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What matters most to people with metastatic uveal melanoma? A qualitative study to inform future measurement of health-related quality of life

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Metastatic uveal melanoma (mUM) is a rare cancer with poor prognosis, but novel treatments are emerging. Currently, there are no mUM-specific health-related quality of life (HRQL) questionnaires available for clinical research. We aimed to explore how mUM and its treatment affect HRQL and assess the content validity of existing questionnaires. Participants were patients with mUM and healthcare professionals involved in their care. Qualitative data were collected using semi-structured interviews and focus groups. Data collection and analysis used an integrative approach involving inductive questions/coding to elicit new concepts and deductive questions/coding based on domains of existing HRQL questionnaires. Initial interviews/focus groups focussed on HRQL questionnaires designed for patients with uveal melanoma or liver metastases. As new concepts were elicited, domains and items from other questionnaires were subsequently added. Seventeen patients and 16 clinicians participated. HRQL concerns assessed by uveal melanoma-specific questionnaires were largely resolved by the time of metastasis. The Functional Assessment of Cancer Therapy - Immunotherapy Module (FACT-ICM) adequately captured most immunotherapy-related side effects during initial treatment cycles. However, most patients emphasised emotional impacts over physical ones, focussing on the existential threat posed by disease amidst uncertainty about treatment accessibility and effectiveness. Patients were also concerned with treatment burden, including time commitment, travel, need for hospitalisation, and expenses. The relative importance of HRQL issues varied over time and across treatment modalities, with no single questionnaire being sufficient. Pending further development and psychometric testing, clinical researchers may need to take a modular approach to measuring the HRQL impacts of mUM. *Melanoma Res* 34: 248–257 Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc.

Melanoma Research 2024, **34**:248–257

Keywords: metastatic, patient reported outcome measures, psychometrics, qualitative research, quality of life, uveal melanoma

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Received 6 December 2023 **Accepted** 10 February 2024.

Introduction

Uveal melanoma is a relatively rare tumour with a mean age-adjusted incidence of 5.1 cases per million per year, constituting 3% of all melanomas [1]. Uveal melanoma is biologically distinct from cutaneous melanoma and has limited response to therapies developed for the latter [2]. More than 50% of people with uveal melanoma develop metastatic disease, most commonly occurring in the liver (91%), followed by the lung (16%) and bone (9%), with multiple sites in 24% patients [3,4]. Metastatic uveal melanoma (mUM) has a poor prognosis, with a 1-year overall survival of approximately 50% [5]. Recently, tebentafusp, a T-cell receptor-based agent, was the first treatment approved by the US Food and Drug Administration to treat mUM, but is restricted to the 30% of patients who have the relevant HLA subtype [6,7]. Clinical trials of tebentafusp and other novel therapies remain a focus for improving patient outcomes in patients with mUM [8].

The survival benefits and burdens of new treatments increase the importance of assessing impacts on health-related quality of life (HRQL) to evaluate net benefit. However, no mUM-specific HRQL questionnaire is available for use. Trials that have explored HRQL impacts in mUM patients most commonly utilised generic HRQL questionnaires, such as the EQ-5D [9–12], or questionnaires that were developed for

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.melanomaresearch.com.

cancer of any type, such as the Functional Assessment of Cancer Therapy – General (FACT-G) or European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core (QLQ-C30) [13–15].

HRQL questionnaires for uveal melanoma (e.g. EORTC Quality of Life Questionnaire – Ophthalmic Oncology (QLQ-OPT30) [16], Measure of Outcome in Ocular Disease (MOOD) [17], Collaborative Ocular Melanoma Quality of Life (COMS-QOL) [18]) have been validated in patients with early, rather than advanced, disease and focus on domains that may become less relevant for mUM, such as worry about disease recurrence. Furthermore, assessment of visual impairment by these questionnaires may be irrelevant to patients who have had enucleation after 12 months [19]. While HRQL questionnaires are available for patients with advanced melanoma [e.g. FACT – Melanoma (FACT-M) [20]; EORTC Quality of Life Questionnaire – Melanoma (QLQ-MEL38) [21]], these focus on aspects of HRQL ('domains') impacted by cutaneous melanoma, such as surgical removal and concerns about sun exposure, which are unlikely to be key issues in patients with mUM [22]. HRQL questionnaires for liver cancer, such as the FACT – Hepatic (FACT-Hep), have also been used in trials in mUM patients [23], but these are not relevant or sensitive in patients with metastases to sites other than the liver [9,13,24].

