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A prospective longitudinal study investigating outcomes including patient-reported outcome measures after surgery for metastatic bone disease

PROTOCOL FOR THE BOMA-PRO MULTI-CENTRE MBD OUTCOMES STUDY

S. Downie,
A. Stillie,
M. Moran,
C. Sudlow,
A. H. R. W. Simpson

From University of Edinburgh, Edinburgh, UK

Aims

Surgery is often indicated in patients with metastatic bone disease (MBD) to improve pain and maximize function. Few studies are available which report on clinically meaningful outcomes such as quality of life, function, and pain relief after surgery for MBD. This is the published protocol for the Bone Metastasis Audit — Patient Reported Outcomes (BoMA-PRO) multicentre MBD study. The primary objective is to ascertain patient-reported quality of life at three to 24 months post-surgery for MBD.

Methods

This will be a prospective, longitudinal study across six UK orthopaedic centres powered to identify the influence of ten patient variables on quality of life at three months after surgery for MBD. Adult patients managed for bone metastases will be screened by their treating consultant and posted out participant materials. If they opt in to participate, they will receive questionnaire packs at regular intervals from three to 24 months post-surgery and their electronic records will be screened until death or five years from recruitment. The primary outcome is quality of life as measured by the European Organisation for Research and the Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ) C30 questionnaire. The protocol has been approved by the Newcastle & North Tyneside 2 Research Ethics Committee (REC ref 19/NE/0303) and the study is funded by the Royal College of Physicians and Surgeons of Glasgow (RCPSG) and the Association for Cancer Surgery (BASO-ACS).

Discussion

This will be the first powered study internationally to investigate patient-reported outcomes after orthopaedic treatment for bone metastases. We will assess quality of life, function, and pain relief at three to 24 months post-surgery and identify which patient variables are significantly associated with a good outcome after MBD treatment.

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Introduction

Metastatic bone disease (MBD) accounts for around 5% of all orthopaedic trauma referrals[1] and is increasingly prevalent as modern treatment continues to improve survival in systemic cancer.[2] Due to the largely palliative nature of orthopaedic treatment for MBD, even those with a very poor prognosis are likely to be offered surgery in order to improve pain and maximize function.[1] However, most of these patients are not routinely followed up clinically and outcomes measurement generally focuses on objective outcomes such as survival, surgical complications, and weight-bearing status.[3,4]

Correspondence should be sent to Samantha Downie; email: samantha.downie3@nhs.scot

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Few studies have been published to date which focus on patient-reported outcomes after surgery for bone metastases. Two studies from the USA and Canada published in 2018 recorded patient-reported outcomes after surgery for MBD with limited follow-up (maximum six months and mean five months, respectively).[5,6] Both demonstrated an early reduction in pain and improvement in function as early as two weeks from surgery but 'failed' to demonstrate any improvement in quality of life up to one-year post-surgery. This is not surprising in view of the progressive nature of systemic cancer, and is perhaps not the most appropriate focus for studies investigating post-surgical outcomes in MBD.

Two studies are available detailing patient factors that are associated with poor outcome in MBD.[7,8] Though moderate in sample size (n = 184 and n =202, respectively), both are cross-sectional in nature and focus on quality of life outcomes as a result of the presence of bone metastases, rather than the effect of surgery. Patient variables found to be associated with a poorer outcome in terms of quality of life, pain, and depression include younger age, smoking status, medical comorbidities, and primary cancer diagnosis.[7,8] Pathological fractures were associated with poorer function in a study by van der Vliet et al,[8] but only 10% of this cohort (21/202) had undergone surgery. The findings from these studies can be taken to indicate the levels of function and pain in the general MBD population but not necessarily variables which can impact on function after surgery.

To the best of our knowledge, there are no powered studies in the literature which comprehensively record patient-reported outcomes after MBD surgery. Such a study would allow us to determine patient satisfaction, identify the simplest way to measure outcome after surgery, and identify which variable patient factors can lead to improved outcomes in this group.[9]

The aim of this study is to ascertain patient-reported outcomes after surgery for MBD at up to two years post-surgery. The primary objective is to establish patient-reported quality of life (QoL, assessed through use of the EORTC-QLQ C30 PROM tool) at three months post-surgery. The secondary objectives are to: assess outcome after surgery for MBD in terms of other patient-reported outcomes (pain, function, and mobility) at three to 24 months post-surgery; identify which patient and disease factors independently predict QoL at three months post-surgery (Table I); and identify any variation in patient-reported outcomes for surgical versus non-surgical patients at three to 24 months from referral.

