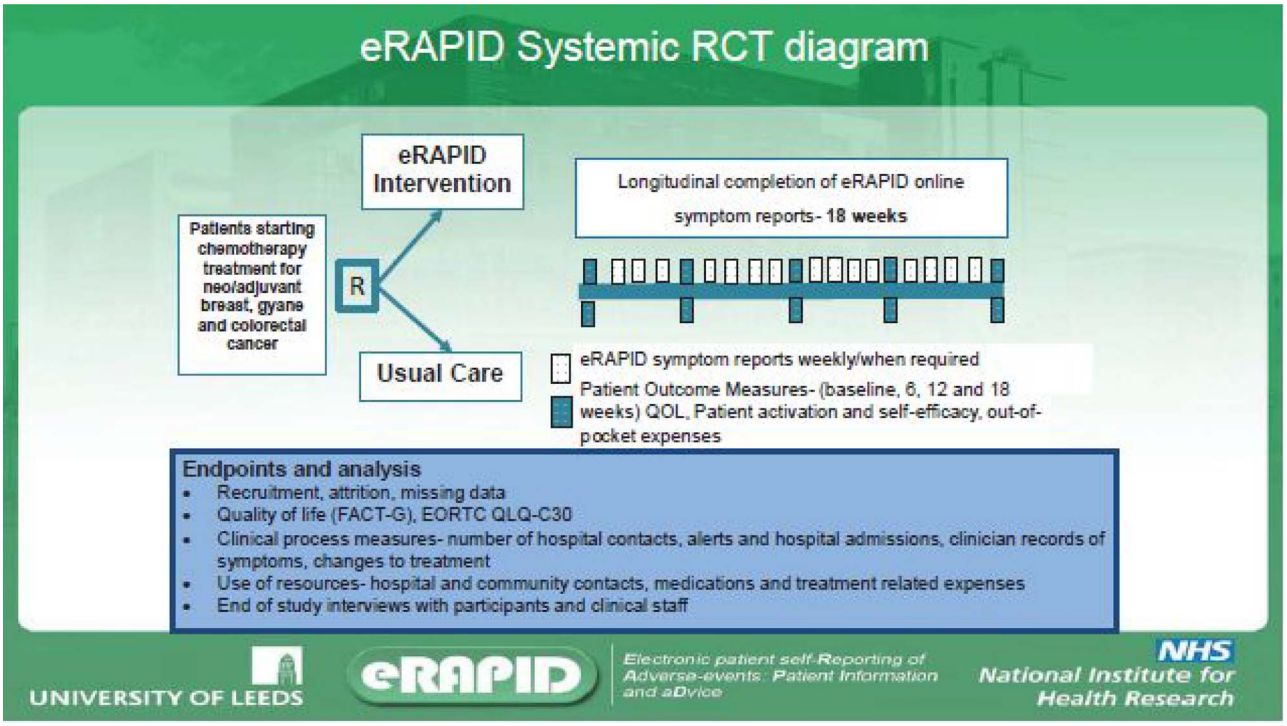

Figure 1. eRAPID systemic RCT diagram.

assessments in the trials of each tumor type was 37.5% (3/8) in lung cancer, 75% (3/4) in gastrointestinal cancer, 0% (0/3) in lymphoma, 100% (2/2) in urological cancer and 14.2% (1/7) in breast cancer. Overall, the QOL assessment was completed in only 37.5% (9/24) of all JCOG trials with QOL assessment. Some of the questionnaires or modules used in these trials were *ad hoc* questionnaires, and no person was in charge of data management for the collected QOL data in 15 out of the 24 trials.

Given the situation, the JCOG QOL unit was founded in 1997 to establish a feasible and valuable QOL assessment method in the JCOG with limited budget and human resources. Consecutively, the QOL unit conducted a feasibility study JCOG9803 aiming to evaluate the feasibility of QOL assessment and establish a method to manage QOL assessment, including data management. All the patients enrolled in the JCOG9802 (a randomized phase III trial to compare doxorubicin plus cyclophosphamide (AC), single-agent docetaxel (D) and an alternating regimen of AC and D (AC-D) as first-line chemotherapy in metastatic breast cancer) (24) were consulted and registered in an additional QOL study JCOG9803. The questionnaires used were the Functional Assessment of Cancer Therapy (FACT)-Breast cancer (25) and FACT-Taxane (26), and time points of assessment were baseline, 6 weeks after treatment initiation and 18 weeks after treatment initiation. Data were managed and reminders were sent by the JCOG QOL unit, and total 150 patients were enrolled. The data collection rates were 99, 89 and 87% at baseline, 6 and 18 weeks, respectively. Although the data collection rate was favorable, the practical administrative burden on the JCOG QOL unit for collecting the data rigorously was larger than expected; thus, it was concluded that it was not feasible for the JCOG Data Center and the QOL unit to support QOL data management of all the JCOG trials, considering the limited resources.

