RESEARCH ARTICLE

Health Science Reports   WILEY

Optimizing brief, focused assessment of priority symptoms and concerns in recurrent and/or metastatic squamous cell carcinoma of the head and neck: Content validation of the Functional Assessment of Cancer Therapy/National Comprehensive Cancer Network Head and Neck Symptom Index-10 (FHNSI-10)

Sara Shaunfield[1] | Susan E Yount[1] | Lara Boyken[2] | Mark Agulnik[3] | Sandeep Samant[4] | David Cella[1]

[1]Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[2]Buehler Center on Aging, Health and Society, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[3]Department of Medical Oncology & Therapeutics Research, City of Hope, Duarte, California, USA

[4]Department Otolaryngology - Head and Neck Surgery, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

Correspondence
Sara Shaunfield, Department of Medical Social Sciences Northwestern University Feinberg School of Medicine, 625 N. Michigan Ave. Suite 2100, Chicago, IL 60611, USA.
Email: sara.shaunfield@northwestern.edu

Abstract

Background and Aims: Patients with recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) experience vast disease and treatment burdens. Brief, focused instruments are needed to assess patient-reported priority symptoms and concerns as targeted outcome assessments for use in clinical research. Although the instrument was developed based on expert and patient input and is psychometrically valid, the Functional Assessment of Cancer Therapy (FACT)/National Comprehensive Cancer Network (NCCN) Head and Neck Symptom Index-10 (FHNSI-10) has yet to undergo content validation from the perspective of R/M SCCHN patients to evaluate its use as a brief symptom-focused targeted endpoint assessment for use in clinical research.

Methods: Interviews conducted with R/M SCCHN patients explored priority symptoms and concerns, followed by cognitive debriefing of the FHNSI-10 to evaluate face validity. Transcripts were analyzed, and results were mapped to the FHNSI-10. In accordance with published recommendations, expert input from the original development and published literature was considered for content validity assessment.

Results: A total of 18 patients participated in a concept elicitation interview; saturation was obtained at interview 17. Most (83%) were undergoing active treatment, male (94%), white (72%), and did not have a college degree (67%). The most commonly mentioned symptoms were lumps/swelling, pain, sore throat, difficulty swallowing, and voice changes. For all items, ≥75% reported each question was relevant to their R/M SCCHN experience and 94% reported the instrument captured their experiences with R/M SCCHN.

Conclusion: Results provide support for the content validity of the FHNSI-10, inasmuch as all 10 items were spontaneously reported and considered relevant to R/M SCCHN. Content validity might be enhanced by adding cough and hearing impairment items; however, the existing FHNSI-10 covers the majority of symptoms uncovered in interviews with a small sample of R/M SCCHN patients.

1 | INTRODUCTION

Head and neck cancers (HNC) are a heterogeneous group of cancers accounting for approximately 4% of cancers in the United States (US), representing more than 53 000 estimated new cases in 2019, and are among the top 10 most common malignancies worldwide.[1-3] More than 90% of HNCs are squamous cell carcinomas (SCCHN), which include epithelial cancers of the oral cavity, sinuses, nasopharynx, pharynx, and larynx.[4] It is well known that sustained exposure to tobacco and alcohol increases the risk for SCCHN.[5] However, the incidence of SCCHN associated with tobacco and alcohol is falling or stabilizing in Western countries, while oropharyngeal carcinoma related to human papillomavirus (HPV) is increasing.[6]

In the US, 79% of SCCHN patients present with local or regionally advanced disease and treated with combined modality therapy with a goal of disease eradication.[7] However, 16% are diagnosed with metastatic disease at presentation and about 50% with locally advanced disease at recurrence[8]; for these groups, the currently available treatments (ie, surgery, radiotherapy, immunotherapy) aim for palliation and extension of survival.[7,9-12] People with SCCHN face a number of challenges, including poor prognosis, high disease- and treatment-related symptom burden,[13-16] and limited treatment options,[17] which impact patient health-related quality of life (HRQL).[18,19] SCCHN often affects vital anatomic structures involved in important physiological (eg, swallowing, eating) and social functions (eg, communication).[8,15,20]

Cancer-specific HRQL measures, such as the University of Washington Quality of Life Questionnaire (UW-QOLv4),[21] European Organisation for Research and Treatment of Cancer—Head & Neck 35 (EORTC H&N35),[22] Functional Assessment of Cancer Therapy-General (FACT-G) and its head & neck cancer scale (FACT-H&N),[23-25] are widely used HRQL measures that capture common symptoms (eg, pain, fatigue) within a multidimensional assessment. However, there are limited symptom-specific measures for HNC patients, and they differ in content, treatment continuum specificity (eg, treatment naïve, acute, late treatment effects), and length.[26] Thus, a need remains for a brief, psychometrically sound, and content valid measure to evaluate patient-reported priority symptoms and concerns for assessing targeted endpoints for R/M SCCHN in the context of clinical research, including clinical trials.[17,27] The US Food and Drug Administration (FDA) emphasizes delays in symptom progression or improvement as evidence of clinical benefit in oncology drug trials. Brief patient-reported outcome (PRO) measures such as the Functional Assessment of Cancer Therapy (FACT)/National Comprehensive Cancer Network (NCCN) Head and Neck Symptom Index-10 (FHNSI-10) are useful tools for assessing symptoms in clinical research.[27]