Because currently available HRQL questionnaires have not been developed with input from mUM patients, they may miss HRQL impacts specific to this patient group – that is, they may lack 'content validity' for mUM [25]. 'Concept elicitation' refers to the process of identifying HRQL issues of importance by canvassing the views of people from the target population themselves and other stakeholder groups with insight, with as little influence as possible from the researchers [26].

The aim of this study was to inform future HRQL measurement in patients with mUM by eliciting the views of patients and clinicians on how mUM and its treatment affect HRQL and assessing the content validity of existing questionnaires.

Methods

Study design

A qualitative approach was used to enable deep exploration of the lived experiences and perspectives of people with mUM and clinicians involved in their care [27]. The study was conducted between August 2022 and October 2023, and received ethical approval from St Vincent's Hospital Sydney Human Research Ethics Committee (2022/ETH01013). All participants gave informed verbal consent. Reporting adheres to the COnsolidated criteria for REporting Qualitative research [28].

Participants

Eligible participants were adult patients (aged ≥18 years) living with mUM and clinicians from any discipline (medical, nursing or allied health) with experience of providing care to this patient group in any setting (inpatient, outpatient or community). Patients were excluded if they were unable to provide informed consent or participate due to cognitive impairment or limited proficiency in English.

Due to the relative rarity of uveal melanoma, sampling was international to enable an adequate sample size. Patients were recruited through email lists for consumer organisations including Melanoma Patients Australia and Rare Cancers Australia, OcuMelUK, Ocular Melanoma Ireland and Ocumel Canada, as well as social media. Australian recruitment also occurred through outpatient services at two quaternary referral centres in Sydney and Melbourne. Clinicians were recruited via the authors' international networks and email circulars and notifications at relevant meetings of the Australasian Melanoma and Skin Cancer Trials group and Australasian Ocular Melanoma Alliance. The approach to recruitment meant that the number of people who were invited but did not participate could not be recorded.

Data collection

Patient data were collected by means of semi-structured individual interviews in recognition that patients might be sharing personal information and at risk of becoming distressed. In contrast, clinician data were collected using focus groups because these offered the most efficient means for enabling differing perspectives to be explored and integrated to identify group norms and individual variability [29,30]; interviews were offered as a second option where scheduling proved difficult. Data were collected via video-conference (Zoom or Microsoft Teams) to enable international participation, minimise burden and reduce risk of COVID-19 transmission. Video-conference was preferred over telephone to enable screen-sharing of questionnaire domains and items. Interviews and focus groups were conducted by one (T.L.) or two (T.L. and C.N.) researchers – a male social scientist (PhD) with experience in qualitative research on experiences of individuals facing life-limiting illnesses, and a female health economist (PhD) with no experience of qualitative research but expertise on HRQL questionnaires used in cancer. The interviewers had no prior or continuing relationships with any of the participants. Participants knew the researchers were not involved in their care and the purpose of the research. To our knowledge, no one else was present besides the participants and researchers.

Interviews began with open-ended questions about the HRQL impacts of mUM and its treatment. Once

unprompted issues were exhausted, participants were asked whether existing questionnaire domains and items were relevant to their HRQL. In the first interviews/focus groups existing HRQL questionnaires included only those designed for people with uveal melanoma (QLQ-OPT30, MOOD, and COMS-QOL) or metastases to the liver (Quality of Life Questionnaire – Colorectal liver metastases (QLQ-LMC21) [31], Quality of Life Questionnaire – Hepatocellular carcinoma (QLQ-HCC18) [32]). As data collection progressed, domains and items from other questionnaires were added as needed to measure new concepts elicited in previous interviews/focus groups. To ensure a standard of quality and maintain consistency in response formats and recall period, items from the two most widely used suites of cancer-specific HRQL questionnaires – EORTC and FACIT – were prioritised where possible. Decisions on domain and item inclusion were made collaboratively by the interviewers. By the final interview, a total of 103 domains (235 items in total) derived from 20 EORTC, FACIT and other questionnaires were collated. For domains identified to be relevant, participants were asked the degree to which related items were necessary and sufficient to capture their experience and their preference between these. Where HRQL issues were raised that were not covered by the evolving list, probes were used as needed to facilitate the depth of understanding required to select further domains/items for future interviews/focus groups.

In addition to qualitative data, patients were asked to provide demographic information (gender, age), time since initial diagnosis and metastases, and treatments received. Corresponding data from clinicians included gender, discipline and number of patients with mUM they had cared for over the past year.

Interviews and focus groups were audio-recorded and transcribed, after which data were deidentified. The researchers made field notes on observations during and after the interviews. Recruitment continued until 'information power' was reached (i.e. no new HRQL issues emerged) [33]. No repeat interviews were carried out. Data were imported into NVivo v12 software for management and analysis.

