available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for patients with Bone Metastases: The EORTC QLQ-BM22

Edward Chow[a,], Amanda Hird[a], Galina Velikova[b], Colin Johnson[c], Linda Dewolf[d], Andrea Bezjak[e], Jackson Wu[f], Jesmin Shafiq[g], Orhan Sezer[h], Dimitrios Kardamakis[i], Yvette van der Linden[j], Brigette Ma[k], Monica Castro[l], Palmira Foro Arnalot[m], Sam Ahmedzai[n], Mark Clemons[e], Peter Hoskin[o], Albert Yee[a], Michael Brundage[p], Andrew Bottomley[d], on behalf of the EORTC Quality of Life Group [v]*

[a]*Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5*
[b]*Cancer Research UK Clinical Centre, University of Leeds, St James's University Hospital, Leeds, UK*
[c]*University Surgical Unit, Southampton General Hospital, UK*
[d]*European Organization for Research and Treatment of Cancer, Brussel, Belgium*
[e]*Princess Margaret Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada*
[f]*Tom Baker Cancer Centre, University of Calgary, Calgary, Alberta, Canada*
[g]*Liverpool Hospital, Liverpool, New South Wales, Australia*
[h]*Charité, Universitaetsmedizin Berlin, Germany*
[i]*University of Patras Medical School, Patras, Greece*
[j]*Radiotherapeutic Institute Friesland, Leeuwarden, The Netherlands*
[k]*Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, China*
[l]*Instituto de Oncologia Angel H. Roffo, Universidad de Buenos Aires, Argentina*
[m]*Hospital de l'Esperança, Sant Josep de la Muntanya, Barcelona, Spain*
[n]*St Lukes Hospice, Little Common Lane, Sheffield, UK*
[o]*Mount Vernon Hospital, Northwood, Middlesex, UK*
[p]*Kingston Regional Cancer Centre, Kingston, Ontario, Canada*

ARTICLE INFO

Article history:
Received 17 October 2008
Accepted 11 November 2008
Available online 25 December 2008

Keywords:
Bone metastases
Health-related quality of life

ABSTRACT

Aim: The aim of this study was to develop a bone metastases module to supplement the European Organisation for Research and Treatment of Cancer Core Questionnaire (EORTC QLQ-C30) or the EORTC QLQ-C15-PAL for patients with bone metastases.

Methods: Phases 1–2 of module development were conducted in Canada, Australia and Germany according to EORTC QOL group guidelines. Phase 3 was conducted in nine countries in seven languages.

Results: Sixty-one health-related quality of life (HRQOL) issues were generated from health care professionals ($n = 152$) and patients ($n = 413$). This resulted in a 22-item provisional

* *Corresponding author:* Tel.: +1 416 480 4998; fax: +1 416 480 6002.
E-mail address: edward.chow@sunnybrook.ca (E. Chow).

[v] We thank all collaborators and research assistants, who assisted with the accrual: Michael Barton[q], Robert Coleman[r], Richard Eek[g], Candi Flynn[a], Kristin Harris[a], Liying Zhang[a], Georgina Keenleyside[s], Marc Kerba[f], Jane Koh[t], Sam Kyerematenge[s], Jessica Rademacher[h], Elaine Rogers[u], Vassilios Vassiliou[i], [q]Collaboration for Cancer Outcomes Research & Evaluation (CCORE), Liverpool Hospital, Liverpool, NSW, Australia; [r]Weston Park Hospital, Cancer Research Centre University of Sheffield; [s]St Lukes Hospice, Little Common Lane, Sheffield, UK; [t]Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, China; [u]University of Sheffield, Academic Unit of Supportive Care, School of Medicine & Biomedical Sciences, Sheffield, UK.
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.11.013

Questionnaire
Cancer
Pain symptoms
EORTC

module. Further testing in 170 patients from nine countries resulted in the EORTC QLQ-BM22 module, containing 22 items, conceptualised into both symptom scales, with five painful sites and three pain characteristics, and also functional scales, with eight functional interference and six psychosocial aspects.