The FHNSI-10 is a symptom-focused index developed for use in patients with advanced and/or recurrent/refractory HNC. The FHNSI-10 comprises a subset of 10 items from the FACT-H&N, a well-established multidimensional HRQL[25] assessment of physical, social/family, emotional, functional well-being, and 12 HNC-specific symptoms developed from patient and expert input.[23,24,28] To develop the FHNSI-10, disease-related symptoms and concerns from the validated FACT-H&N were presented to 65 HNC experts who selected the five most important (priority) symptoms/concerns for evaluating treatment in advanced HNC.[28] The 10 items included in the FHNSI-10 represent items endorsed by ≥20% of HNC experts. The FHNSI-10 is an existing symptom-focused index developed for use as a clinically relevant symptom assessment of 10 priority HNC symptoms and concerns.[28]

FDA has stressed the importance of documenting the content validity of endpoint measures, including empiric qualitative evidence conducted with people from the trial's target population.[29] Although the FHNSI-10 is psychometrically reliable and valid,[27,30] its content validity has yet to be evaluated by patients with recurrent and/or metastatic (R/M) SCCHN. As the next step in the validation process, we sought to examine the face and content validity of the FHNSI-10 from the perspective of R/M SCCHN patients, as a brief symptom focused index for targeted endpoint assessment in clinical research.

2 | MATERIALS AND METHODS

2.1 | Study design

Content validity of the FHNSI-10 was assessed via concept elicitation (CE) and cognitive interviews (CI). Semi-structured CE interviews were conducted with patients diagnosed with R/M SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx. Patients were eligible to participate if they: (a) were ≥ 18 years old, (b) had a self- or clinician-reported eastern cooperative oncology group (ECOG) status of 0 or 1, and (c) beginning treatment, currently receiving treatment, or completed treatment within 60 days. Individuals who were (a) not fluent in English; (b) receiving treatment for an infection; or (c) had uncontrolled type 1 or 2 diabetes mellitus were ineligible. (*Note. Exclusion criteria b and c were to reduce probability that patients might conflate symptoms of infection or diabetes with R/M SCCHN symptoms.) The study was approved by

the Northwestern University Institutional Review Board (STU00203514), and informed consent was obtained for all participants.

A clinical recruitment specialist identified eligible patients via chart review and a member of the study team approached patients, explained the study, and obtained consent. Of the 43 patients approached, 32 were eligible. Of those 32, 10 declined (due to communication challenges, pain, or disinterest) and three were lost to follow-up, leaving 19 who signed informed consent to participate. Of those consented, one became too ill to participate. Eighteen interviews were completed, 17 in-person, and one telephone. Interviews were audio-recorded and detailed field notes were taken. Audio-recordings were transcribed and de-identified for analysis. Relevant disease and treatment history were obtained from medical records.

Interviews were conducted using a semi-structured interview guide, modeled after guides from prior work,[31-33] designed to explore R/M SCCHN symptoms, emotional concerns, and HRQL impact. After collecting sociodemographic information, participants were asked to list all R/M SCCHN symptoms. A series of targeted probes were used to gather details concerning each symptom. Next, participants discussed emotional concerns related to R/M SCCHN (Table 1). For each symptom/concern, participants were asked: "On a 0 to 10 scale, with 0 = Not at all bothersome and 10 = Extremely bothersome, please rate the importance of each of these symptoms/concerns to your health-related quality of life" to capture impact.

Next, all participants completed the FHNSI-10, a symptom-focused measure that assesses 10 priority symptoms and concerns of HNC patients over the past 7 days using a four-point Likert scale of 0 (Not at all) to 4 (Very much). Lastly, participants were invited to participate in a CI to assess item relevance and comprehension. Face validity was assessed using responses to the following questions: (a) Do these questions capture your experience with HNC? [yes/no; explain]; (b) Are there any other important questions we did not ask? [yes/no; explain]; and following discussion of each item, (c) Is this question relevant to your experiences with your cancer? [yes/no; explain]. Additionally, CI participants answered open-ended questions regarding interpretation and considerations when responding to each item, instructions, recall period, response options, and questionnaire length (full CI methods and results available upon request).

2.2 | Analysis

CE interview data were analyzed by three qualitative health researchers (S.S., S.Y., L.B.) via constant comparative approach.[34] Detailed interviewer field notes were entered into Excel for preliminary analysis. First, a list of symptoms/concerns from the first 12 interviews was compiled. Second, symptoms and concerns were collapsed, redundant categories removed, and remaining categories were used to track saturation and form the initial codebook. The codebook was developed by SS, a qualitative researcher with PRO measure development and validation expertise. Next, three transcripts were independently reviewed and coded in Dedoose, a cross-platform application for analysis[35] using the draft codebook. Analysts made notes about missing or problematic codes and met to review coded transcripts, discuss discrepancies, and edit the codebook. Following codebook revision, remaining transcripts were divided among the analysts and independently coded. The codebook was refined throughout analysis via team discussion. After transcripts were coded, text for each code was exported and analyzed in a "coding review process," during which data for each code were independently reviewed and summarized by two analysts. Next, both data summaries for each code were reviewed with the team, discrepancies flagged, and resolved. Saturation, the point at which no new relevant information is obtained,[36] was assessed following the 12th interview and attained at the point in which no new concepts emerged for three interviews. Face validity was evaluated by tabulating the total participants who reported each item as relevant and the total who reported the FHNSI-10 captured their experiences.

Qualitative results were mapped to the FHNSI-10 to assess content validity. Mapping involved an iterative process of comparing instrument content and interview data to: (a) identify themes from the data (ie, "universe of content") covered by the FHNSI-10; (b) FHNSI-10 content not aligned with the data; and (c) data not represented by FHNSI-10 content. A strong content validity match need not be inclusive of all patient-provided concepts but should represent a majority of input.[29] Responses to CI questions to evaluate face validity were summarized and considered for content validity assessment.