Analysis

Analysis used an integrated approach involving both deductive and inductive coding to ensure results were both grounded in existing questionnaires and open to new insights shared by participants [34]. Initially, transcripts were coded inductively line-by-line to identify impacts on HRQL from disease and treatment. Next, these concerns were mapped to domains and items of existing questionnaires, creating new codes for any additional issues. We followed the EORTC and FACIT suites in regarding 'core' HRQL domains of the identified impacts to be physical, role, emotional and social functioning/well-being.

TL and CN coded the initial five patient interviews line-by-line; coding discrepancies were resolved by discussion between the authors until consensus was reached. CN coded the remaining interviews. Coding was conducted after each batch of three consecutive interviews/focus groups, so that emerging HRQL issues could be revisited during the next round of data collection for verification and further development.

Analysis focussed primarily on patient rather than clinician data as the 'primary source' regarding experience and appraisal of HRQL. Clinician data were then coded against the tree developed for patient data, creating new codes as needed for verification in subsequent patient interviews. The credibility of findings was interrogated through exploration of negative cases and 'member checking'; participants were invited to review a one-page summary of findings and disagree or suggest refinements if needed.

Results

Participants

Seventeen patients and 16 clinicians participated in the study. All patients were on anti-cancer treatment at the time of being interviewed, except for three who were deliberating treatment options. Clinician data were collected via two focus groups (n = 2 and n = 8) and six interviews. The mean durations of interviews/focus groups with patients and clinicians were 60 and 25 min respectively. Tables 1 and 2 summarises patients' and clinicians' characteristics respectively. Two patients from New Zealand were living in Australia to access tebentafusp, while another received darovasertib/crizotinib therapy in Australia before returning to New Zealand.

Impacts on HRQL

Most patients placed greater emphasis on the emotional, rather than physical, impacts of disease and treatment. Emotional concerns were centred on the existential threat posed by metastatic disease within the context of uncertainty about treatment access and effectiveness. More variably, patients were concerned with burden from treatment in the form of time commitment, travel, need for hospitalisation, and expense. Of the treatments received, immunotherapy – especially tebentafusp – conferred the heaviest inconvenience and symptom burden. The most prevalent and bothersome symptoms were fatigue, short-term skin reactions and fever, appetite loss, pain, diarrhoea and nausea. However, even patients who had experienced severe symptoms from treatment regarded these as tolerable in return for benefits to survival. Few patients reported symptoms from their disease, although a small number had symptoms of unknown cause. All patients maintained near-normal

Table 1 Characteristics of patient participants

	Patients (n = 17)
Gender	
Male	7 (41%)
Female	10 (59%)
Country of treatment	
Australia	10 (59%)
UK	2 (12%)
New Zealand	1 (6%)
Switzerland	1 (6%)
Sweden	1 (6%)
USA	1 (6%)
Canada	1 (6%)
Age (years)	
31–40	2 (12%)
41–50	3 (18%)
51–60	4 (24%)
61–70	6 (35%)
71–80	1 (6%)
81 or over	1 (6%)
Time since diagnosis of primary uveal melanoma	
< 3 years	2 (12%)
3–4 years	1 (6%)
5–10 years	7 (41%)
>10 years	7 (41%)
Experience of treatment for primary uveal melanoma	
Enucleation only	4 (24%)
Plaque brachytherapy only	7 (41%)
Plaque brachytherapy followed by enucleation	3 (18%)
Laser therapy followed by enucleation	1 (6%)
Proton beam therapy only	1 (6%)
Unclear	1 (6%)
Time since diagnosis of metastases	
<1 year	5 (29%)
1–2 years	4 (24%)
>2 years	8 (47%)
Site of metastases	
Liver	16 (94%)
Bones	2 (12%)
Lung	2 (12%)
Pancreas	1 (6%)
Kidney	1 (6%)
Breast	1 (6%)
Experience of treatment for metastases	
Systemic therapy	17 (100%)
Tebentafusp	10 (59%)
Ipilimumab and nivolumab	4 (24%)
Darovasertib and crizotinib	3 (18%)
Pembrolizumab	2 (12%)
Darovasertib alone	1 (6%)
Nivolumab and relatlimab	1 (6%)
Surgery	6 (35%)
Radiotherapy	3 (18%)
Chemotherapy	2 (12%)