In 2003, the JCOG QOL *ad hoc* committee was established to develop a policy regarding QOL assessment in the JCOG trials. The committee members discussed the experience and reached the following consensus recommendations: validated questionnaires with a patient self-reporting format should be used, and at least one investigator from each study group should be appointed as the QOL study coordinator. This policy is available at the following link: http://www.jcog.jp/basic/policy/index.html.

2005–2017: after the establishment of the JCOG QOL policy. In this latter time frame, 8 of the 62 randomized phase III trials and 1 of the 43 nonrandomized and/or phase I and II trials included QOL assessment as their endpoint (Table 3b); further, the proportion of JCOG trials with QOL assessment has reduced from 20.7% (24/116; 1990–2004) to 8.1% (9/111; 2005–2017). However, QOL assessment has been completed in all the trials with patient accrual completion (5/9) according to the QOL policy. Although the proportion of trials with QOL assessment has decreased, the completion of QOL assessment has improved because of the efforts of the exclusive QOL coordinator who was in charge of data management.

For higher use of QOL assessment in JCOG trials, some issues need to be resolved at both the JCOG Data Center and local sites. Considering the limited resources at the JCOG Data Center, it is not feasible for the center to manage all data collection activities. In addition, the infrastructure for clinical trials at local sites could still be under developed for QOL assessment, while the support from the clinical research coordinator has improved.

The reason for unwillingness to use QOL assessment for clinical trials

HF (Director, JCOG Date Center, Tokyo, Japan) presented some inherent issues regarding the consideration of PRO/HRQL data in open-label clinical trials. First, he argued that the value of collecting

Table 3a. Number of JCOG trials with or without QOL assessment (1990–2004)

Groups	Randomized phase III trials		Nonrandomized and/or phase I/II		Total	% CTs having QOL
	With NO QOL	With QOL	With NO QOL	With QOL		
LCSG	4	7	26	1	38	21%
LCSSG	3	0	6	0	9	0%
GICG	2	1	8	0	11	9%
GCSSG	4	2	4	0	10	20%
JEOG	3	0	3	0	6	0%
CCSG	2	1	0	0	3	33%
BCSG	2	4	3	3	12	58%
LSG	3	2	13	1	19	16%
GyCSG	1	0	2	0	3	0%
UOSG	0	2	0	0	2	100%
BSTTSG	0	0	1	0	1	0%
RTSG	0	0	1	0	1	0%
BTSG	1	0	0	0	1	0%
Total	25	19	67	5	116	21%

LCSG, lung cancer study group; LCSSG, lung cancer surgical study group; GICG, gastrointestinal cancer group; GCSSG, gastric cancer surgical study group; JEOG, Japan esophageal oncology group; CCSG, colorectal cancer study group; BCSG, breast cancer study group; LSG, lymphoma study group; GyCSG, gynecologic cancer study group; UOSG, urologic oncology study group; BSTTSG, bone and soft tissue tumor study group; RTSG, radiation therapy study group; BTSG, brain tumor study group.

Table 3b. Number of JCOG trials with or without QOL assessment (2005–2017)

Groups	Randomized phase III trials		Nonrandomized and/or phase I/II		Total	% CTs with QOL
	With NO QOL	With QOL	With NO QOL	With QOL		
LCSG	3	4	2	0	9	44%
LCSSG	6	0	2	0	8	0%
GCSG	8	2	5	0	15	13%
JEOG	4	1	3	0	8	13%
CCSG	8	1	2	0	11	9%
HBPOG	4	0	4	0	8	0%
GIESG	2	0	5	0	7	0%
BCSG	3	0	1	0	4	0%
LSG	3	0	5	0	8	0%
GyCSG	3	0	3	0	6	0%
UOSG	2	0	0	0	2	0%
BSTTSG	3	0	0	0	3	0%
RTSG	2	0	5	1	8	13%
BTSG	6	0	1	0	7	0%
HNCSG	2	0	2	0	4	0%
DOG	1	0	2	0	3	0%
Total	60	8	42	1	111	8%

GCSG, gastric cancer study group; HBPOG, hepatobiliary and pancreatic oncology group; GIESG, gastrointestinal endoscopy study group; HNCSG, head and neck cancer study group; DOG, dermatologic oncology group.