Endorsement thresholds to evaluate content validity support for each item were calculated based on sample size. For example, an item with spontaneous support from ≤11% CE interview participants was considered to have weak CE support. An item endorsed as relevant by

TABLE 1 Interview questions and probes from the concept elicitation interview

Symptoms
We'll start by making a list of the *symptoms* of HNC you've experienced and then we will discuss each one in more detail. What symptoms of HNV have you experienced? *As needed, clarify whether due to medication, disease, or some other cause.*
Probes:
• What does it feel like when you experience this symptom?
• Where in your body do you experience the symptom?
• Can you describe this symptom in greater detail?
• Thinking of the past week, how often did you experience this symptom?
• How does it feel at its best/on a good day?
• How does it feel at its worst/on a bad day?
• How long does the symptom usually last?
• Thinking of the last week, how severe was it when you experienced this symptom?
• Do you experience any pain or discomfort from this symptom? If yes, please describe,
• Please list the ways in which this symptom impacts your life.
• Is there anything else you would like for us to know about this symptom?
Emotional concerns
Finally, I'd like your input on the emotional impact of HNC. Could you tell me how HNC has affected you emotionally? *Probe as needed to ensure participant provides clear description of each emotional impact.*

Abbreviation: HNC, head and neck cancers.

≥75% of CI participants was considered to have strong CI support. Level of support from CE and CI findings was considered in tandem when determining content validity support for each item. For example, an item with weak CE support and strong CI support was considered to have moderate content validity support. In accordance with published guidelines for evaluating content validity, expert input from the measure development and extant literature was consulted to inform decisions regarding retention, removal, or addition of items.[29]

3 | RESULTS

CE interviews were completed with 18 patients with confirmed R/M SCCHN. Due to time constraints or fatigue, two were unable to complete the item-by-item CI questions and instead completed the FHNSI-10 and answered global questions regarding instrument coverage of R/M SCCHN experiences and missing content. Thus, 16 completed the entire CI. Together, interviews lasted 59 minutes on average. Sample characteristics are shown in Table 2. Participants' mean was 65 years (range 49-86). Most (94%) were male, white (72%), did not have a college degree (67%), and were undergoing active treatment (83%). Two reported having no symptoms before beginning treatment. Saturation occurred at interview 17. The most common spontaneously mentioned symptoms were lumps/swelling (n = 12), pain (n = 6), sore throat (n = 6), difficulty swallowing (n = 5), and voice changes (n = 3). Other symptoms listed by a minority were difficulty breathing (n = 2), cough (n = 2), hearing impairment (n = 2), fatigue (n = 1), and tooth loss (n = 1). Table 3 shows the mean and range of impact ratings for all patient-reported symptoms and select emotional concerns.

3.1 | Mapping of patient-reported symptoms and concerns to the FHNSI-10

Participants spontaneously described symptoms/concerns in ways consistent with the 10 items. The qualitative findings provide moderate to strong support for relevance of all 10 items. CI findings revealed that participants considered all FHNSI-10 items relevant to their experience—for all but one item at least 14 of 16 (88%) reported each item as relevant (see Table 4). Below are representative participant quotes for each item (participants identified by study ID), item relevance, and additional interpretation, and discussion is provided for items with nuanced support.

3.1.1 | Item GP4. I have pain

Pain was mentioned by 6 (33%) during the CE interview. Pain was experienced in different forms, sometimes arising on its own or associated with other symptoms (growths, inflammation). Pain sites included ear, head, mouth, neck, jaw, throat, and chest. The most common form of pain was earache, reported by 4 (22%) and described as highly bothersome. Participant 005 explained, "The [swollen] lymph

TABLE 2 Characteristics of interview sample (N = 18)

Characteristic	Mean	(range, median)
Age	65.3	(49-86, 65)
FHNSI total score[a]	23	(10-38)
Gender	N	(%)
Male	17	(94%)
Female	1	(6%)
Education		
Some high school	1	(6%)
High school	4	(22%)
Some college	7	(39%)
College	3	(17%)
Advanced degree	3	(17%)
Ethnicity		
Hispanic or Latino origin	1	(94%)
Non-Hispanic or Latino origin	17	(6%)
Race		
White	13	(72%)
African American or black	4	(22%)
Other	1	(6%)
ECOG status (self-report)		
0	3	(17%)
1	4	(22%)
2	7	(39%)
3	4	(22%)
ECOG status (clinician-report)		
0	6	(33%)
1	9	(50%)
2	1	(6%)
Missing[b]	2	(11%)
Disease histology		
Oral cavity	3	(17%)
Oropharynx	13	(72%)
Hypopharynx	1	(6%)
Larynx	1	(6%)
HPV/p16 positive		
Yes	12	(67%)
No	6	(33%)
Treatment at time of interview		
Receiving treatment[c]	15	(83%)
Within 60 days of finishing treatment	3	(17%)

[a]Lower scores indicate greater symptom burden (poorer quality of life). FHNSI-10 score range: 0 to 40.
[b]Missing clinician-reported eastern cooperative oncology group (ECOG) for two, but self-reported ECOG was 0 to 1.
[c]Treatment: chemotherapy and/or radiotherapy.

caused pressure on my ear it was pulling, causing an earache...a sharp painful earache and the bigger my lymph node got the more it hurt, the pain never went away it was there 24 hours a day." Headache was another form of pain mentioned by 2 (11%) participants, like 013, "I get headaches right between the eyes...in the temple is a

TABLE 3 R/M SCCHN patient reported symptoms/concerns and importance ratings (N = 18)

Patient concern	Number that spontaneously mentioned concern in interview	Mean impact rating and range	
Lumps and swelling	12	4.1	(0-10)
Disease/ treatment burden	11	8.3	(3.5-10)
Mortality	10	8.7	(5-10)
Pain[a]	6	9	(6-10)
Sore throat	6	3.4[b]	(1-6)
Difficulty swallowing[a]	5	8	(4-10)
Voice changes	3	4[b]	(3-5)
Cough[a]	2	8	(8)
Difficulty breathing[a]	2	8	(8)
Hearing impairment	2	6	(2-10)
Fatigue	1	8	(8)
Nausea[a]	1	10	(10)
Tooth loss	1	10	(10)

[a]Concerns and ratings applicable to more than one code.
[b]Missing one impact rating not represented in mean/range.