Table 2 Characteristics of clinician participants

	Clinicians (n = 16)
Gender	
Male	9 (56%)
Female	7 (44%)
Country	
USA	10 (63%)
Australia	2 (13%)
UK	2 (13%)
Poland	1 (6%)
Germany	1 (6%)
Profession	
Medical oncologist	9 (56%)
Ophthalmologist	2 (13%)
Radiation oncologist	1 (6%)
Radiologist	1 (6%)
Oncology physician assistant	1 (6%)
Nurse practitioner	1 (6%)
Clinical nurse consultant	1 (6%)
Number of patients with metastatic uveal melanoma cared for over past year	
0–20	2 (13%)
21–30	5 (31%)
31–50	8 (50%)
50–100	0 (0%)
>100	1 (6%)

physical functioning/well-being, except for some patients receiving tebentafusp who reduced activity on the day of infusion each week due to feeling generally unwell. Role functioning/well-being was impacted by symptoms and treatment burden, with several patients reducing or ceasing employment or more physically demanding leisure activities. Impacts on social functioning/well-being were less pronounced, with most patients receiving support from family and friends. However, many patients expressed concern about the impact of their prognosis on their loved ones, and a small number found repeated discussion of their illness to be challenging. Compared with patients, clinicians generally over-emphasised the impact of symptoms compared with emotional impacts and other treatment burdens. Each of these concerns is discussed in more detail below, with illustrative quotations available in Supplementary Table 1, supplemental digital content 1, *http://links.lww.com/MR/A373*.

Supplementary Table 2, supplemental digital content 1, *http://links.lww.com/MR/A373* provides a summary of the questionnaire domains identified by patients to be relevant to their HRQL, along with exemplar questions for each domain endorsed by at least two participants and considerations regarding their content.

HRQL concerns assessed by existing uveal melanoma questionnaires

Most participants reported having gotten '*used to*' (P09, Australian woman aged 51–60) impacts from early disease and treatment during the period between the primary diagnosis and their cancer metastasising. Thus, items from the MOOD, QLQ-OPT30 and COMS-QOL were noted as largely irrelevant. However, there was inconsistency in the relationship between time elapsed and degree of adaptation; one patient who received brachytherapy still found visual impairment and ocular irritation to be important 4 years later (P11, American man aged 71–80), whereas another patient (P04, New Zealand woman aged 41–50) reported adapting well to enucleation after only 1 year. Two clinicians reported that patients who had radiotherapy for early-stage disease were more likely to suffer from long-term side effects than those who eventually had enucleation ('*Some [patients] see improvement in their quality of life because the side effects of the radiation therapy have basically been resolved by enucleation*'. (C04, American medical oncologist)). Indeed, all seven patients who had been treated with enucleation for early-stage disease reported having adapted to loss of sight in one eye, with

only two reporting residual problems in the form of relatively minor aspects of visual impairment ('*there's a depth perception issue that causes a few problems … I [also] had a phantom eye type thing, where I had flashing lights … [but] now very rarely*' (P02, British man aged 51–60); '*I might say that I'm probably more clumsy than usual*' (P14, New Zealand woman aged 61–70)). Less common ongoing issues were ocular irritation, and cosmetic concerns.

Symptoms

Most patients reported at least one symptom of the kind assessed by questionnaires that measure common problems across all cancers like the EORTC QLQ-C30 and FACT-G. Fatigue was the most common symptom reported by patients and clinicians regardless of treatment modality. Common descriptions included having decreased energy and needing to sleep. Two clinicians identified fatigue as one of the main impacts on quality of life in patients with mUM.

The greatest treatment burden was during the initial cycles of immunotherapy, and accordingly, a majority of their side effects could be captured by the Functional Assessment of Cancer Therapy - Immunotherapy Module (FACT-ICM). Skin-related adverse effects shortly after immunotherapy administration were reported by almost all patients and clinicians. A majority of patients experienced itching, with severity ranging from '*not a big problem*' (P06, Swedish woman aged 41–50) to '*scratching the skin on your legs with the intention of trying to rip it off your bones*' (P11, American man aged 71–80). Some patients reported that skin-related effects accompanied only early infusions, and most patients experienced a reduction in severity over the course of immunotherapy. However, two patients reported itching to persist even after treatment cessation.

While itching was identified as an important side effect of immunotherapy, the concomitant skin rash, vitiligo and hair bleaching were not identified by patients as bothersome ('*I'll take every white skin and white hair over feeling sick*' (P05, Swiss woman aged 41–50)). Clinicians placed greater emphasis on rash because it was associated with cytokine release syndrome '*to the point where [patients] need inpatient care or active management*' (C16, British medical oncologist).