QOL data in clinical trials for decision-making of cancer treatment remained uncertain. He mentioned the following reasons:

(a) Clinical meaning: difference or improvement in the QOL scores cannot be translated into clinical significance. 'Reducing %Grade3-4 diarrhea by 10%' is understandable by the patients as well as physicians; however, the clinical meaning of 'reducing QOL score by 10%' is not understandable by everyone.
(b) Usefulness in the choice of better treatment: in the noninferiority trial, survival was non-inferior in the NEW therapy group, toxicity was equivalent, and the QOL score was better in the NEW group; thus, NEW was chosen as the new standard therapy. In the superiority trial, survival did not differ, NEW was more toxic, and the QOL score was better in the NEW group; however, NEW was not chosen. Therefore, the QOL results in superiority trials do not affect the treatment choice.

Second, HF presented concerns about the validity of the QOL data:

(a) Information bias: cancer treatment trials are rarely masked (formerly called 'blinded') for assigned treatment, except

supportive treatment trials (e.g. antiemetic drug) because notification of the expected toxicity to the patients is essential to minimize patient risk during treatment. However, notification of toxicity information inevitably causes information bias in the patient's responses to the questionnaires (e.g. patients receiving cisplatin are likely to give a low [bad] score for gastrointestinal toxicity questions). This bias is never eliminated in open-label trials and is rarely mentioned as a limitation in trials on HRQOL and PROs.

(b) Missing data/informative censoring: missing data is a common source of bias in HRQOL. No solution has been established despite the proposal of many methods.

(c) Physician's underestimation of the severity of symptoms: similar underestimation that may have occurred in the treatment arms may not cause significant biases in treatment evaluation.

Finally, HF expressed apprehension regarding the respondent burden of patients. The HRQOL questionnaire is not a burden-free intervention. It requires not only time but also may cause mental burden for the patients, such as increased risk of depression. Mills et al. found that lung cancer patients who completed regular QOL questionnaires that were not reviewed by their physicians reported worse QOL (27).

HF concluded that most of the above problems cannot be resolved and HRQOL/PRO would only be useful in double-masked supportive treatment trials in the field of oncology. In double-masked crossover randomized trials, the following simple question should be asked to the patient, 'Which do you prefer, the former drug or the latter?'. If significantly more patients choose drug A over drug B, we can confidently conclude that drug A is the better drug. HRQOL/PRO could provide a very complicated answer to a simple question.

Experience of involvement in the EORTC QLG and module development

KN (MD, PhD, Kobe University Hospital Cancer Center, Hyogo, Japan) is a medical oncologist of head and neck cancer (HNC). He presented some unique QOL issues of patients with HNC who were treated with surgery, chemotherapy and radiation therapy; such alterations in the QOL due to disease and treatment could not be captured via conventional assessment of adverse events or symptoms. Thus, KN started to implement some modules (e.g. the EORTC QLQ-HN35) for assessing the HRQL in HNC patients. However, he has realized that it is not enough to only use a module developed in another region and translated the module into Japanese, in consideration of the cultural and, possibly, psychosocial differences between Western countries and Japan. In order to reflect the Japanese perspective in module development, he has been involved in the HNC module update and development projects (EORTC QLQ-HN43, QLQ-THY34) (28–31) and has been attending the EORTC QLG meeting since 2013, being the first active Japanese member of the QLG since 2015. He stressed that for further progress of HRQL and PRO research in Japan, a more organized collaboration between the EORTC and JCOG is crucial so that the role of HRQL assessment in cancer patients is increasingly recognized and implemented by Japanese researchers, physicians and patients.

Part 3: QOL from the perspective of the cancer patient

LG (President, Japan Brain Tumor Alliance) and YM (President, PanCAN Japan) presented the value of PRO in clinical trials and practice based on their experiences as patients. LG mentioned her experience first and then discussed the importance of tracking PRO data. With respect to clinical care, given the discrepancy between the reports by the physicians and patients (32,33), the use of clinical reports from both the physicians and patients is crucial for proper treatment decision and symptom control. For the administration of new drugs, such as molecularly targeted therapy and immunotherapy, PRO data could be useful to assess and manage the unique symptoms of each patient because these new drugs exert diverse adverse effects.

YM stressed on the importance of PRO, considering the cost and benefit balance of treatment, that is, the treatment value. Recently, there has been a shift toward enhancing evidenced-based medicine with value-based medicine (VBM). VBM is more than just managing the drug costs and forms a part of the broader debate on access to treatment that includes different stakeholder expectations regarding value in cancer care. Another shift has been observed from a product-oriented approach, rooted in science and efficacy, to a broader assessment that includes pharmacy economics, therapy management, compliance issues and QOL. Considering these global trends, the role of patient advocacy groups among stakeholders will become more important, and the PRO data will help in understanding patient experiences in cancer care and using patient perspectives for drug development.