TABLE 4 R/M SCCHN patient reported relevance of FHNSI-10 items (n = 16)[a]

Item ID	Item stem	Is this question relevant to your experiences with head and neck cancer?
GP4	I have pain	Yes = 14 (87.5%) No = 2 (12.5%)
GP1	I have a lack of energy	Yes = 14 (87.5%) No = 2 (12.5%)
H&N7	I can swallow naturally and easily	Yes = 15 (93.8%) No = 1 (6.3%)
H&N12	I have pain in my mouth, throat, or neck	Yes = 14 (87.5%) No = 2 (12.5%)
H&N3	I have trouble breathing	Yes = 12 (75.0%) No = 4 (25.0%)
H&N10	I am able to communicate with others	Yes = 15 (93.8%) No = 1 (6.3%)
GP2	I have nausea	Yes = 15 (93.8%) No = 1 (6.3%)
H&N11	I can eat solid foods	Yes = 15 (93.8%) No = 1 (6.3%)
GE6	I worry that my condition will get worse	Yes = 15 (93.8%) No = 1 (6.3%)
GE7	I am content with the quality of my life right now	Yes = 15 (93.8%) No = 1 (6.3%)

[a]Due to time constraints or fatigue, 2 CE participants declined to participate in the full CI.

lightning feeling." While most described localized pain, 016 described pain that "shoots down the jaw, up to the ear, and clings around on this side of my head..." Furthermore, 88% of CI participants said the item was relevant to their experience.

3.1.2 | Item GP1. I have a lack of energy

One (6%) participant listed fatigue as a symptom that was experienced before beginning treatment, "by the end of the day I was dragging. I had a hard time keeping my eyes open" (009). Although only one listed fatigue, many described experiences indicative of lack of energy when relaying their process for responding to the item, such as, "how much I am on the couch" (006), "not wanting to get out of bed" (007), "my current level of energy, which is down" (014), and "[putting off] physical activity" (003). Moreover, 88% of CI participants reported the item was relevant.

3.1.3 | Item H&N7. I can swallow naturally and easily

Difficulty swallowing was reported as a symptom by 5 (28%) and involved problems swallowing food, liquids, or pills and was often attributed to the tumor mass or globus sensation. Two (11%) described feeling like something was stuck in their throat, 018 explained, "like

something was caught in my throat but...not from the tumor...when you chew down food...sometimes it gets caught in your throat." Two reported difficulties swallowing and associated anxiety. For example, 013 said, "I try to [swish and] swallow a little water...I get strangled... [now] I don't swallow. I spit it out unless you get strangled." Furthermore, 94% of CI participants said the item was relevant.

3.1.4 | Item H&N12. I have pain in my mouth, throat, or neck

Six (33%) reported pain in the mouth, throat, or neck as a symptom. Specifically, two reported mouth pain, describing it as shooting from the mouth to other areas or a sharp, pinching, intermittent pain of one's tongue. Throat pain was reported by six (33%) and was described as an ache or discomfort, as 019 explained, "...it was not a really strong sore throat, it was just a little achy sore throat." Further, 88% of CI participants said the item was relevant.

3.1.5 | Item H&N3. I have trouble breathing

Difficulty breathing was reported by two (11%). One described difficulty from a nasal cavity tumor, "I [have] trouble breathing...a week

TABLE 5 Match between Functional Assessment of Cancer Therapy (FACT)/National Comprehensive Cancer Network (NCCN) Head and Neck Symptom Index-10 (FHNSI-10) items and R/M SCCHN universe of content[29]

Instrument content		Subscale	Content validity support	Recommendations
GP4	I have pain	DRS-P	Strong	Retain item. Strong support in qualitative content validity data.[a,b] Strong support in prior scale development work with experts.[c]
GP1	I have a lack of energy	DRS-P	Moderate	Retain item. Weak support in CE interview data.[a] Strong support CI data.[b] Strong support in prior scale development work with experts.[b] Consistent with NCI recommendations to include fatigue as a cross-cutting symptom for assessment in cancer clinical trials.
H&N7	I can swallow naturally and easily	DRS-P	Strong	Retain item. Moderate support in CE interview data.[a] Strong support in CI data.[b] Strong support in prior scale development work with experts.[c]
H&N12	I have pain in my mouth, throat, or neck	DRS-P	Strong	Retain item. Strong support in qualitative content validity data.[a,b] Strong support in prior scale development work with experts.[c]
H&N3	I have trouble breathing	DRS-P	Moderate	Retain item. Weak support in CE interview data.[a] Strong support in CI data.[b] Strong support in prior scale development work with experts.[c] Literature notes trouble breathing as SCCHN symptom.
H&N10	I am able to communicate with others	DRS-P	Moderate	Retain item. Moderate support in CE interview data.[a] Strong support in CI data.[b] Moderate support in prior scale development work with experts.[c] Literature notes impaired communication as SCCHN symptom.
GP2	I have nausea	DRS-P	Moderate	Retain item. Weak support in CE interview data.[a] Strong support in CI data.[b] Moderate support in prior scale development work with experts.[c] Consistent with NCI recommendations to include nausea as a cross-cutting symptom for assessment in cancer clinical trials.
H&N11	I can eat solid foods	DRS-P	Moderate	Retain item. Moderate support in CE interview data.[a] Strong support in CI data.[b] Moderate support in prior scale development work with experts.[c] Literature notes dysphagia as SCCHN symptom.
GE6	I worry that my condition will get worse	DRS-E	Strong	Retain item. Strong support in qualitative content validity data.[a,b] Moderate support in prior scale development work with experts.[c]
GF7	I am content with the quality of my life right now	FWB	Strong	Retain item. Strong support in qualitative content validity data.[a,b] Moderate support in prior scale development work with experts.[c]

Abbreviations: DRS-E, disease-related symptoms-emotional; DRS-P, disease-related symptoms-physical; FWB, functional well-being.