Methods

Study design. This will be a prospective, longitudinal study involving patients presenting with MBD to six hospitals across the UK from January 2021 to December 2022. These hospitals include two specialist orthopaedic oncology units, four major trauma centres, and two trauma units, and have been chosen due to geographical location and availability of supervisory teams. The study oversight and reporting criteria have been designed with reference to the Mayo Clinic's position statement around measuring PROMs in healthcare centres.[17]

Inclusion and exclusion criteria. All adult patients (male and female) presenting to the study centres with bone lesions confirmed/highly suspicious of systemic cancer will be considered (including patients managed non-surgically). Prior to approach, potential participants must be aware of their diagnosis and aged 18 or over. Individuals with primary bone cancer, a cognitive impairment precluding ability to consent (assessed by treating surgeon using 4AT[14] or Mini Mental State Exam[15] (MMSE)), and those deemed too frail to participate by their orthopaedic team will not be approached for the study. Patients with MBD who have not had surgery will be eligible to participate and reason for not undertaking surgery will be recorded. There are no predetermined exclusions for non-English speaking patients; however, as the questionnaires are validated in English only, inability to speak English is considered a relative contraindication to participation.

Recruitment and data collection. The initial plan had been to recruit patients during hospital admission for orthopaedic treatment for their bone metastasis. However, in light of restrictions in physically approaching patients to participate in research due to the COVID-19 pandemic, this has been amended to a postal-only recruitment strategy. Individuals will be identified by their treating orthopaedic consultant and screened according to the eligibility criteria (see Figure 1). If eligible to participate, they will be sent a Letter of Invitation (Supplementary Material a), Participant Information Sheet (PIS; Supplementary Material b), Consent Form, and Baseline Questionnaire (for upper or lower limb lesions as appropriate; Supplementary Material c) by their treating orthopaedic consultant. Individuals will have a minimum of 24 hours to consider participation before choosing to return their completed baseline questionnaire and signed consent form, 'opting-in' to proceed to first follow-up at three months post-surgery.

Once the baseline questionnaire and signed consent form are returned, baseline patient and disease-specific data will be collected from patient electronic records (Table I) and this will be updated at regular intervals until the patient passes away or five years from recruitment date, whichever is earliest. Table II details the variables which will be collected for each patient.

Baseline data will be collected from patients on a retrospective basis between presentation and six weeks post-surgery (or six weeks post first-orthopaedic review for patients managed nonoperatively).

Table I. Summary information for the Bone Metastasis Audit — Patient Reported Outcomes multicentre metastatic bone disease study.

