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ORIGINAL ARTICLE

Experiences with the FACT-EGFRI-18 instrument in EGFRI-associated mucocutaneous adverse events

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Abstract
Purpose The functional assessment of cancer therapy epidermal growth factor receptor inhibitor 18 (FACT-EGFRI-18) is a patient-reported outcomes questionnaire developed to assess the effect of EGFRI on health-related quality of life (HRQoL).
Methods Ten native-speaking residents of The Netherlands who reported EGFRI-associated mucocutaneous adverse events (mcAEs) were administered the questionnaire. Patients were subsequently asked a standardized series of questions about the items' personal relevance.
Results Responses reflected a major negative impact of mcAEs due to EGFRI on physical, social/emotional, and functional domains. In some cases, especially in the social/-emotional domain, the responses to the qualitative interview indicated a greater impact on HRQoL than the numerical ratings previously selected for the Dutch FACT-EGFRI-18 questions.
Conclusions Based on these interviews, we identified that the physical items associated with mcAEs interfere most with HRQoL. The results suggest that the FACT-EGFRI-18 can be applied to measure mcAE-related HRQoL in cancer patients undergoing EGFRI therapy. In addition, patients feel the need to rate their symptom burden, too, and we recommend additional adverse event items to be incorporated into the questionnaire.

Keywords Epidermal growth factor receptor inhibitors (EGFRI) · FACT-EGFRI-18 · Mucocutaneous adverse events (mcAE) · Health-related quality of life (HRQoL) · Patient-reported outcome questionnaire · Symptom burden

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Background

Epidermal growth factor receptor inhibitors

The use of targeted therapies such as epidermal growth factor receptor (EGFR) inhibitors is increasing. It is well know that mucocutaneous adverse events (mcAEs) are the primary side effects associated with agents targeting the EGFR signal transduction pathway [1]. The most common mcAEs are defined as those affecting the skin, hair, nail bed, mucosa, or eyelids. mcAEs can result in skin rash (papulo-pustular eruption), itching (pruritus), abnormally dry skin (xerosis cutis), painful mucosal surfaces, dry conjunctivae of the eye, periungual inflammation, and edema in up to 90 % of patients during treatment with EGFR inhibitors (EGFRI) [2–4]. They can have significant impact on health-related quality of life (HRQoL) because they can hinder daily activities and make it difficult to maintain the patients' privacy about their illness, even when the

treatment is effective in combating the cancer. The mcAEs result in discomfort, which is frequently associated with a burning sensation, itching, or painful skin or nails and can lead to a decreased HRQoL, that may lead to dose reduction and even to a refusal to continue with further treatment [5]. Oral complications can cause pain and affect oral function such as oral intake of food and medications; they may impact nutrition, affect speech, the ability to maintain oral hygiene, and patients may be forced to remove their oral prostheses. Other oral symptoms can include taste change or taste reduction and dry mouth.

Many practitioners assume the cosmetic appearance of the rash to be the most bothersome for patients, but they may have a tainted perspective on patient's mcAEs influence on HRQoL. However, patients' concerns and emotions were most adversely impacted by associated symptoms of irritation, pain, stinging, and itching [6]. This discrepancy may exist because the mcAE grade seems inversely correlated with the impact on the HRQoL. This discrepancy between assessment of mcAEs and the effect on HRQoL may lead to inadequate management.

Symptom burden and HRQoL

Symptoms are subjectively experienced responses of a patient to a disease, injury, a physical disturbance, or produced by treatment side effects and can cause changes in HRQoL. Conversely from signs that can be observed by others, symptoms can only be known from reports provided by the patient [7–9]. The concept of symptom burden can be described as a summary of the severity and impact of symptoms, reported by patients with a specific disease, or due to a certain treatment. It is not only measurements of HRQoL that can be divided in physical and mental domains; symptoms also can be described to be either physical, psychological (more associated with well-being and mental health), or emotional (frustration, worry), where the classification relates to the origin of the symptoms [7, 9, 10]. Symptom burden can be pronounced and can thereby negatively influence different domains in life, leading to an impaired HRQoL [11].