[a]Content validity support from CE interviews with R/M SCCHN patients (weak = spontaneously mentioned by ≤2 [11%]; moderate = spontaneously mentioned by 3 [17%] to 5 [28%]; strong = spontaneously mentioned by ≥6 [33%]).

[b]Content validity support from CIs with R/M SCCHN patients (strong = endorsed relevant by n ≥ 12 [75%]).

[c]Support in prior scale development work with experts (moderate = ranked as top 6 to 10 priority symptoms/concerns; strong = ranked as top 1 to 5 priority symptoms/concerns).

ago and I noticed…I can't breathe through my nose" (008). The second reported trouble breathing from a persistent cough: "I would just cough, cough, cough, till I'm out of breath" (013). While trouble breathing was only spontaneously listed by two, when responding to the item, six CI participants reported experiencing trouble breathing in the past 7 days. Moreover, 75% of CI participants said the item was relevant.

3.1.6 | Item H&N10. I am able to communicate with others

Three (17%) reported voice changes or difficulty speaking as a symptom that impacted their ability to communicate and be understood. Voice changes were described as sounding different to oneself or others or periodic loss of one's voice. For example, 003 explained, "I just lost my voice and I couldn't talk…" Most CI participants attributed the following symptoms as related to difficulties communicating: voice changes, misunderstood by others, sounding differently, coughing while talking, and difficulty speaking from excess saliva or mucous, tongue resection, or cancer-related dental issues. Most reported the item as clear; however, three recommended adding "verbally" to specify form of communication. Further, 94% of CI participants said the item was relevant.

3.1.7 | Item GP2. I have nausea

While nausea was commonly reported as a treatment side effect, nausea spontaneously emerged as a symptom for one (6%). Specifically, 006 described nausea as a response to intense disease-related pain of the mouth, ear, neck, and jaw, "…the amount of pain causes me to get nauseous it is so intense." Furthermore, 94% of CI participants reported the item as relevant.

3.1.8 | Item H&N11. I can eat solid foods

Three (17%) listed difficulty eating. For example, 012 reported loss of lower teeth as a symptom and the impact on eating, "I just can't chew...It has to be something I can spoon in, with meats it has to be crushed or ground up." CI participants considered their (in)ability to eat solid foods when responding to H&N11. Some thought of specific foods that cause difficulty (eg, steak, hamburgers, pulled pork, hot foods). Those who had difficulties explained the symptom hinders attendance of social events that involve eating, including dinners with friends, holidays, or work functions. While trouble eating solid foods was spontaneously described by only three, 14 reported difficulty eating/drinking as a residual treatment side effect that added to symptom burden at recurrence. Nearly half (n = 8; 44%) of participants indicated they were "not at all" able to eat solid foods when responding to the questionnaire and nearly all (n = 15, 94%) said the item was relevant to their experience.

3.1.9 | Item GE6. I worry my condition will get worse

When asked to list their emotional concerns, 10 (56%) expressed mortality concerns, which is consistent with worsening condition. As 004 explained, "...you try to focus on the positive, but your mind wants to wander off and say 'What if it really doesn't work? What if you're going to die?'" Mortality concerns involved regrets or fears of what they would not live to see and concerns over the impact of their death on loved ones. Further, 94% of CI participants reported the item as relevant.

3.1.10 | Item GE7. I am content with the quality of my life right now

Much support for this item was found in the emotional concerns findings of the CE interviews (available upon request). Specific to this item, our analysis revealed 11 (61%) felt discontentment from the cumulative disease and treatment burden and impact on life quality including managing treatment decisions and scheduling, lengthy travel to appointments, family burden, and the cumulative burden of symptoms and side effects, described as "disruptive," "worrisome," "overwhelming," and "stressful." Moreover, 94% of CI participants reported the item as relevant.

3.2 | Additional R/M SCCHN symptoms mentioned by patients

Interview findings revealed four symptoms not currently on the FHNSI-10 that were reported ≥2 patients.

3.2.1 | Lumps/swelling

Twelve (66%) listed lumps or swelling which typically occurred on one side of the neck, chin, or jaw, was painless, and often subsided soon after beginning treatment. On a scale of 0 to 10, mean HRQL impact rating was 4.08.

3.2.2 | Earache

Four (22%) listed earache as a symptom. Adjectives to describe earaches were radiating, intense, painful, and constant. On a scale of 0 to 10, the mean HRQL impact rating was 8.25.

3.2.3 | Hearing impairment

Two (11%) listed impaired hearing, described as hearing loss, or reduced volume. One was unsure whether it was a symptom or treatment side effect. The mean HRQL impact rating was 6.

3.2.4 | Cough

Two (11%) listed cough; one reported coughing while eating and another reported a recurrent cough that continues until running out of breath. In both cases, cough improved following treatment. The mean HRQL impact rating was 8.