Conclusion: This study provides a provisional comprehensive HRQOL measurement tool for future trials, which will continue to undergo further validation.

1. Introduction

Bone metastases are a frequent complication of cancer. Breast and prostate cancer patients are the most common to develop metastases to the bone, followed by lung, thyroid and renal cell carcinomas.[1] Among patients with multiple myeloma, more than 80% develop symptomatic lytic bone lesions. Bone metastases have been reported in 70–85% of cancer patients at autopsy.[2]

Previous clinical trials examining bone metastases have largely focussed on the objective end-points such as analgesic consumption, hypercalcaemia, pathological fractures, spinal cord compression and use of surgery and radiation.[3–16] The World Health Organisation (WHO) describes health as 'not merely the absence of disease or infirmity, but a state of physical, mental and social well-being'.[17] Health-related quality of life (HRQOL) is a subjective, multidimensional construct reflecting functional status, psychosocial well-being, health perceptions, disease- and treatment-related symptoms from the patient's perspective.[18] It incorporates expectation, satisfaction, value systems and the many aspects of a patient's life. Since most bone metastases-specific interventions are palliative in nature, HRQOL is arguably a more meaningful end-point together with symptom control, when compared with the traditional end-points such as survival times and local control. HRQOL issues are of critical importance for patients, when making decisions in the treatment of bone metastases. More interventional studies now aim towards enhancing patient's HRQOL, often by reducing the toxicity.

With advances in effective systemic treatment and supportive care, survival of patients with bone metastases has improved substantially. Certain subsets of patients with bone metastases (e.g. breast and prostate cancers with predominately bone or bone-only metastases) have life expectancies which range between 2 and 5 years. Successful management of bone metastases during these years is essential for reducing skeletal complications and for maximising patient HRQOL.[19]

A number of clinical trials from various disciplines have addressed the optimal management of bone metastases. With advances in the systemic treatment of advanced cancer patients with osseous metastases (i.e. radiopharmaceuticals, bisphosphonates, chemotherapies, orthopaedic interventions and additional systemic treatments), there is a fundamental requirement for the development of a HRQOL assessment tool that is specific to patients with bone metastases, in order to provide a comprehensive evaluation of the benefits and possible side-effects of any interventions. Often the objective effects of treatments on bone metastases have proven difficult to measure (using traditional investigations such as X-rays, bone scintigraphy, CT or MRI scans and blood biochemistry) and the assessment of patients' subjective benefit is, therefore, critically important. However, our literature search found that robustly developed bone metastases-specific HRQOL instruments are lacking.

The EORTC Quality of Life Group (QLG) has developed a 30-item core cancer questionnaire, the EORTC QLQ-C30, which is extensively used to measure HRQOL in cancer clinical trials.[20] Additional modules are subsequently developed to assess specific disease sites, symptoms and/or treatment-related HRQOL issues. To ensure scientific rigour, detailed guidelines for module development have been published.[21,22]

The aim of this study was to develop a bone metastases module to supplement the European Organisation for Research and Treatment of Cancer Core Questionnaire (EORTC QLQ-C30) or the EORTC QLQ-C15-PAL measure (for palliative cancer patients). Here, we report the first three phases of the development of the HRQOL module questionnaire specific to patients with bone metastases.

2. Materials and methods

2.1. Study design

The development of the provisional module was in accordance with the guidelines published by the EORTC QLG.[21,22] The module development process has four distinct phases aimed at ensuring validity and reliability (Table 1).

2.1.1. Phase 1: generation of HRQOL issues

Relevant HRQOL issues/themes for patients with bone metastases were identified by the Medline and Psycho info databases (1966–2005) with restrictions to English articles using the following keywords: bone neoplasms/bone metastases combined with quality of life; quality of life combined with terminal cancer. Additional articles on bone metastases in the major oncology and palliative medicine textbooks were reviewed with the aim of creating a list of known side-effects and complications of the treatment that may affect HRQOL. Existing questionnaires assessing HRQOL aspects in patients with bone metastases were identified and reviewed for relevant issues. Patients and health care professionals (HCPs) were also interviewed to generate a list of relevant HRQOL items specific to bone metastases.