The concept of HRQoL can be defined as the extent to which one's usual or expected physical, emotional, and social well-being is affected by a medical condition or its treatment [12]. One difficulty for clinicians trying to conceptualize a patient's HRQoL is due to its multidimensional nature that encompasses multiple aspects of a person's well-being [13]. Empirical investigation of the aspects of mcAEs that have the most detrimental impact on patients' HRQoL can help guide interventions to manage these toxicities and maximize patients' HRQoL [14]. Joshi et al. measured the effect of EGFRI-induced mcAEs on HRQoL. They concluded that toxicities including rash, xerosis, paronychia, and pruritus adversely affect HRQoL, with rash associated with a greater decrease. Younger patients reported a lower overall HRQoL than older patients with the same toxicities [11].

Assessment of symptom burden and HRQoL in EGFRI patients with patient reported outcomes

In the care of EGFRI-treated patients, it is essential to explore the patient's experiences and effects of living with mcAEs. A patient-reported outcomes (PROs) instrument is defined as any measure of a patient's health status that is elicited directly from the patient and assesses how the patient "feels or functions with respect to his or her health condition" [15], giving valuable information and cannot be replaced by health-care provider assessments. PROs can be achieved by interview, diaries, or questionnaires [7, 16]. Assessment of symptom burden and HRQoL can be the primary outcome during a treatment or after an intervention [17, 18].

If EGFRI treatment-related HRQoL is to be improved, data on the prevalence, severity, and impact of mcAE on HRQoL must be obtained, and the effectiveness of various (medical) interventions on the HRQoL, documented. Efforts have been made to develop objective documentation of the effects of mcAEs on HRQoL due to these agents. Documentation by the health-care provider can be achieved by using the National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE v4.0) scoring [19], and the Functional Assessment of Cancer Therapy Epidermal Growth Factor Receptor Inhibitor 18 (FACT-EGFRI-18) can be used by patients to assess HRQoL associated with dermatological side effects.

FACT-EGFRI-18 questionnaire

The FACT-EGFRI-18 [20] is a symptom-specific subscale of the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system used for assessing dermatological adverse events [21]. The FACT-EGFRI-18 is an 18-item Likert-scaled questionnaire, arranged in three HRQoL dimensions: physical (seven items), social/emotional (six items), and functional well-being (five items) [14]. To provide a better fit for scale items, the item groups are reorganized in skin, nail and hair side effect domains. The response scores ranged from 0 to 4, and the response categories include "not at all," "a little bit," "somewhat," "quite a bit," and "very much." Negatively worded items (e.g. "My skin bleeds easily" or "My skin condition affects my mood") are reverse-scored, so that participants who experience a higher impact of symptom burden on HRQoL receive a lower score. The FACT-EGFRI-18 was developed according to the FACIT measurement system [21, 22].

The FACT-EGFRI-18 was originally developed and validated in English [20] and was recently translated and linguistic-validated into Dutch. To create a Dutch version,

the standard multilingual translation and validation methodology developed by Bonomi et al. [23] and adopted by the FACIT organization [21, 22, 24, 25] was followed.

As part of the linguistic validation, a part of a translation process, participants with EGFRI-associated mcAEs residing in The Netherlands were invited to review the recently translated FACT-EGFRI-18 questionnaire. While for the linguistic validation itself, it is relevant whether the translation is culturally correct, linguistically correct, clear about the information the instrument is trying to elicit from the patient, and if the questions are understood; the actual answers given are not part of the linguistic validation. Here, we report these data.

The aim of this study was to identify how the18-item symptom specific, patient-reported outcome (PRO) measurement (FACT-EGFRI-18) reveals the impact of the mcAEs on HRQoL.

Patients and methods

Participants

Following the FACIT validation methodology [21], the required ten participants needed for the linguistic validation were recruited by clinical investigators from three hospitals in The Netherlands. The hospitals were selected from the participating hospitals for the BeCet trial (NCT01136005), where the formal validation of the Dutch FACT-EGFRI-18 is ongoing. Participants were eligible if they spoke Dutch as their native and primary language and had the ability to read standard Dutch; had been diagnosed with cancer; treated with an EGFRI; experiencing mcAEs; if they had an Eastern Cooperative Oncology Group Performance Status ≤ 2; and were at least 18 years of age and provided verbal informed consent to participate in the study. Demographic data collected included age, sex, diagnosis, EGFRI agent, primary language spoken, country of origin, current place of residence, and functional performance status.