Fever was reported by both patients and clinicians to be a further short-term side effect of immunotherapy. Most patients described this as a change in temperature. Around half of the patients who had fevers described having concurrent chills or '*shaking*' (P07, Australian man aged 31–40), while two specified having '*hot flashes*' (P05, Swiss woman aged 41–50; P12, British woman aged 41–50) instead. Concerns that fever might lead clinicians to withhold immunotherapy or surgery were also expressed by two patients. Although fevers were noted as a frequent adverse event of tebentafusp, a few clinicians expressed that they '*fortunately [do not] last very long*' (C06, American medical oncologist) or were '*short-lived*' (C05, Irish medical oncologist).

Appetite loss was reported by most patients who were asked, with most of them expressing concerns about being '*low in nutrition*' (P04, New Zealand woman aged 41–50), '*going to get sicker*' (P17, Australian man aged 51–60) or experiencing seemingly-associated weight loss. Pain was experienced at various sites, including the abdomen, joints, muscles and shoulder, which commonly impacted physical activities of daily living. Some patients had localised swelling around lymph nodes and joints, which impacted their physical functioning/well-being. Several patients also reported bothersome diarrhoea, nausea, vomiting or trouble sleeping, and some patients described taking medication for symptomatic relief of these issues. However, two patients expressed reluctance to take opioids due to side effects of constipation and cognitive impairment, or opioid-related stigma. Conversely, no clinician spontaneously raised issues regarding taking medication for symptomatic relief.

Dizziness and headaches were experienced by a few patients shortly after treatment. However, these – like many symptoms – seemed to be tolerable unless compounded by other side effects. Additionally, a few patients expressed a belief that the severity of side effects was associated with treatment efficacy ('*When you're in pain, it's pain with purpose*' (P01, Australian woman aged 31–40)), and certain side effects were even desirable ('[*The oncologists] have a saying, "No rash, no good*"*… It's just something you have to tough it out and go through if you want this treatment to work*' (P10, Canadian man aged 61–70)). Drug-related inflammation of the liver, gut or bladder were reported by three patients, which required hospitalisation or treatment discontinuation.

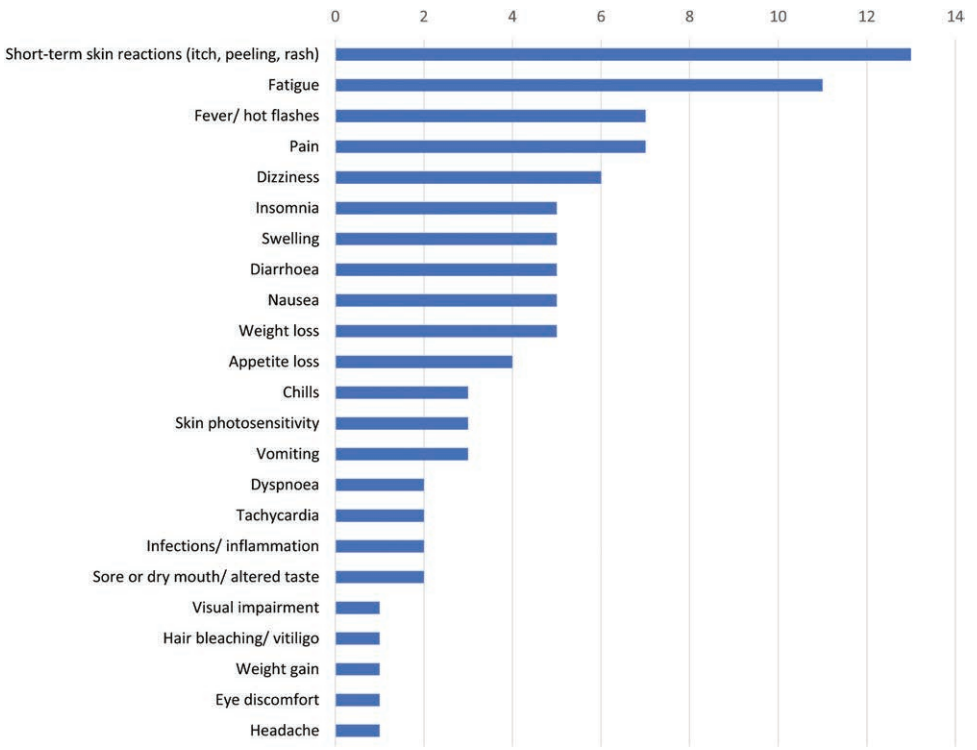
Patients who experienced abdominal swelling stated that it was palpable only on examination or occurred following liver resection, and did not find it bothersome. Several clinicians agreed that abdominal swelling and jaundice were symptoms in late-stage disease or '*pre-terminal events*' (C10, American interventional radiologist). A few patients also reported having weight gain, dry mouth and change in taste but these were likewise described as not bothersome.