A list of issues was compiled and presented to HCPs, who were treating patients with bone metastases from Canada, Australia and Germany. They were asked to consider the relevance of each issue (how frequently each issue arises and

Table 1 – Guidelines for development of EORTC HRQOL modules.

Phase	Aim	Procedure
Phase 1	Generation of HRQOL issues relevant to the selected group of patients	1. Literature search 2. Semi-structured interviews with health care professionals and patients 3. Quantitative and qualitative data analysis 4. Combination of results from interviews to produce a list of issues
Phase 2	Construction of the issues into a provisional questionnaire	1. Consultation with the EORTC QOL group Item Bank database for existing items 2. Construction of new items – items are worded to be compatible with the QLQ-C30 response categories 3. Translation of provisional questionnaire according to EORTC QLG guidelines
Phase 3	Testing of the provisional questionnaire for acceptability and relevance	1. Patient completion of questionnaire and interview 2. Quantitative and qualitative data analysis 3. Modification of questionnaire 4. Formal development report reviewed by EORTC QLG
Phase 4	International field testing	Psychometric testing of reliability, validity and sensitivity to change of the questionnaire

the trouble it may cause) and to report any missing issues. The HCPs were asked to rate the issues from 1 – 'not relevant' to 4 – 'very relevant', to select the 5–10 core issues to be definitely included in the questionnaire and to add any missing items.

The list of issues was also presented to patients from five cancer hospitals (three in Canada, one in Australia and one in Germany). Ethics approval was obtained from each centre. Eligible patients included those with bone metastases, who were able to understand the language of the questionnaire and give written informed consent. Patients were asked to indicate the degree to which they experienced each issue during the past week, to select which 5–10 issues they considered as the most important and to list any issues they had experienced which were missing from the questionnaire.

2.1.2. *Phase 2: construction of provisional questionnaire*

The selected issues were constructed into items according to the following criteria: (a) questions should be compatible with EORTC QLQ-C30 response categories 'not at all', 'a little', quite a bit' and 'very much'; (b) questions compatible to the 1-week time frame of EORTC QLQ-C30 wherever possible; and (c) questions should refer to states (i.e. ongoing) rather than to changes.

Existing questionnaire items were harmonised to ensure comparability of items across the modules. This was done using the EORTC QOL Item Bank.[23] The Item Bank comprises all existing EORTC QOL questionnaire items along with their translations. The Item Bank is organised by themes, with identification of the original module and all other modules containing each item.

2.1.3. *Phase 3: testing of the provisional questionnaire for acceptability and relevance*

This phase identified problems relating to the wording and clarity of items, and determined the need for adding or deleting items. The provisional module was tested in additional patients from participating countries. This phase was critical to determine whether the set of module items are comparable cross-culturally, particularly among non-English speaking countries.

Patients were asked to complete the EORTC QLQ-C30 and the bone metastases module indicating if they found any questions annoying, confusing, upsetting or intrusive, and if so, they were asked to rephrase the question. Patients were also asked whether any questions were irrelevant or whether there were additional issues that were not included in the module.

2.2. *Data analyses and criteria for item selection*

The results from Phase 1 interviews were analysed using descriptive statistics: (1) mean score for each item; (2) range of responses; (3) prevalence (number of patients who experienced each complaint, i.e. who scored 2, 3 or 4, divided by the total number of patients who completed that item, multiplied by 100); and (4) the proportion of patients or professionals prioritising the issue. In Phase 1, items were selected using the following criteria:

- mean score at least 2.5;
- range of responses at least two points, i.e. 1–3 or 2–4;
- prevalence ratio at least 30%;
- at least 33% of patients or health care professionals prioritising the item.

Items were retained if they met at least three of four of the above criteria. The scores were considered in conjunction with patient comments made during interviews.

In Phase 3, decisions for retaining or deleting items were made in conjunction with patient comments during the interviews. Comments on difficulties with comprehension due to wording or language were taken into consideration. The final wording was achieved using a consensus methodology, where all co-authors considered the data on comprehensibility, and then agreed on appropriate rewording.