Research question	Which patient and disease factors independently predict good outcome after orthopaedic treatment for metastatic bone disease?
Primary objective	Identify which patient and disease factors independently predict QoL after surgery for bone metastases at three months
Primary outcome measure	Overall QoL as measured by the EORTC-QLQ C-30 question: "How would you rate your overall quality of life during the past week" at three months post-orthopaedic treatment for MBD.
Secondary objectives	■ Assess outcome after surgery for MBD in terms of other patient-reported outcomes (pain, function and mobility) at 3 to 24 months post-surgery ■ Identify which patient and disease factors independently predict QoL at three months post-surgery ■ Identify any variation in patient-reported outcomes for surgical versus non-surgical patients at 3 to 24 months from referral
Secondary outcome measures	■ Pain (VAS and FACT-BP bone pain[10]) ■ Function & mobility (MSTS,[11] EORTC-QLQ BM22) ■ Satisfaction (adapted from score used by Hamilton and colleagues in 2013[12]) ■ Objective outcomes, including survival, postoperative complications, length of hospital stay, and presence/absence of fracture union
Patient variables of interest (VOIs)	■ Patient age in years ■ Primary cancer diagnosis ■ Pre-injury functional status (Karnofsky index)[13] ■ Location of bone metastasis ■ Complete or incomplete pathological fracture ■ Time from referral to surgery ■ Type of surgical management ■ Postoperative surgical site infection ■ Postoperative radiotherapy ■ Metalwork failure
Design	A multicentre prospective cohort study of patients undergoing orthopaedic surgery for bony metastatic disease across six orthopaedic centres in the UK
Inclusion	■ Age 18 or over ■ Confirmed/highly suspicious of metastatic cancer ■ Patient aware of diagnosis ■ Orthopaedic treatment (including non-surgical management) for metastasis
Exclusion	■ Primary bone cancer (e.g. osteosarcoma) ■ Unable to consent to participate (cognitive impairment as assessed on hospital admission for delirium screening via 4AT[14] screening tool or MMSE[15] ■ Patient too medically frail to be approached by research team for participation (subjectively measured by treating orthopaedic surgeon or senior orthopaedic nurse) ■ Patient chooses not to participate ■ Non English-speaking patient (relative contraindication)
Identification & eligibility screening	Patients identified by treating orthopaedic surgeon and screened according to eligibility criteria (see Figure 1). If preliminary criteria met, Letter of Invitation sent (Supplementary Material a) posted to patient along with Participant Information Sheet and Consent Form (Supplementary Material b) and Baseline Upper/Lower Limb Questionnaire (Supplementary Material c).
Consent	If willing to participate, individuals will opt in to participate by returning the completed consent form and baseline questionnaire.
Follow-up	Participants will receive follow-up questionnaire packs at the following dates from their surgery (or date of referral if managed nonoperatively): ■ 3 months ■ 6 months ■ 9 months ■ 1 year ■ 18 months ■ 2 years After the last active follow-up questionnaire, participants will continue to be followed up remotely via their electronic patient records until their death or five years post-surgery, whichever is soonest.
Dates	Recruitment: 01/01/2021 to 31/12/2022 Last follow-up: 31/12/2027
Number of participants	Patients referred to orthopaedics for management of symptomatic bone metastases account for 5% of trauma referrals.[1] Of these, approximately 70% undergo surgery, with a 54% survival rate at three months.[1] Based on the total populations for the six centres participating over a one-year period (3,705,000) and a referral rate of 1/8,000 per year, we predict 465 patients will be referred to these centres. With a 70% operative rate, 54% three month survival rate and 10% attrition rate, the projected sample size completing three month follow-up is 158 surgical participants.
Sample size	Using Green's rule-of-thumb method incorporating 0.8 power (80% chance of rejecting null hypothesis) with ten independent variables, n = 104+ k (k = number of independent variables), a target sample size of 114 participants completing three month follow-up is required to power the study.[16]

EORTC-QLQ, European Organisation for Research and the Treatment of Cancer Quality of Life questionnaire; FACT-BP, Functional Assessment of Cancer Therapy - Bone Pain; MBD, metastatic bone disease; MMSE, Mini Mental State Exam; MSTS, Musculoskeletal Tumor Society; QoL, quality of life; VAS, visual analogue score

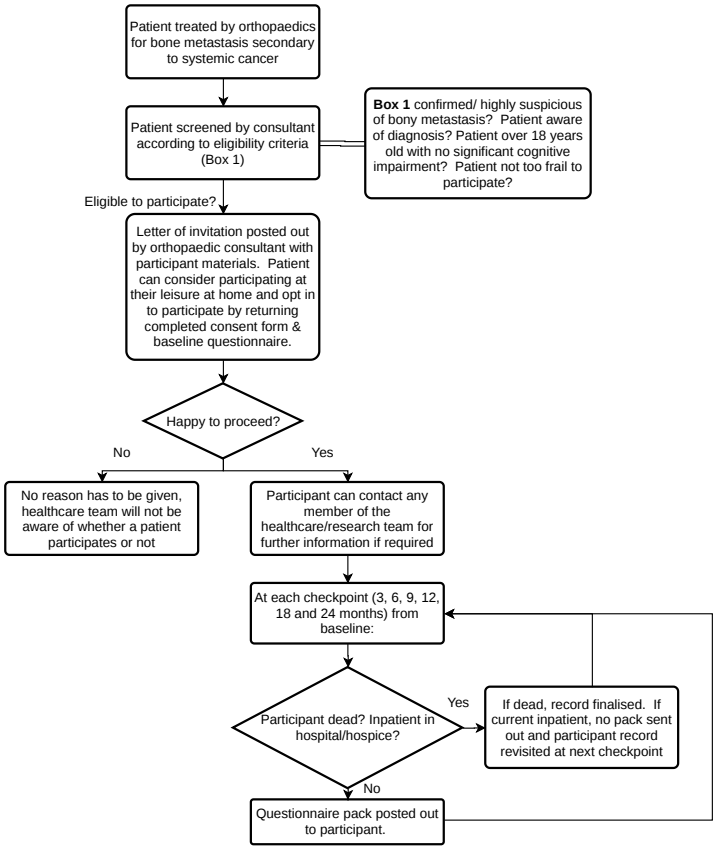

Fig. 1

Flowchart detailing process of participant identification, consent and follow-up for the Bone Metastasis Audit - Patient Reported Outcomes (BoMA-PRO) multicentre study.