3.3 | Patient evaluation of the FHNSI-10

3.3.1 | Face validity

When asked (yes/no) whether the FHNSI-10 captured their R/M SCCHN experiences, nearly all (n = 17, 94%) said yes. The outlier wanted greater detail, context, and definitions for terms like nausea. When asked if there were important questions not on the questionnaire, a majority (67%) reported all aspects were covered; the remainder, recommended adding items to assess satisfaction with medical care (n = 3), hopefulness (n = 1), impaired hearing (n = 1), fatigue (n = 1), and depression (n = 1). While most had no other suggestions for improving the questionnaire, two suggested incorporating free-form response options and clarifying the intent of the two HRQL items (GE6, GE7).

4 | DISCUSSION

Patients with R/M SCCHN experience vast disease- and treatment-related symptom burden that hinders HRQL.[17,20,37,38] The FHNSI-10 was developed as a symptom-focused measure of patient-reported

priority symptoms and concerns of individuals with HNC. Initial evidence supports the psychometric properties of the FHNSI-10[27,39,40]; however, the measure has not been evaluated for content validity from the perspective of R/M SCCHN patients. We sought to evaluate the content and face validity of the FHNSI-10 from the perspective of R/M SCCHN patients for use as a targeted endpoint assessment in R/M SCCHN clinical research. Prior to clinical research in a trial context, the validity of the measure must be evaluated in the population of interest.[29] Thus, an assessment of the face and content validity of the FHNSI-10 for use in R/M SCCHN was undertaken. In accordance with recommended methods for content validity assessment of PROs,[41,42] CE interviews with R/M SCCHN patients to explore their symptoms and concerns followed by CIs to evaluate the face validity of the FHNSI-10 instrument were conducted.

Our findings support the content validity of the FHNSI-10 as a targeted assessment of symptoms and concerns of R/M SCCHN patients, as content from all 10 items was spontaneously described by patients. Moreover, findings provide moderate to strong support for validity of all 10 items, as patient descriptions covered concepts related to pain, difficulty swallowing, communication, eating, fatigue, nausea, and a range of emotional and functional well-being concerns that we believe are captured by the items GE6 and GE7. While three of the 10 items were spontaneously reported by ≤2 CE patients (ie, trouble breathing, lack of energy, nausea), CI results revealed strong support for these items in that ≥75% reported the items as relevant. Taken together, the CE and CI data reveal moderate support for these three items. Further, all three symptoms were spontaneously reported in CE interviews, were considered impactful when they occurred, and were identified as priority symptoms for evaluating HNC treatments in prior measure development work with experts.[28] The energy and nausea items are further supported by NCI recommendations to include fatigue and nausea as cross-cutting symptoms for PRO assessment in cancer clinical research,[20] and extant literature supports trouble breathing (dyspnea) and fatigue as symptoms of SCCHN.[5,43] Given all items were spontaneously supported by patient descriptions in the CE interviews, reports that the symptoms/concerns are highly impactful, strong CI evidence regarding relevance to RM SCCHN, all 10 items were deemed to have moderate to strong content validity support (Table 5). Content validity is further enhanced by the fact that the items were identified by experts as priority symptoms and concerns for assessing HNC treatment outcomes and are supported by the extant literature.

Guidance for content validity assessment of existing PROs recommends a strong match for content validity should represent a majority of patient input but does not need to incorporate all patient-reported concepts.[29] Our findings revealed four symptoms listed by a minority of R/M SCCHN patients that are not on the instrument. FHNSI-10 does not have a lumps/swelling item, which was the most common symptom reported. However, lumps/swelling was described as painless, subsided soon after beginning treatment, and rated low in terms of impact. Although nearly a quarter listed earache as an impactful symptom of R/M SCCHN, the CI findings revealed this symptom is captured by the existing pain item; therefore, adding an earache item is not warranted. Two listed impaired hearing as a symptom which is not covered by the FHNSI-10. However, one was unsure whether it was a symptom or treatment side-effect. Hearing loss and tinnitus is a documented toxicity for several therapeutic agents or combined therapies.[44] Given few reported hearing impairment as a symptom, uncertainty as to whether it is a symptom, and documentation of hearing impairment as a common treatment toxicity, we elected not to add a hearing impairment item to the FHNSI-10 if used as a targeted disease-symptom-focused endpoint assessment for R/M SCCHN clinical research. Fourth, two patients listed cough as a symptom; however, one reported coughing while eating/drinking and therefore is covered by H&N11 (eating) and H&N7 (swallowing) and both reported the cough improved following treatment. Mapping the FHNSI-10 to the qualitative data showed it covers all patient-reported symptoms except for cough and hearing impairment, which were not spontaneously reported frequently, but were impactful when they occurred. For all items, at least 75% considered them relevant to their experience and 94% reported the instrument captured their R/M SCCHN experiences.

There are several limitations of this study. First, although eligibility criteria are in line with SCCHN clinical research samples, recruitment was difficult because patients with advanced R/M disease are susceptible to cumulative symptom and treatment burden. Five of the 32 patients approached for the interview declined to participate citing difficulty speaking or mouth pain; thus, interviews with R/M SCCHN patients introduces selection bias and findings may not fully represent the degree of symptoms and experiences (eg, communication difficulties). Second, while experiences of women with R/M SCCHN are underrepresented in these data, SCCHN incidence rates are two to four times more likely in men.[45] Third, participants were recruited from a single institution. Fourth, while this study involved a small sample, our sample size was based on well-established qualitative research practices for obtaining saturation.[36] Evidence suggests saturation often occurs within the first 12 interviews[46]; thus our sample of 18 is consistent with qualitative research standards. Fifth, 76% had oropharyngeal cancer, many of which were HPV/p16 positive. It is possible that a larger sample with other forms of R/M SCCHN may have identified symptoms not represented on the FHNSI-10. Finally, although brief symptom-focused indexes are appealing for their stated purpose (to track group differences in treatment outcome over time), they are limited in providing a full picture of the impact of R/M SCCHN and its treatment on people's lives. The FHNSI-10 does not represent the full range of R/M SCCHN symptoms; however, our findings along with evidence from the measure development and literature, support its use as a brief symptom-focused targeted endpoint assessment for R/M SCCHN clinical research. Future researchers interested in applying this measure in other contexts should consider administering the FHSNI-10 to a larger sample of R/M SCCHN patients to explore other important symptoms not currently assessed by the FHNSI-10.