To compare the responses of patients with bone metastases or with multiple myeloma, Wilcoxon rank-sum test or Fisher exact test was performed to search for the difference in mean score or in prevalence ratio in the two groups. The Bonferroni p-value adjustment ($0.05/n$; where n is the number of tests) was used to determine the level of significance. A

p-value < 0.0023 (0.05/22) was considered as statistical significance for two-sided test. All calculations were performed using SAS (version 9.1.3 for Windows; SAS Institute, Cary, NC) statistical software package.

3. Results

3.1. *Phase 1: generation of issues*

Forty-seven articles on HRQOL and psychosocial issues in patients with bone metastases were identified. Twenty-five different instruments were used to evaluate HRQOL with study specific questionnaires. The EORTC QLQ-C30 was most commonly employed. None of the instruments identified were bone metastases specific and validated across cultures.

Sixty-one patients and fifty-eight HCPs were also interviewed to generate a list of relevant HRQOL items specific to bone metastases. A list of 61 relevant symptoms/issues was complied and summarised into the following domains (Table 2):

- symptom (13 issues);
- function (15 issues);
- side-effects from treatment of bone metastases (3 issues);
- psychosocial (27 issues);
- treatment expectation (2 issues);
- financial (1 issue).

This list of 61 items was formatted into a questionnaire and administered to 413 patients (174 males and 239 females) and 152 HCPs across five centres in three countries. Patients had a median age of 64 years (range 30–93 years). The most common primary cancer sites were breast (39%), prostate (17%) and multiple myeloma (15%) (Table 3). At the time of interview, most patients had received chemotherapy (70%), radiation therapy (70%), hormonal therapy (56%) or bisphosphonate treatment (55%) for their cancer. Few patients had experienced pathological fractures (8%), spinal cord compressions (6%) or hypercalcaemia (4%).

Of the 152 HCPs interviewed, majority were radiation oncologists (30%), medical oncologists (26%) or nurses (22%); however, palliative care physicians, social workers, surgeons, a radiation therapist, a pharmacist and a psychosocial worker were also interviewed (Table 3). Quantitative analysis (mean scores, range, prevalence and proportions of priority ratings) of both HCP and patient interviews resulted in the deletion of 39 issues.

3.2. *Phase 2: construction of provisional questionnaire*

Items (questions addressing HRQOL issues) were constructed from the 22 retained issues. Wordings were modified based on the items available in the EORTC QOL Item Bank. The draft module was reviewed for the clarity of wording and overlapping of items by two members of EORTC QLG. It was subsequently translated to German, Chinese, Spanish, Greek and Dutch according to the EORTC QLG translation procedure.

3.3. *Phase 3: testing of the provisional questionnaire for acceptability and relevance*

The EORTC QLQ-C30 and the provisional module were pretested on 170 patients from nine countries (Table 4). The majority of patients (68%) were non-English speaking. Overall, 83 patients were male (49%) and 87 were female (51%). The median age was 60 years (range 29–92 years). Median time from primary cancer diagnosis to diagnosis of bone metastases was one year (range: 0–21 years). Patients interviewed were from a variety of ages and primary cancer sites that were undergoing various therapies.

Analysis of Phase 3 results was conducted to examine the mean score, prevalence ratio, range of responses and completion rate for each item on the questionnaire. There were no significant ceiling or floor effects. The mean score of all EORTC QLQ-BM22 items exceeded 1.50; with the exception of item 16 ('*Have you felt isolated from those closest to you?*'). During the Phase 1 interviews with bone metastases patients and HCPs, isolation from friends and family was indicated to be highly relevant by both the groups. To maintain consistency with EORTC phrasing of items, this question was adapted to coincide with an item from the High Dose Chemotherapy Module (HDC29).[24]