Follow-up questionnaires will be posted to participants at regular intervals (three, six, nine, 12, 18, and 24 months) from recruitment date. Due to the high mortality in this patient group, the research team will confirm via electronic records/the participant's GP that they are alive and well enough to approach before sending out each follow-up questionnaire. Questionnaires returned by participants will be reviewed within three working days to identify any clinical problems requiring action (e.g. a patient experiencing significant pain or a deterioration in their mobility).

Consent and confidentiality. Patient records will only be reviewed by the research team after the participant has returned a valid and signed consent form. All analyses will be on linked, anonymized data to prevent risk of unintended disclosure outside the research team.

Outcomes. The primary outcome measure for this study is QoL as measured by the European Organisation for Research and the Treatment of Cancer Quality of Life questionnaire[19] (EORTC-QLQ) C30 question: "How would you rate your overall quality of life during the past week?" at three months post-surgery for MBD. Full details of secondary outcome measures are listed in Table I.

The EORTC QLQ-C30 and adjunct BM22[20] questionnaires were chosen for the primary outcome measure as they are bone-metastasis-specific PROM tools with the most comprehensive research evidence[19,20] The bone tumour-specific Musculoskeletal Tumor Society Score (MSTS) was chosen to measure function due to its validation in the MBD population, significant evidence base, and comparable validity and utility to the alternative TESS and PROMIS scores.[6,11,21] The pain assessment questionnaires used in the study include the visual analogue scale[10] (VAS) and the Functional Assessment of Cancer Therapy in Bone Pain[22] (FACT-BP) scores. The VAS score was chosen for its ubiquity of use in the MBD literature and the FACT-BP for its validation in the MBD patient population.[22]

Follow-up. The primary study endpoint of three months post-surgery was chosen due to the high early mortality in this patient group (46% (89/195) at 90 days in proximal femoral metastases)[1] to maximize the number of patients able to participate. In order to assess the trend

Table II. Patient factors affecting outcome after surgery for metastatic bone disease.

Variables	Notes
Patient	
Age	
Sex	
Comorbidities	
Functional status	American Society of Anesthesiologists (ASA) grade[18]
Body mass index	
Oncological prognosis	Primary cancer clinical profile, Karnofsky score,[13] and number of visceral/brain metastases[12]
Disease	
Primary cancer diagnosis	According to primary site (and histopathology if available)
Primary cancer grade	(Histopathology if available)
Primary cancer stage	Assessed via recent (last six months) chest radiograph, systemic body imaging (CT chest/abdomen/pelvis) and/or nuclear medicine bone scan
Metastases yes/no	Assessed via recent (last six months) imaging as above
Location of metastases	Assessed via recent (last six months) imaging as above
Current/recent chemotherapy	
Current/recent radiotherapy	
Current/recent hormone therapy	
Lesion	
Lesion site, size, and shape	Assessed via recent (last 30 days) imaging of affected area: radiograph, CT, or MRI
Single/multiple lesions within affected bone	Assessed via recent imaging (last 30 days) as above
radiograph appearance (e.g. lytic / sclerotic / mixed)	Assessed via recent imaging (last 30 days) as above
Completed fracture?	Assessed via recent imaging (last 30 days) as above
Speed of lesion growth	Assessed via two recent images of affected area (radiograph, CT, or MRI) at least 30 days apart
Mirels score	Scoring system used for estimating risk of pathological fracture incorporating radiological and clinical parameters
Surgery	
Delay from referral to surgery	Date of surgery minus date of first documented referral to orthopaedics
Preoperative optimisation of biochemical abnormalities	(e.g. transfusion in Hb < 100, antibiotics for infection etc.)
Type of surgery	Type of surgery procedure as documented on operation note
Use of cement adjunct?	As documented on operation note
Confirmation of diagnosis using intraoperative pathology samples?	(Histopathology from intraoperative specimens if available)
Perioperative complications	Perioperative complications as documented on electronic patient records and national imaging archive (e.g. infection, bleeding, nerve damage/CRPS, iatrogenic fracture, thromboembolism)

in outcome over a wider postoperative period, PROM follow-up will be conducted up until two years post-recruitment date and remote analysis of patient electronic records (for objective outcomes including mortality and revision surgery) until five years post-recruitment date.