Procedures

The newly developed Dutch FACT-EGFRI-18 was used in ten patients undergoing EGFRI treatment and experiencing mcAEs. Participants were interviewed in their homes as it was assumed that they would feel more comfortable and talk more candidly there. A field tester proctored the administrations, and then participants were asked to complete the FACT-EGFRI-18. Afterwards, the field tester conducted an interview with each participant in a structured interview fashion to assess the items' personal relevance as well as the patients' overall comprehension of them.

In keeping with regulatory guidelines and good clinical practice, interview information was captured on a data collection form. Any difficulties that the patients experienced with the questionnaire were recorded during the time they completed the questionnaire. The patients' problems in completing the questionnaire were reviewed. Patients could rate the items of the three domains between 0 (not at all) and 4 (very much). In scoring the FACT-EGFRI-18, the possible range of scores is from 0 to 72. To obtain the 0–72 score, each item response was subtracted from 4 so that 0 indicates low HRQoL and 4 indicates high HRQoL [21].

Due to the noninterventional design of this study, it was exempt from review by the local ethics committee, per national and institutional standards and policies.

Results

All questionnaires were thoroughly checked when handed in, and if there were answers missing, the patients were approached and given the chance to complete.

Participants

Interviews were conducted with ten participants with EGFRI-associated mcAEs from The Netherlands. Participants were a select recruited. The study coordinator contacted the hospitals if they treated at that moment patients who met the inclusion criteria. All patients who were approached were included. No one refused. The participants ranged in age from 63 to 81 years; mean age was 70 years. Among the ten participants, six patients were male, and colon cancer was the most common cancer diagnosis. Three patients rated their Eastern Cooperative Oncology Group Performance Status a 0, four a 1, and two a 3. Table 1 summarizes the major demographic variables that were collected.

Response to the Dutch FACT-EGFRI-18 questionnaire

Most patients were able to complete the questionnaire by themselves, with little assistance from their partners/family. Based purely on the way the questions were worded, patients initially tended to rate the severity of the mcAEs without incorporating the impact of mcAEs on their HRQoL. Patients were instructed to circle or mark one number per line to indicate their response as it applied to the past 7 days. Table 2 shows the 18 items by subscale. Several subjects asked the researcher about the general aim of the questions, whether we were interested in the experienced intensity of the mcAEs or whether we wanted to know if they were emotionally or functionally distressed by it. After an explanation that their responses should incorporate the impact of the mcAEs on their HRQoL, patients often chose another response level than they had originally planned.

Table 1 Demographic and clinical characteristics of the participants ($N=10$)

	Patient no.									
	1	2	3	4	5	6	7	8	9	10
Gender	Female	Female	Male	Male	Male	Male	Male	Female	Male	Female
Year of birth	1947	1946	1929	1937	1947	1943	1946	1933	1936	1936
Cancer diagnosis	Colon	Colon	Lung	Lung	Colon	Colon	Lung	Colon	Colon	Breast
EGFRI therapy	Panitumumab	Panitumumab	Gefitinib	Erlotinib 4th package	Panitumumab (12×)	Panitumumab (4×)	Erlotinib	Panitumumab	Panitumumab	Lapatinib
Concurrent cytotoxics	No	No	No	No	No	No	No	No	No	Capecitabine
Patient-rated PS	2	0	2	1	1	1	0	1	0	2

EGFRI epidermal growth factor receptor inhibitor, *PS* performance status rating (0–4) (0 = fully active, able to carry on all pre-disease performance without restriction; 4 = completely disabled, cannot carry on any self-care, totally confined to bed or chair)

During the interviews, patients gave a wide range of information about their dermatological experiences with EGFRI therapy. Overall, patients commented that the FACT-EGFRI-18 items were relevant. They reported difficulties in questions 1, 2, 6, 16, and 17 pertaining to the exact location and the relationship of the experienced mcAEs with EGFRI treatment; e.g. how a flaky scalp should be scored if a patient already experienced dandruff, and how to respond on the question about the interference with household tasks when the patient does not have to do any, but is bothered by sensitivity around the fingernails (Table 3).

It was remarkable that with all the eight patients where a partner/child was present during the pilot testing, the partner/child helped remind the patient that there was a greater impact of the symptom burden on the HRQoL than the patient wanted to rate in the first place. While patients stressed being grateful for receiving anticancer treatment, because of their strong will to live, their families were more focused on the HRQoL including the mcAEs. Patients did express an appreciation for the opportunity to discuss their difficulties coping with their mcAEs.