The prevalence ratio of all additional EORTC QLQ-BM22 items exceeded 30% with the exception of items 3, 4, 5 and 8 (which are all pain-related items). Pain is the most common symptom associated with bone metastases – severe pain is present in 50–75% of all bone metastases patients. Not only is pain the most prevalent symptom associated with osseous metastases, but also the most debilitating. During Phase 1 interviews with HCPs, it was uniformly expressed that pain is a significant issue that must be addressed in the final questionnaire. The treatment objective in managing bone metastases is to either minimise pain or prevent it altogether. Therefore, if the EORTC QLQ-BM22 is to be used as a HRQOL questionnaire in a clinical setting, it is essential to include pain items in order to accurately assess patient's response to treatment. For example, a patient who presents with inability to walk due to pain may experience a significant pain reduction following radiotherapy or hormone therapy. As a result, ambulation may be possible once more. The assessment of characteristics of the pain (i.e. questions 6–8 & 15) and the gradient that assesses pain during various movements (i.e. questions 9–14) will enable clinicians to assess changes in functional status over time.

Bone metastases frequently affect more than one region of the bone. Successful localised treatment to one specific bony metastatic site may 'unmask' pain in other metastatic bone regions. Therefore, questions that specify the exact location of pain (i.e. questions 1–5) will enable clinicians to differentiate pain scores in multiple metastatic sites and to accurately assess if treatment impacts locally or systemically.

Although the prevalence ratio was lower for items 3 (14%), 4 (15%), 5 (15%) and 8 (23%), the mean scores of all pain-related items were >1.5. It is necessary to include a detailed breakdown of both location of pain and functional interference in order to accurately assess changes over time. For these reasons, we have decided to keep all pain items in the EORTC QLQ-BM22 HRQOL questionnaire. The original

Table 2 – List of 61 HRQOL issues from the literature and qualitative interviews grouped by symptoms.

Symptom
1. Long-term (or chronic) pain[a]
2. Short-term (or acute), severe pain[a]
3. Pain at rest (i.e. when sitting) [a]
4. Pain with activity (i.e. when walking) [a]
5. Pain aggravation with movement or weight bearing[a]
6. Uncontrolled, unmanageable pain[a]
7. Pain at night preventing sleep[a]
8. Aches and stiffness
9. Lack of energy[b]
10. Numbness
11. Tingling
12. Burning sensation
13. Postural problems

Function
14. Limited movement due to pain[a]
15. Difficulty planning activities outside the home
16. Difficulty travelling outside the home (i.e. using public transportation, driving, sitting in a car)
17. Difficulty in carrying out meaningful activity (including employment) [a]
18. Able to perform self-care[b]
19. Able to return to work promptly
20. Difficulty in carrying out usual daily tasks (i.e. grocery shopping, work outside the home, housework) [b]
21. Difficulty in bending[a]
22. Difficulty in lifting[a]
23. Difficulty in standing up[a]
24. Difficulty in climbing stairs[a]
25. Difficulty in sitting[a]
26. Difficulty in lying in bed[a]
27. Difficulty lying flat
28. Ability to have sex

Side-effects from treatment of bone metastases
29. Drowsiness
30. Confusion
31. Dizziness

Psychosocial
32. Able to perform role functioning (including domestic and family roles)[b]
33. Feeling socially isolated[a]
34. Strengthened relationships with family/friends
35. Have a clear, alert mind[b]
36. Feel in control, positive and confident[a]
37. Hope to live as long as possible
38. Reluctance to pain medication
39. Fear of addiction to pain medication
40. Anxiety[b]
41. Frustration
42. Mood changes[b]
43. Emotional stress of diagnosis of advanced, incurable cancer
44. Increased focus on spiritual issues
45. Loss of interest in activities you normally enjoy
46. Loss of interest in sex
47. Worry about pain
48. Worry about suffering
49. Worry about loss of mobility compromising independence[a]
50. Worry about becoming dependent on others[a]
51. Worry about current health status[a]
52. Worry about the future[a]
53. Worry about becoming bed-bound[a]
54. Worry about disease progression, deterioration in condition and future complications[a]
55. Worry about running out of medical treatments
56. Worry about hospitalisation
57. Worry about ending days in a hospital or nursing home
58. Worry about death

Treatment expectation
59. Hope for sustained pain relief (reduce pain for as long as possible)[a]
60. Hope treatment will reduce pain as much as possible[a]

Other issue
61. Financial burden due to the illness[b]

a Phase I final items in relation to questionnaire development.
b Issues are in the EORTC QLQ-C30.

questionnaire asked if there are problems in sitting or lying down. This item was split into two questions at the request of patients in several countries. The question 'have you been thinking about your illness?; has been deleted given Phase 3 feedback that the question is self-evident, upsetting and depressing.