The numbers of patients spontaneously reporting each symptom are represented in Fig. 1.

Physical and role functioning/well-being

Limitations to daily and leisure activities were described as fluctuating over the course of disease and treatment ('*I've had severe side effects for periods of time, but then I've also been pretty much able to do what I want to do for the last 18 months*' (P07, Australian man aged 31–40)). Side effects from tebentafusp, in particular, were associated

Fig. 1



Numbers of patients with metastatic uveal melanoma spontaneously reporting each symptom (N = 17).

with severe limitations to physical and role functioning/well-being during the first few treatments, lessening over time except for the day each week that patients received their infusion. Those with fatigue also reported an impact on physical and role functioning/well-being. Limitations to physical functioning was scarcely spontaneously reported by clinicians – one reported that patients' preoccupation with their treatment regime '*may be related to a decrease of daily activities as they're focussing more and more on their disease*' (C14, German medical oncologist).

At the time of interviewing, many patients reported having almost no limitations to their usual activities, described in terms of 'do[ing] *everything I used to do*' (P06, Swedish woman aged 61–70) or '*my life is relatively normal*' (P09, Australian female aged 51–60). Indeed, some patients described their goal in terms of maintaining normalcy for as long as possible in the face of certain deterioration ('*trying to keep things as normal as much as possible to try and limit that effect for as long as I can*' (P07, Australian man aged 31–40)). Even given relative normalcy, however, some patients had given up strenuous recreational activities due to a pervasive lack of energy.

Some patients focussed on making lifestyle changes, including for diet and exercise, to improve their health or even combat mUM ('*I'm also exploring what are all the other things that I can do to help myself and maybe heal my cancer*' (P16, New Zealand woman aged 51–60 receiving treatment in Australia); '*it becomes your job to stay alive*' (P05, Swiss woman aged 41–50)). A few patients also mentioned turning to alternative medicine, such as hyperthermia, naturopathy and acupuncture. Two patients reported modifying their activities of daily living to avoid infections or malnourishment so that they would '*be healthy [enough] to participate in a new clinical study*' (P06, Swedish woman aged 61–70). One clinician mentioned that dietary recommendations were occasionally sought by patients.

The ability to work was perceived by two patients and some clinicians to be important to HRQL. Some patients had to stop working or reduce work hours due to the treatment side effects or schedule. Patients who were able to continue working despite interruptions from their treatment schedule and symptoms described being grateful for the support they received from work. One patient chose to reduce work hours to spend her remaining life on activities she felt were more worthwhile ('*I want to make sure there's enough left of me for everyone else in my life and not just my job*' (P12, British woman aged 41–50)). Continuation of normal role function was seen as a reason to pursue treatment by one clinician.

Patients who had experienced times during treatment where they were not able to continue usual roles

and responsibilities reported feelings of frustration and shame ('*I felt very useless*' (P05, Swiss woman aged 41–50)). Patients also expressed a concern that their ill health might ruin others' enjoyment of shared activities ('*I'm going to feel really stressed … [I am a] box of misery, and it's not going to be much of a family holiday*' (P04, New Zealand woman aged 61–70)).

Emotional functioning/well-being

Most patients and some clinicians included uncertainty regarding disease course and treatment access and effectiveness among the most important factors influencing HRQL. Many patients talked about being in a state of '*limbo*' (P03, Australian woman aged 41–50; P09, Australian woman aged 51–60; P15, Australian woman aged 61–70) or similar, wherein it was difficult to plan far ahead due to uncertainty regarding prognosis and demands from potential new treatment regimens ('*if there is a trial and I switch, I know there's an extra commitment*' (P01, Australian woman aged 31–40)).

Fear of disease progression was most often manifest as a preoccupation with investigative tests as an indicator of treatment efficacy and the need to seek alternatives. Feelings of anxiety increased from a few days leading up to a test to when results were received. Patients' experience of time waiting for results varied from 1 day to 3 weeks, depending on whether they needed to schedule an appointment. Difficulties during the investigative procedures, such as having MRI-related claustrophobia or problems finding a suitable vein for drawing blood, also increased anxiety. Some patients also feared disease progression when experiencing physical symptoms ('*every little pain I feel, I wonder whether the cancer spread to somewhere else*' (P03, Australian woman aged 41–50)).