As outlined in Table 2, responses reflected a major impact of mcAEs on physical, social/emotional, and functional domains. The physical domain items received the highest ratings (indicating a more negative impact), followed by the functional domain and the social/emotional domain. The mcAEs "change in the skin's sensitivity to the sun," "itching of skin or scalp," and "easy skin bleeding" had the greatest impact on patients' HRQoL.

As per the FACIT.org protocol, patients rated first the influence of the mcAEs on their HRQoL and then provided comments about their ratings (why they gave that rating). We found that some comments matched the rating and some were discordant.

Patient no. 5 experienced the highest impact of symptom burden on his HRQoL. He rated question no. 5, physical domain about skin's sensitivity to the sun, with a 4 (very much), while his comment was as follows:

> I wear shirts with long sleeves and long trousers; I wear a cap, even when swimming. It has been a torture. If I do not do this, I get second degree burns (I had these on hands). It hinders in the freedom and interaction with others. The situation is just worthless, restricting movement, 'bothered' is too mild; I have had a lot of trouble. It is now limited, because I always sit under the umbrella out of the sun now.

Patient no. 8 rated with a 3 (quite a bit) on question no. 7, social/emotional domain: "My skin condition affects my mood," while her comment was the following:

> Do you see how I look? I even no longer have a face; I look stupid; that makes me sad.

Table 2 FACT-EGFRI 18 questionnaire, arranged by the original subscores and by highest numerical ratings per dimension

			Patient no.										
			1	2	3	4	5	6	7	8	9	10	SUM
Instructions to the patients: Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.													
Physical	Q5	I am bothered by a change in my skin's sensitivity to the sun.	4	2	2	1	4	1	4	2	2	0	22
	Q3	My skin or scalp itches.	3	2	3	3	2	1	0	3	1	3	21
	Q4	My skin bleeds easily.	3	0	2	3	2	4	1	4	2	0	21
	Q2	My skin or scalp is dry or "flaky."	2	3	3	2	1	0	0	3	3	2	19
	Q1	My skin or scalp feels irritated.	2	2	2	1	1	1	0	3	2	3	17
	Q14	My eyes are dry.	1	3	3	1	3	1	0	3	0	2	17
	Q15	I am bothered by sensitivity around my fingernails or toenails.	1	0	1	2	2	2	0	4	0	1	13
Social/emotional	Q7	My skin condition affects my mood.	2	1	0	0	2	1	0	3	0	1	10
	Q11	I feel unattractive because of how my skin looks.	4	0	0	0	0	1	0	2	2	0	9
	Q9	I am embarrassed by my skin condition.	0	0	0	0	3	1	0	1	0	0	5
	Q10	I avoid going out in public because of how my skin looks.	3	0	0	0	1	1	0	0	0	0	5
	Q18	I am bothered by increased facial hair.	3	0	0	0	0	0	1	0	0	0	4
	Q17	I am bothered by hair loss.	0	0	0	1	1	0	0	0	0	0	2
Functional	Q8	My skin condition interferes with my social life.	3	0	0	0	4	1	0	2	1	0	11
	Q16	Sensitivity around my fingernails makes it difficult to perform household tasks.	2	0	0	1	1	2	0	4	0	0	10
	Q6	My skin condition interferes with my ability to sleep.	0	0	2	0	2	1	0	3	0	0	8
	Q12	Changes in my skin condition make daily life difficult.	2	0	0	0	3	1	0	0	1	1	8
	Q13	The skin side effects from treatment have interfered with household tasks.	3	0	0	0	2	1	0	1	0	0	7
Sum individual item score			38	13	18	15	34	20	6	38	14	13	
FACT-EGFRI symptom index score			34	59	54	57	38	52	66	34	58	59	

FACT-EGFRI symptom index score, the possible range of scores is from 0 to 72. To obtain the 0–72 score, each item response was subtracted from 4 so that 0 indicates low QoL and 4 indicates high QoL. Numerical ratings: 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much

FACT-EGFRI-18 Functional Assessment of Cancer Therapy Epidermal Growth Factor Receptor Inhibitor 18; *Q* question number of FACT-EGFRI-18; *SUM* item subscore: responses of all ten patients per item together