We compared the responses of patients with bone metastases from solid cancers to those in our study with multiple myeloma. There was no significant difference in mean score and prevalence ratio in the two groups. Therefore, the inclusion of patients with multiple myeloma in the validation of the EORTC QLQ-BM22 did not alter our results.

The development process and the final questionnaire were reviewed and approved by the executive members of the EORTC QOL Module Development Committee (Table 5).

4. Discussion

The EORTC QLQ-BM22 module has been successfully developed to measure the HRQOL in cancer patients with bone metastases. It contains 22 items conceptualised into both symptom scales, with five painful sites and three pain characteristics, and also functional scales, with eight functional interference and six psychosocial aspects.

The content of the questionnaire has been the result of the extensive literature review, interviews with HCPs and most importantly with bone metastases patients. Compared with many other measures, our module development has involved large patient and HCP samples from multiple countries. The initial list of items was derived following interviews with 61 patients and 58 HCPs. This list of 61 items was then presented to 413 patients and 152 HCPs in three countries for comments in Phase 1. The provisional module of 22 items underwent Phase 3 testing in 170 patients over nine countries. Of these, 116 patients were from six non-English speaking countries. The inclusion of diverse, non-English speaking populations ensures that the questionnaire is comprehensive, reflects the practice across continents and is culturally acceptable.

To facilitate reliable comparisons in bone metastases clinical trials, we aimed to develop a single module that will cover patients experiencing different treatments and complications. Patients interviewed during the module development process were carefully selected to reflect different ages, genders, durations of diagnosis of bone metastases and various types of bone metastases-specific treatments. During the

Table 3 – Phase 1 patient and health care professional demographics.

Patient demographics (N = 413)[a]	Number (%)
Centre/Country	
PMH/Canada	132 (32.0%)
OCC/Canada	131 (31.7%)
TBCC/Canada	67 (16.2%)
Liverpool/Australia	42 (10.2%)
Charité/Germany	41 (9.9%)
Sex	
Female	239 (57.9%)
Male	174 (42.1%)
Age (years) (n = 409)	
Median (range)	64 (30–93)
Mean ± SD	63.4 ± 11.8
Primary cancer site (n = 412)	
Breast	160 (38.8%)
Prostate	71 (17.2%)
Multiple myeloma	61 (14.8%)
Lung	57 (13.8%)
Others	22 (5.3%)
Renal	20 (4.9%)
Gastrointestinal	16 (3.4%)
Unknown	5 (1.2%)
Treatment (current/past)	
Radiation (n = 348)	242 (69.5%)
Chemotherapy (n = 329)	231 (70.2%)
Bisphosphonates (n = 322)	177 (55.0%)
Hormonal therapy (n = 314)	175 (55.7%)
Surgery (n = 372)	20 (5.4%)
Skeletal-related event	
Pathological fracture (n = 371)	29 (7.8%)
Spinal cord compression (n = 372)	21 (5.6%)
Hypercalcaemia (n = 372)	16 (4.3%)
Health care professional demographics (N = 152)	**Number (%)**
Centre/Country	
PMH/Canada	47 (30.9%)
OCC/Canada	45 (29.6%)
Liverpool/Australia	26 (17.1%)
TBCC/Canada	23 (15.1%)
Charité/Germany	11 (7.2%)
Speciality	
Radiation oncologists	46 (30.3%)
Medical oncologists	40 (26.3%)
Nurses	33 (21.7%)
Palliative care physicians	18 (11.8%)
Surgeons	7 (4.6%)
Social workers	5 (3.3%)
Others	3 (2.0%)

a The *n* value differs depending on the item evaluated because of missing data.