Patients varied as to whether they felt emotionally able to discuss end-of-life concerns assessed by questionnaires designed for palliative care (Quality of Life at the End of Life (QUAL-E) Instrument, and the McGill Quality of Life Questionnaire–Revised). Most who were asked were focussed on positive coping in the here and now, that they had not contemplated end-of-life as yet ('*I never actually thought about it, to be honest. Just trying to stay positive*'. (P04, New Zealand woman aged 61–70); '*I guess I haven't got to that point where I'm thinking that way yet*' (P07, Australian man aged 31–40)). Only a small number elaborated on end-of-life planning such as financial matters and advance care directives. One of these patients highlighted the importance of end-of-life questionnaire items to '*evaluate how much somebody is impacted by the anxiety, fear and worries of dying*' (P05, Swiss woman aged 41–50), but acknowledged how some may not have considered an end-of-life plan, and recommended having these questions as optional – a view endorsed by all patients who were asked subsequently. A few clinicians expressed the importance of assessing existential worry, and one reported that '*for uveal metastases, those issues are the same issues as anybody with bad metastatic cancer*' (C03, American medical oncologist).

Social functioning/well-being

About half of the patients described the support received from close family or friends as being important for emotional support, assisting in decision-making or practical support such as transport, finances, understanding of medical information, and support with activities of daily living when they were unwell. Of these patients, most specified their partner as their main source of support. However, some of them expressed regret for the emotional and practical burden their disease and treatment conferred to their family ('*I wish my wife didn't have to deal with this*' (P10, Canadian man aged 61–70)), as well as concern about how their family might cope financially and practically after they had died.

A small number of patients also appreciated interest and emotional support from their wider family and friendship circle. Conversely, however, an equal number of patients found these conversations difficult or stressful, with one patient describing '*conversation fatigue*' (P01, Australian woman aged 31–40) from having to repeat the same information and deal with others' questions and emotional responses. One patient (P04, New Zealand woman aged 61–70) reported having decreased interest in social activities even though she was '*normally a very social person*' because she found them '*mentally draining*'. One clinician expressed the need for patients with connect with other with similar experiences ('*because [mUM] is an orphan condition, it's hard for patients to really share their concerns or find somebody to cry on their shoulder. Usually, they can talk to their relatives, but it'd be nice to have patient advocacy groups*' (C14, German medical oncologist)). No other clinician spontaneously discussed social functioning/well-being as impacting HRQL in patients with mUM.

Other treatment-related issues

Patients tended to find the FACT-G and QLQ-MEL38 items relevant regarding role, social and emotional functioning/well-being. QLQ-MEL38 items under the domains of disease prognosis/acceptance and care delivery/communication were also important to HRQL. However, several treatment-related issues, including time commitment, travel and expenses were not sufficiently captured by existing questionnaires.

Most patients commented on the time-intensiveness of treatments for mUM, especially those that were experimental or specialised, meaning they not only required regular clinic visits but were also accessible only at certain hospitals, sometimes requiring substantial travel and waiting times. Related disruption had '*quite an impact in terms of lifestyle*' (P02, British man aged 51–60) for some patients, especially those who were still working. Clinicians expressed the same views as patients.

However, it was also seen as necessary ('*it's just something I do once a week to keep me alive*' (P01, Australian woman aged 31–40); '*if something is necessary to keep you alive, how can it be inconvenient?*' (P10, Canadian man aged 61–70)). Some treatments required patients to travel interstate or even overseas to access them, in two cases separating women from their family for long periods. In these instances, financial burden from travel and accommodation became a significant issue. Patients also commented on their inability to travel far afield whilst on weekly treatment regimens, with one woman being separated from her partner who was working overseas.

Discussion

In this qualitative study, patients with mUM and clinicians experienced in caring for this patient group reported that issues assessed by questionnaires for uveal melanoma have generally resolved by the time of metastasis. Instead, primary concerns have shifted towards the existential threat posed by disease, and burdens from treatment in the form of time commitment, travel, need for hospitalisation, and expenses. These concerns and side effects from treatment were reported to vary over time and between treatment modalities, highlighting the complexity of assessing HRQL in patients with mUM and the inadequacy of any one questionnaire.

A majority of immunotherapy-related side effects during the initial cycles of treatment could be adequately captured by the FACT-ICM [35]. Several FACT-ICM domains such as those relating to fatigue, itching, fever, loss of appetite and short-term treatment reactions impacted HRQL in patients with mUM. Assessment of other symptoms may be achieved via a selection from Supplementary Table 1, supplemental digital content 1, *http://links.lww.com/MR/A373* and relevant item libraries, in accordance with recently published recommendations by Piccinin *et al.* (2023) [36]. This approach allows for a more comprehensive assessment of HRQL issues while limiting respondent burden. However, caution should be exercised when adopting this modular approach as it is unclear if the psychometric validity of items or domains will remain unchanged, and there may be unexpected effects that this approach fails to capture. Additionally, patient reports of side effects have a complex relationship with HRQL in patients with melanoma. While reduced toxicity may result in better health status, an increase in toxicity may not necessarily translate to a decrease in HRQL scores, especially when patients are willing to tolerate side effects for prolonged life or believe that the severity of side effects are associated with better tumour response [37,38].