Sample size. The study is powered to assess both the primary and secondary objectives, including identifying the association of ten independent variables (Table I) on quality of life at three months after orthopaedic surgery for MBD. Using Green's rule-of-thumb method incorporating 0.8 power (80% chance of rejecting null hypothesis) with ten independent variables, n = 104+ k (k = number of independent variables), a target sample size of 114 participants completing three-month follow-up is required to power the study.[16] Based on the calculated potential patient cohort in the six centres, of the 465 patients referred to orthopaedics for MBD over a one-year period, 326 will undergo surgery for their bony metastasis. We will aim to recruit all of these potential participants. With a calculated attrition rate of 10% and three-month survival of 54%,[1] we estimate that 158 participants will complete three-month follow-up to meet our primary objective. We have the funding to continue data collection for up to two years if required to ensure minimum necessary numbers are met for this study.

Data analysis and missing data. If participants do not reply to two consecutive postal follow-up packs, they will be removed from the prospective arm of the study but their previous data will be retained unless they request that this is removed. They will continue to be followed up remotely via electronic patient records. Because of the high mortality in this patient group, it is estimated that less than 20% of participants will complete the study to final follow-up and this will be accounted for in the final analysis.

Numerical data will be reported using range and measures of central tendency (mean and SD for parametric data, median and interquartile range (IQR) for non-parametric data). Where study groups are directly compared with one another, dataset analysis will comprise the chi-squared test for categorical variables

and the t-test or non-parametric Wilcoxon test as appropriate for continuous variables (paired or independent as appropriate, significance $p < 0.05$).

Ethics. This protocol has been approved by the Newcastle & North Tyneside 2 Research Ethics Committee (REC ref 19/NE/0303) and received Research & Development (R&D) office for every participating health board. The initial approval was granted on 27 September 2019 and an amendment to change to a postal-only recruitment strategy was approved on 25 August 2020 (ref 19/NE/0303/AM03).

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Discussion

This will be the first powered study worldwide to investigate patient-reported outcomes after orthopaedic treatment for bony lesions due to systemic cancer. We will also seek to correlate a list of key patient variables with outcome after surgery. This will provide better information for shared decision-making and the opportunity to intervene where patient factors are modifiable. We expect to identify areas in which orthopaedic practice in managing MBD could be improved with a view to improving care for all these patients.

Supplementary material

The supplementary material includes the letter of Invitation to participate in study, the participant information sheet, informed consent form (ICF), and baseline questionnaire for upper/lower limb

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Author information:
- S. Downie, MRCS (Ed) MBChB, Honorary Clinical Fellow
- M. Moran, FRCS (Orth), Consultant Orthopaedic Oncology Surgeon
- A. H. R. W. Simpson, PhD, FRCS (Orth), Professor
  Orthopaedics and Trauma Department, The University of Edinburgh, Edinburgh, UK.
- A. Stillie, FRCP, Consultant Clinical Oncologist, Department of Clinical Oncology, Western General Hospital, Edinburgh, UK.
- C. Sudlow, PhD, Head of Centre for Medical Informatics, Division of Clinical Neurosciences, The University of Edinburgh, Western General Hospital, Edinburgh, UK.

Author contributions:
- S. Downie: Conceptualized the study, Developed the methodology, Gained ethics approval, Planned the analysis, Prepared and edited the manuscript.
- A. Stillie: Developed the methodology, Reviewed and edited the manuscript, Supervised the study.
- M. Moran: Developed the methodology, Reviewed and edited the manuscript, Supervised the study.
- C. Sudlow: Developed the methodology, Reviewed and edited the manuscript, Supervised the study.
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Ethical review statement:
- This protocol has been approved by the Newcastle & North Tyneside 2 Research Ethics Committee (REC ref 19/NE/0303) and the study is funded by the Royal College of Physicians and Surgeons of Glasgow and the Association for Cancer Surgery (BASO-ACS).