Table 4 – Phase 3 overall patient demographics (N = 170).

Country	
Canada	35 (21%)
Greece	29 (17%)
The Netherlands	22 (13%)
China (Hong Kong)	20 (12%)
Germany	20 (12%)
Australia	16 (9%)
Argentina	14 (8%)
Spain	10 (6%)
The United Kingdom	4 (2%)
Gender (n = 170)	
Female	87 (51%)
Male	83 (49%)
Age (n = 146) in years	
Median (range)	60 (29–92)
Primary cancer site (n = 170)	
Breast	52 (31%)
Multiple myeloma	33 (19%)
Lung	22 (13%)
Prostate	20 (12%)
Colorectal	19 (11%)
Others	16 (9%)
Renal Cell	8 (5%)
Time from bone metastases diagnosis to interview (years) (n = 134)	
Median (range)	1 (0–21)

Table 5 – Issues included in the bone metastases quality of life questionnaire.

Symptom scales

Painful sites
1. Back
2. Leg(s) or hip(s)
3. Arm(s) or shoulder(s)
4. Chest or ribs
5. Buttocks

Pain characteristics
6. Constant pain
7. Intermittent pain
8. Pain not relieved by medications

Functional scales

Functional interference
9. Pain while lying down
10. Pain while sitting
11. Pain when trying to stand up
12. Pain while walking
13. Pain with activities such as bending or climbing stairs
14. Pain with strenuous activity
15. Pain interfered with your sleeping
16. Modify your daily activities

Psychosocial aspects
17. Felt isolated from those close to you
18. Worried about loss of mobility
19. Worried about becoming dependent on others
20. Worried about your health in the future
21. Felt hopeful your pain will get better
22. Felt positive about your health

analysis, the sub-group results were compared (data not shown), and items relevant for various groups were retained. This vigorous procedure ensures that the resulting module can be used for different treatment modalities.

The next phase of development involves administration in a large multicultural population to provide essential data on the psychometric properties of the questionnaire. This will involve the use of the module in clinical trials or field studies so as to collect the data centrally and perform psychometric analyses. We have also used the EORTC QLQ-C15-PAL together

with the EORTC QLQ-BM22 in our cancer centre. Both questionnaires were well received by our patients.

Our study has a limitation in that the initial item generation was done only in Canada, with Phase 1 contribution from Australia and Germany. This is compensated by involving six non-English speaking countries to help test the module in Phase 3. The module is now available in English, German, French, Japanese, Chinese, Spanish, Greek, Italian, Korean, Danish, Swedish, Norwegian, Turkish and Dutch.

The EORTC QLQ-C30 and/or the EORTC QLQ-C15-PAL, supplemented by the EORTC QLQ-BM22, will provide a comprehensive HRQOL measurement for international clinical trials involving bone metastases patients. This is also of value in the longitudinal follow-up of patients with bone metastases by providing information on disease symptoms and the effects of treatment on patients' lives.

Conflict of interest statement

None declared.

Acknowledgements

This project is generously supported by grants from the National Cancer Institute of Canada, Deutsche Krebshilfe, Bonn, Germany in Berlin, and an unrestricted educational grant from Novartis Oncology. We thank Drs. Juan Ignacio Arraras, Eva Greimel, Bernhard Holzner, John Ramage and Teresa Young for their review of Phases 1 to 3 reports and also Stacy Lue for secretarial assistance.