In all, the results of this study provide support for the content validity of the FHNSI-10, inasmuch as all 10 items were reported by patients in interviews and considered relevant to R/M SCCHN experiences. Full content validity might be enhanced by adding cough and hearing impairment to the list of 10 items for use in clinical research,

if considered relevant symptoms by patients and experts for evaluating R/M SCCHN treatment. Nevertheless, the FHNSI-10 is in line with FDA guidance for PRO content and face validity assessment.[29] Although the FHNSI-10 does not cover every possible R/M SCCHN symptom, our findings reveal the instrument covers the most important symptoms and was reported to capture the experiences of R/M SCCHN patients.

TRANSPARENCY STATEMENT

This manuscript represents an honest, accurate, and transparent account of the study, no important aspects of the study were omitted, and any discrepancies from the study as planned have been explained.

AUTHOR CONTRIBUTIONS

Conceptualization: Sara Shaunfield and David Cella.

Data curation: Laura Boyken Sara Shaunfield.

Formal analysis: Sara Shaunfield, Susan Yount and Laura Boyken.

Funding acquisition: Sara Shaunfield and David Cella.

Investigation: Laura Boyken and Sara Shaunfield.

Methodology: Sara Shaunfield, David Cella, and Susan Yount.

Project administration: Sara Shaunfield and Laura Boyken.

Resources: Mark Agulnik and Sandeep Samant.

Supervision: Sara Shaunfield and David Cella.

Visualization: Sara Shaunfield, Laura Boyken, Susan Yount, and David Cella.

Writing—original draft preparation: Sara Shaunfield, Susan Yount, Laura Boyken, and David Cella.

All authors made substantial contributions to the study design, development of the publication, critical review of the drafts, and provided final approval of the submitted manuscript. Authors Sara Shaunfield, Susan Yount, Laura Boyken, and David Cella also contributed to data collection, analysis, and interpretation of results.

All authors are accountable for all aspects of the work including accuracy and integrity of the work presented.

CONFLICT OF INTEREST

Authors Shaunfield, Yount, Boyken, and Cella received research funding from Daiichi Sankyo. Agulnik serves as a consultant for the following companies: Eisai, Inc., Eli Lilly and Company, Novartis, and Janssen Pharmaceuticals Inc.; Samant has investment interest in Y-Trap Inc.; Cella is the President of FACIT.org and serves as a consultant to Pfizer, Novartis, and AbbVie Inc.

ORCID

Sara Shaunfield https://orcid.org/0000-0003-2878-7223

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67(1):7-30.
2. Gupta B, Johnson NW, Kumar N. Global epidemiology of head and neck cancers: a continuing challenge. *Oncology*. 2016;91(1):13-23.
3. American Cancer Society. *Cancer Facts & Figures 2019*. Atlanta: American Cancer Society; 2019.
4. Gregoire V, Lefebvre JL, Licitra L, Felip E. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010;21(Suppl 5): v184-v186.
5. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. *Mayo Clin Proc*. 2008;83(4):489-501.
6. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. *J Clin Oncol*. 2013;31(36):4550-4559.
7. SEER. SEER Stat Fact Sheets: Oral Cavity and Pharynx Cancer. National Cancer Institute. https://seer.cancer.gov/statfacts/html/oralcav.html. Accessed December 29, 2016.
8. Reich M, Leemans CR, Vermorken JB, et al. Best practices in the management of the psycho-oncologic aspects of head and neck cancer patients: recommendations from the European head and neck cancer society make sense campaign. *Ann Oncol*. 2014;25(11):2115-2124.
9. Pfister DG, Ang KK, Brizel DM, et al. Head and neck cancers, version 2.2013. Featured updates to the NCCN guidelines. *J Natl Compr Cancer Netw*. 2013;11(8):917-923.
10. Cohen EEW, Bell RB, Bifulco CB, et al. The society for immunotherapy of cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC). *J Immunother Cancer*. 2019;7(1):184.
11. Saada-Bouzid E, Peyrade F, Guigay J. Immunotherapy in recurrent and or metastatic squamous cell carcinoma of the head and neck. *Curr Opin Oncol*. 2019;31(3):146-151.
12. Szturz P, Vermorken JB. Immunotherapy in head and neck cancer: aiming at EXTREME precision. *BMC Med*. 2017;15(1):110.
13. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol*. 2008;26(21): 3582-3589.
14. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol*. 2008;26(22):3770-3776.
15. Machiels JP, Lambrecht M, Hanin FX, et al. Advances in the management of squamous cell carcinoma of the head and neck. *F1000Prime Rep*. 2014;6:44.
16. Rathod S, Livergant J, Klein J, Witterick I, Ringash J. A systematic review of quality of life in head and neck cancer treated with surgery with or without adjuvant treatment. *Oral Oncol*. 2015;51(10): 888-900.
17. Murphy BA. To treat or not to treat: balancing therapeutic outcomes, toxicity and quality of life in patients with recurrent and/or metastatic head and neck cancer. *J Support Oncol*. 2013;11(4):149-159.
18. Klein J, Livergant J, Ringash J. Health related quality of life in head and neck cancer treated with radiation therapy with or without chemotherapy: a systematic review. *Oral Oncol*. 2014;50(4):254-262.
19. Singer S, Krauß O, Keszte J, et al. Predictors of emotional distress in patients with head and neck cancer. *Head Neck*. 2012;34:180-187.
20. Chera BS, Eisbruch A, Murphy BA, et al. Recommended patient-reported core set of symptoms to measure in head and neck cancer treatment trials. *J Natl Cancer Inst*. 2014;106(7):1-4.
21. Rogers SN, Gwanne S, Lowe D, Humphris G, Yueh B, Weymuller EA Jr. The addition of mood and anxiety domains to the University of Washington quality of life scale. *Head Neck*. 2002;24(6):521-529.
22. Bjordal K, Hammerlid E, Ahlner-Elmqvist M, et al. Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of cancer quality of life questionnaire-H&N35. *J Clin Oncol*. 1999;17(3):1008-1019.
23. D'Antonio LL, Zimmerman GJ, Cella DF, Long SA. Quality of life and functional status measures in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg*. 1996;122(5):482-487.