Table 3 Site of adverse event and symptom burden

Patient no.	Question by the interviewer: Would you please tell me which items were difficult to understand and why they were difficult?	Answers given
4	Q16: Sensitivity around my fingernails makes it difficult to perform household tasks.	Q16: I do not have household tasks, but I experience hinder from the sensitivity around my fingernails.
	Q17: I am bothered by hair loss.	Q17: I have hair loss, but I'm not bothered by it.
5	Q1: My skin or scalp feels irritated. Q6: My skin condition interferes with my ability to sleep.	Q1: Depending on where it is. On the scalp since a little while (appeared first in the face, body). Now also on the head, neck and sideburns.
	Q17: I am bothered by hair loss.	Q6 and Q17: Do you want to know if it developed or if I suffer from it?
7	Q2: My skin or scalp is dry or "flaky."	Q2: I had already dandruff, that's why difficulty to tell.
	Q17: I am bothered by hair loss.	Q17: Hair is flatter and curlier, so different.

Patient nos. 1, 2, 3, 6, 8, 9, and 10 reported no difficulties

Patient no. 5 rated with a 3 (quite a bit), on question no. 12, functional domain: "Changes in my skin condition make daily life difficult," while his comment was as follows:

> I have very much difficulty with sitting and lay down because of my pimples between my buttocks, and all day care; I rub twice a day with various ointments.

On the other hand, there were comments from the patient which did not match the previously given numerical ratings of the same question. For example, patient no. 6 rated a 1 (a little bit) on question no. 5, physical domain: "I am bothered by a change in my skin's sensitivity to the sun," while his comment was the following:

> It burns while sitting in the car and the sun burns on the window; then I have to change my seat to the opposite side in the car.

The greatest inconsistency between the numerical rating and the given comments was in the social/emotional domain. Patient no. 9 rated a 0 (not at all) on question no. 7, social/emotional domain: "My skin condition affects my mood," while his comment was as follows:

> I get grumpy, easily irritated; I don't allow the grandchildren to kiss me, I find it unpalatable.

Also, patient no. 9 rated a 1 (a little bit) on question no. 8, functional domain: "My skin condition interferes with my social life," while his comment was the following:

> Greetings are cooler and I avoid touching others.

Six patients gave feedback that not all the mcAEs they wanted to report were included in the questionnaire. For example, questions regarding sensitive eyes, a runny nose, bloody or crusty nasal cavity due to pimples, dry mouth, tickling and tingling sensations, and pain touching the hair were symptoms patients mentioned that, in their view, should be added to the questionnaire.

Discussion

Major findings

In our study, a number of major findings are noted. Items that assess physical symptoms cause the highest HRQoL impact; an inverse correlation between the intensity of mcAEs and HRQoL is found. Patients wanted additional items added to the FACT-EGFRI-18 questionnaire. Overall, patients found it useful to discuss their experienced mcAE burden.

Many health-care practitioners assume the cosmetic appearance of rash to be most troublesome to the patients; however, this was not supported by patient data. Based on the interview results, we identified that symptom burden associated with mcAEs are interfering most with HRQoL. The physical discomfort, "Increased sensitivity to sunlight (burning sensation)," "itching of the skin or scalp," and "bleeding of the skin" were symptoms patients identified as having the most impact on their HRQoL. Results of our study were consistent with the results in the study of Wagner and Lacouture [6], who also identified physical discomfort as the most troublesome with sensations of pain, burning, and skin sensitivity having the most HRQoL impact.

The patients' natural inclination was to rate their symptom severity rather than the extent to which it interfered with HRQoL. Based on some inconsistencies between numerical rating and the associated comments, there is a possibility that our instructions were not clear enough. Our participants felt the need to rate the experienced mcAEs instead of the experienced influence of the mcAEs on their HRQoL. When patients can separately rate the mcAEs and the influence of the mcAEs on their HRQoL, they may be able to better capture the effects on HRQoL. Combining the mcAE-related HRQoL with the experienced mcAEs in a two-part scale could be interesting for future research. As more and more patients will be treated with EGFRI, it will become increasingly important to understand the multidimensional experiences of mcAE-associated HRQoL. This is an important challenge for health-care providers in their effort to assess PROs.