REFERENCES

1. Pain palliation of bone metastases – overview. InSightec.com. InSightec Image Guided Treatment Ltd. 1st April 2005 <http://www.insightec.com/135-en-r10/BoneMetastases.aspx>.
2. Heider U, Fleissner C, Zavrski I, et al. Bone markers in multiple myeloma. *Eur J Cancer* 2006;**42**:1544–53.
3. Body J, Diel IJ, Bell R, et al. Oral ibandronate improves bone pain and preserves quality of life in patients with skeletal metastases due to breast cancer. *Pain* 2004;**111**:306–12.
4. Cresswell SM, English PJ, Hall RR, Roberts JT, Marsh MM. Pain relief and quality-of-life assessment following intravenous and oral clodronate in hormone-escaped metastatic prostate cancer. *Brit J Urol* 1995;**76**:360–5.
5. Diel IJ, Body JJ, Lichinitser MR, et al. Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. *Eur J Cancer* 2004;**40**:1704–12.
6. Ernst DS, Tannock IF, Winquist EW, et al. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. *J Clin Oncol* 2003;**21**:3335–42.
7. Fernandez-Conde M, Alcover J, Aaron JE, Ordi J, Carretero P. Skeletal response to clodronate in prostate cancer with bone metastases. *Am J Clin Oncol* 1997;**20**:471–6.
8. Kristensen B, Ejlertsen B, Groenvold M, Hein S, Loft H, Mouridsen HT. Oral clodronate in breast cancer patients with bone metastases: a randomized study. *J Intern Med* 1999;**246**:67–74.
9. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases. *Cancer* 2000;**88**:1082–90.
10. Mancini I, Dumon JC, Body JJ. Efficacy and safety of ibandronate in the treatment of opioid-resistant bone pain associated with metastatic bone disease: a pilot study. *J Clin Oncol* 2004;**22**:3587–92.
11. Purohit OP, Anthony C, Radstone CR, Owen J, Coleman RE. High-dose intravenous pamidronate for metastatic bone pain. *Brit J Cancer* 1994;**70**:554–8.
12. Saad F, Gleason DM, Murray R, et al. Zoledronic Acid Prostate Cancer Study Group. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;**94**:1458–68.
13. Van Holten-Verzantvoort AT, Hermans J, Beex LV, et al. Does supportive pamidronate treatment prevent or delay the first manifestation of bone metastases in breast cancer patients? *Eur J Cancer* 1996;**32A**:450–4.
14. Van Holten-Verzantvoort AT, Kroon HM, Bijvoet OLM, et al. Palliative pamidronate treatment in patients with bone metastases from breast cancer. *J Clin Oncol* 1993;**11**:491–8.
15. Van Holten-Verzantvoort AT, Zwinderman AH, Aaronson NK, et al. The effect of supportive pamidronate treatment on aspects of quality of life of patients with advanced breast cancer. *Eur J Cancer* 1991;**27**:544–9.
16. Wardley A, Davidson N, Barrett-Lee P, et al. Zoledronic acid significantly improves pain scores and quality of life in breast cancer patients with bone metastases: a randomized, crossover study of community vs. hospital bisphosphonate administration. *Brit J Cancer* 2005;**92**:1869–76.
17. World Health Organization. *Constitution of the World Health Organization*. Geneva, Switzerland: WHO Basic Documents; 1948.
18. Soni MK, Cella D. Quality of life and symptom measures in oncology: an overview. *Am J Manage Care* 2002;**8**: S560–73.
19. Harrington KD. Prophylactic management of impending fractures. In: Harrington KD, editor. *Orthopedic management of metastatic bone disease*. CV Mosby; 1988. p. 283–307.
20. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;**85**:365–76.
21. Sprangers MA, Cull A, Bjordal K, Groenvold M, Aaronson NK. The European Organization for Research and Treatment of Cancer. Approach to quality of life assessment: guidelines for developing questionnaire modules. EORTC Study Group on Quality of Life. *Qual Life Res* 1993;**2**:287–95.
22. Blazeby J, Sprangers M, Cull A, et al. *EORTC Quality of Life Group: guidelines for developing questionnaire modules*. 3rd ed. revised. August 2002. <http://groups.eortc.be/qol/downloads/200208module_development_guidelines.pdf>.
23. Bottomley A, Vachalec S, Bjordal K, et al. The development and utilization of the European Organisation for research and treatment of cancer quality of life group item bank. *Eur J Cancer* 2002;**38**:1611–4.
24. Velikova G, Weisb J, Hjermstadc MJ, et alOn behalf of the EORTC Quality of Life Group. The EORTC QLQ-HDC29: a supplementary module assessing the quality of life during and after high-dose chemotherapy and stem cell transplantation. *Eur J Cancer* 2007;**43**:87–94.