Patients generally emphasised the emotional impacts of mUM and its treatment over their physical impacts. This was consistent with findings among patients with metastatic cutaneous melanoma, who similarly experience fewer physical limitations compared to patients with other advanced cancers [38,39]. A qualitative study by Makady *et al.* [40] further reported that patients with metastatic melanoma (18% with mUM) most frequently mentioned 'family' and having 'good medicines' and a 'normal life' as important aspects of their HRQL. While these issues were also discussed in our study, we found that uncertainty was the most prominent concern among patients with mUM given its evolving therapeutic landscape. Related items from the FACT-G and QLQ-MEL38 were generally endorsed by patients. Notably, the FACT-G emotional well-being scale items on 'coping', 'hope' and 'worry about condition getting worse' were considered more relevant compared to the corresponding domain from the QLQ-C30 which focuses on anxiety and depression [41]. Our study further identified QLQ-MEL38 items in the domains of disease prognosis/acceptance and care delivery/communication to be relevant. Single items related to clinical trials were also relevant, although some refinement may be necessary, for instance, rewording 'Is making multiple visits for tests difficult for you?' to 'Is making multiple visits for treatment difficult for you?'. It is also worth noting that the shorter version of the QLQ-MEL38 – the Melanoma Concerns Questionnaire (MCQ-28) – excludes items relevant to patients with mUM, including 'Have you felt able to plan for the future?' and 'How important is it for you to see the same members of your healthcare team at each clinic visit?' [42].

An important finding from our study is that the majority of patients with mUM had responded to uncertainty regarding their prognosis by focussing on maintaining optimism at the expense of planning for end of life. While metastases are sometimes regarded as a trigger for optimal timing of advance care planning [43], our findings suggest that few patients with mUM may be ready and willing to answer questions on end-of-life matters in an unsupported research context. This means that such questions should be included in an optional way at most. For patients who choose to do so, responses from the few participants in our study who commented suggest that standard palliative care questionnaires such as the QUAL-E Instrument [44] and the McGill Quality of Life Questionnaire–Revised [45] will be as appropriate for this patient group as for other advanced cancers.

Strengths and limitations

An advantage of the current study is the incorporation of input from international patients and clinicians, eliciting direct evidence from the patients themselves and also cumulative information from the all the patients treated by the participating clinicians. However, transferability of findings from this study are limited by its relatively small sample size and potential for sampling bias. Although our study included patients with a broad experience related to their disease and treatment, we were not able to interview individuals who had high burden of disease, had not yet initiated treatment for metastases, or had

chosen to discontinue treatment entirely. Interviews with patients in the latter group might be especially important to explore the potential for decisional conflict and regret to impact HRQL. The sample of patient was also not ethnically diverse, but this may be consistent with the demographic most affected by mUM [1]. Due to the large number of HRQL issues identified, information power was achieved only at a more general level for some domains. While the issues we identified were provisionally organised into HRQL domains of symptoms and physical, role, emotional, and social functioning, further psychometric testing would be required to confirm structural validity. Unfortunately, testing of mUM-specific HRQL questionnaires is challenged by the rarity of the disease and the potential for obsolescence in the face of rapidly evolving treatments. In the meantime, domains and items assessing these concerns should only be scored according to the original questionnaires from which they are drawn rather than aggregated in new ways [36].

Conclusion

The most important HRQL impacts from mUM and its treatment are not adequately assessed by currently available early-stage uveal melanoma-specific questionnaires. If evaluating the impact of initial immunotherapy cycles on HRQL in patients with mUM is a focus in clinical research, the FACT-ICM will likely be suitable. However, patients predominantly characterise impacts on HRQL in emotional terms relating to the existential threat posed by metastatic disease amidst uncertainty regarding treatment accessibility and effectiveness. Concerns were reported to vary over time and among different treatment modalities, underscoring the challenge of comprehensively assessing HRQL in patients with mUM and the inadequacy of any single questionnaire. Researchers wishing to measure HRQL in this patient population should be aware of the limitations of existing questionnaires, and are recommended to use domains and items from a number of HRQL questionnaires, adhering to the original scaling or scoring items individually.

Acknowledgements

C.N., T.L. and B.M. received funding from St Vincent's Hospital, Sydney for the conduct of this study.

Conflicts of interest

There are no conflicts of interest.

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