Table 4 Participant recommendations for additional mcAE items

Patient no.	Question by the interviewer: Is there anything else that should have been included related to your skin condition? Would you please tell me what should be added?
1	Dry mouth, little saliva, also in the nose
2	Nothing to add
3	Nothing to add
4	Dry mouth
	Nasal crusts
	I often have to blow my nose (runny nose), at night it is the opposite: very dry
5	Nosebleed because of the pimples in the nose and thin skin on the whole body
6	Hands and feet; cracks, very hard cuticles
	Pain occurs in the skin, not beneath the skin
	Sensitive eyes
	Seeing double
	Eye rubbing
7	Nothing to add
8	Space for notes on the answers chosen
9	Nothing to add
10	Tickling sensation on the skin like an insect walking
	Sore scalp, painful/ stinging (as though your throat is being cut)
	Tingling on hair border, touching the hair hurts

During the qualitative interviews, patients gave a wide range of information about their experiences regarding the FACT-EGFRI-18. They gave additional information regarding the mcAEs they experienced and their struggle to cope with them. It was interesting that patients emphasized being grateful for receiving anticancer treatment, while their family was focused on the HRQoL including the experienced mcAEs.

Six patients responded that they miss the possibility to rate some mcAEs in the FACT-EGFRI-18 (Table 4). This suggests that not all the mcAEs can be reported while patients feel the need to do so. Questions regarding sensitive eyes, a runny nose, bloody or crusty nasal cavity due to pimples, dry mouth, tickling and tingling sensations, and pain touching the hair and some space for additional comment were mentioned by the participants as items that should be added. Other oral issues like sensitive teeth, taste changes, oral sensitivity/pain at rest, eating, and oral burning sensation are additional mcAEs to consider for assessment. As it is important to cover relevant symptoms and domains to find valuable information without making a questionnaire too lengthy, we recommend adding these mcAEs in a next version, since not all mcAEs are assessed now.

Study limitations

One of the study limitations was the relatively small patient sample; however, the data collected were qualitative, and no statistical analyses were completed. It has to be mentioned that the ten patients are required by the FACIT organization as mentioned in the "Background" section. Patients had different kinds of cancer, EGFRI treatment, and mcAEs, which may have caused unbalanced data. At the same time, different cancers and treatment allow testing of the questionnaire across a range of patients. To develop a questionnaire suitable for all mcAEs can be challenging. Different mcAEs can be present with a more or less pronounced symptom burden and the interference with the patients' life situation depending of the experienced mcAEs. The questionnaire addresses mainly the cutaneous AEs (17 questions) and only one question addresses mucosal AEs (dry eyes).

Clinical and research implications

As more and more patients will be treated with targeted therapies including EGFRI, it becomes increasingly important to understand the multidimensional experiences of these agents associated mcAE-related HRQoL. Use of validated and standardized tools will allow comparison of outcomes in different studies and in meta-analyses, to advance patient care and improve outcomes.

A mcAE PRO should consist of three separate parts where part I describes demographic data, part II, the mucocutaneous-specific symptom burden, and part III, the impact of the mucocutaneous-specific symptom burden on HRQoL. Further development with more mcAE items incorporated and combined with symptom assessment will provide more complete information. Since mcAEs are also elicited by other targeted anticancer therapies such as non-EGFRI tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors, and BRAF inhibitors, it would be worthwhile to develop one questionnaire suitable for all these targeted agents instead of only for EGFRIs.

Conclusion

Results from the first experiences with the FACT-EGFRI-18 described how negatively affected patients who receive EGFRI can be with a pronounced symptom burden and impaired HRQoL. Based on the interview data, we identified that the physical items associated with mcAEs are interfering most with HRQoL. These results are consistent with the results in the study of Wagner and Lacouture, who also identified physical discomfort as the most troublesome and having the most HRQoL impact.

Since participants wanted to rate the prevalence, intensity, and also the duration of the symptoms, while we were interested in the distress from the symptoms, a two-step measurement tool assessing both symptom burden and HRQoL would be more appropriate in this population. The fact that the FACT-EGFRI-18 only evaluates HRQoL, not symptoms, that not all the experienced mcAEs can be assessed, and that is developed for one kind of targeted therapy, implicates further research needs.

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Conflict of interest The authors declare no conflicts of interest. All authors had full control of all primary data and agree to allow the journal to review the data, if requested.

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