24. Cella DF, Tulsky DS, Gray G, et al. The functional assessment of cancer therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993;11(3):570-579.

25. List MA, D'Antonio LL, Cella DF, et al. The performance status scale for head and neck cancer patients and the functional assessment of cancer therapy-head and neck scale. A study of utility and validity. *Cancer.* 1996;77(11):2294-2301.

26. Hanna EY, Mendoza TR, Rosenthal DI, et al. The symptom burden of treatment-naive patients with head and neck cancer. *Cancer.* 2015; 121(5):766-773.

27. Oswald LB, Lee JW, Argiris A, Webster KA, Forastiere AA, Cella D. Validation of brief symptom indexes among patients with recurrent or metastatic squamous cell carcinoma of the head and neck: a trial of the ECOG-ACRIN cancer research group (E1302). *Cancer Med.* 2020; 9(23):8884-8894.

28. Cella D, Paul D, Yount S, et al. What are the most important symptom targets when treating advanced cancer? A survey of providers in the national comprehensive cancer network (NCCN). *Cancer Investig.* 2003;21(4):526-535.

29. Rothman M, Burke L, Erickson P, Leidy NK, Patrick DL, Petrie CD. Use of existing patient-reported outcome (PRO) instruments and their modification: the ISPOR good research practices for evaluating and documenting content validity for the use of existing instruments and their modification PRO task force report. *Value Health.* 2009; 12(8):1075-1083.

30. Yount S, List M, Du H, et al. A randomized validation study comparing embedded versus extracted FACT head and neck symptom index scores. *Qual Life Res Int J Qual Life Asp Treat Care Rehab.* 2007;16(10): 1615-1626.

31. Shaunfield S, Webster KA, Kaiser K, et al. Development of the functional assessment of cancer therapy-carcinoid syndrome symptom index (FACT-CSI). *Neuroendocrinology.* 2020;111:850-862. doi: 10.1159/000511482

32. Shaunfield S, Jensen S, Fisher AP, et al. Further content validation of the 18-item NCCN/FACT ovarian symptom index and its disease related symptom-physical (DRS-P) subscale for use in advanced ovarian cancer clinical trials. *Health Qual Life Outcomes.* 2019; 17(1):185.

33. Kaiser K, Shaunfield S, Clayman M, Ruderman E, Cella A. Content validation of the functional assessment of chronic illness therapy (FACIT)-fatigue scale in moderately to highly active rheumatoid arthritis. *Rheumatol.* 2016;6(2):1-7.

34. Glaser B, Strauss A. *The Discovery of Grounded Theory.* London: Weidenfield & Nicolson; 1967.

35. Dedoose. Dedoose: Great Research Made Easy. 2017. www.dedoose.com. Accessed August 23, 2017.

36. Bowen GA. Naturalistic inquiry and the saturation concept: a research note. *Qual Res.* 2008;8(1):137-152.

37. Karvonen-Gutierrez CA, Ronis DL, Fowler KE, Terrell JE, Gruber SB, Duffy SA. Quality of life scores predict survival among patients with head and neck cancer. *J Clin Oncol.* 2008;26(16):2754-2760.

38. de Graeff A, de Leeuw JR, Ros WJ, Hordijk GJ, Blijham GH, Winnubst JA. Long-term quality of life of patients with head and neck cancer. *Laryngoscope.* 2000;110(1):98-106.

39. Cohen EE, Kane MA, List MA, et al. Phase II trial of gefitinib 250 mg daily in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Clin Cancer Res.* 2005;11(23):8418-8424.

40. Stewart J, Cohen E, Licitra L, et al. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol.* 2009;27(11):1864-1871.

41. US Department of Health and Human Services. Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims. Vol 1. Federal Register, 2009, 1–43.

42. U.S. Department of Health and Human Services Food and Drug Administration. Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. 2018.

43. Pugliano FA, Piccirillo JF, Zequeira MR, Fredrickson JM, Perez CA, Simpson JR. Clinical-severity staging system for oral cavity cancer: five-year survival rates. *Otolaryngol Head Neck Surg.* 1999;120(1):38-45.

44. Saba NF, Mody MD, Tan ES, et al. Toxicities of systemic agents in squamous cell carcinoma of the head and neck (SCCHN); a new perspective in the era of immunotherapy. *Crit Rev Oncol Hematol.* 2017; 115:50-58.

45. American Cancer Society. Cancer Facts & Figures, 2018.

46. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. *Field Methods.* 2006; 18(1):59-82.