Panel discussion

First, MT (Medical research fellow, EORTC, Brussels, Belgium) was asked how we should consider the information bias in the QOL/PRO researches. MP responded that the information bias could affect not only the PRO data but also other conventional trial endpoints, such as adverse events according to CTCAE, as assessed by investigators who are aware of the hypothesis; the information bias in open-label trials should be considered; however, this is not a unique issue of PRO assessment. GV commented, based on her oncology practice, that patients are exposed to a lot of information about efficacy, possible complications, adverse effects of treatment as well as the details of the clinical trial. It is often hard for them to retain all this information, and therefore unlikely the knowledge of potential side effects will cause the patients actually experiencing them.

Second, MT asked whether it was feasible to prioritize the assessment of disease symptoms, physical function and symptomatic adverse events over emotional well-being, social well-being and cognitive function, as suggested by the FDA (34). FM responded that the assessment of physical function or adverse events was crucial, considering that they would be affected directly by cancer treatment. However, each domain in a questionnaire is deeply interconnected; therefore, focusing on the assessment of a specific domain could allow missing out on important information about the impact of QOL. GV added that we should consider the type of cancer while assessing the QOL of the patients. For instance, the assessment of social functioning in addition to physical functioning of HNC patients would be useful to measure their HRQL. The domains to be prioritized or assessed should depend on the types of cancer, treatment and trial design.

Given the limited resources for cancer trials in Japan, it is impractical to collect complete QOL data for all domains using a questionnaire or a module. If the QOL endpoint in a trial is the change in the physical functioning score from that at baseline to that after 12 months of treatment, we should only collect data on physical functioning because collecting data about other domains would be less meaningful and add to the investigator burden. However, MP

argued that collecting the whole QOL data would be useful for forming a new hypothesis and would be informative for patients with similar disease evaluated in the trials and investigators who were interested in the treatment strategy of the cancer. It would be regrettable if the chance to collect crucial data on QOL in one trial is lost because the cost of conducting clinical research has been increasing. Collecting as much data as possible in one trial would be more efficient from the long-term standpoint.

The final topic was how we could encourage and reinforce a collaboration between the EORTC QLG and JCOG. YM first mentioned that from the patient perspective, they hoped more cancer patients would participate in clinical trials. The international collaboration could be one of the ways to increase the number of trials for which patients are eligible and facilitate the use of PRO assessment in Japan. For more efficiency and less burden on the patients and investigators, an electronic platform to collect PRO data should be developed. GV and KN (Director, JCOG Operation Office, Tokyo, Japan) proposed a joint development project of an electronic record system as a future collaboration.

Sustainable long-term cooperation would be crucial for further growth in this field of research in both Europe and Japan, as FM stated in the final comment, 'Rome was not build in a day'.

Conclusion/perspective for the future

Through this first-ever collaborative workshop on PRO/QOL research, both the EORTC QLG and JCOG have shared their knowledge, experiences and current issues on PRO research and learned from each other. For instance, as HF mentioned in his presentation, it is still controversial how we should integrate change of QOL score with the clinically significant meaning. Some researchers have investigated minimal clinically important difference (MCID) or minimally important difference (MID) in QOL scores to establish a benchmark for assessing the efficacy of new intervention in clinical trials (35). The EORTC QLG has also been engaged in a project to establish MID for all QLQ-C30 scales according to cancer sites, using individual patient data from archive EORTC trials (36–38). The JCOG investigators will deepen understanding of the impact of MCID or MID through this international collaboration with the EORTC. They have decided to cooperate more closely and work jointly to facilitate PRO research in both groups.

EORTC QLG will actively support future PRO assessments in the JCOG trials; the specialists of PRO/HRQL researches in EORTC QLG will be available for consultation on trial design, selection of proper modules for the trial, data management, statistical analyses and collaboration projects between the EORTC and JCOG. The EORTC QLG would let some Japanese investigators participate in the SISAQOL consortium that has been conducted mainly by the western countries.

The JCOG will also take a new step for PRO/QOL research in Japan. They have decided to establish a QOL *ad hoc* committee; thus, they will develop a task force for amending the current QOL research policy to establish a proper platform and infrastructure for PRO assessment and encourage the JCOG investigators to include QOL objectives and endpoints in their trials. The committee members plan to amend the JCOG QOL policy to update it with the current demand and global trend on QOL researches.

The collaboration between the EORTC QLG and JCOG has just started. Although some Japanese investigators have already worked together with the EORTC QLG for module developments (e.g. EORTC QLQ HN-43, EORTC QLQ THY-34) (23–26), this organized alliance will facilitate more efficient QOL research and patient- centered cancer treatment across Europe and Asia.

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Conflict of interest statement

None declared.

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Mini-abstract

The JCOG-EORTC QOL/PRO workshop was held on Saturday, 1 September 2018 in Tokyo and aimed to share the current status of QOL research and facilitate cooperative ties between the JCOG and EORTC.