PALIATIA
revista de ingrijiri paliative

PALIATIA
journal of palliative care

Vol. 17 / No. 3 / July 2024 https://www.paliatia.eu

Factors influencing quality of life in cancer patients with bone metastases

Marian Drogoman

[1]Institutul Regional de Oncologie Iaşi, România

Abstract

Introduction: Bone metastases are a fairly common complication of cancers such as breast, prostate, or lung cancer, these sites are also the most common sources of bone metastases, to which it also joins others such as thyroid and kidney cancer. With advances in the management of both solid tumors and their bone metastases, an improvement in patients' quality of life has also been achieved, however, patients with bone metastases have a deterioration in quality of life under the impact of certain factors that occur during the course of the disease.

Purpose: This literature review aims to highlight the main factors involved in affecting the quality of life of oncological patients with bone metastases by processing data from the most relevant publications, as well as establishing unexplored areas and issues in previous research.

Materials and methods: PubMed, Google Search Engine (Google Academic), Frontiers, SpringerLink, ResearchGate, BMC Cancer, Elsevier were used to identify relevant publications. The criteria for the inclusion and exclusion of publications have been established. After identifying all studies by searching the databases, they were included in the PRISMA diagram. Of the 127 studies identified, 21 were included in the literature review.

Discussion: Of the quality-of-life assessment tools in patients with bone metastases, the QLQ-C30 questionnaire was found to be most commonly used in the studies, to which is added the additional questionnaire QLQ-BM22, prepared to complete the evaluation. Among the determinants identified in the studies as having an impact on quality of life were: gender, performance status and primary tumor histology. Other factors with significant impact were: age, level of education and employment status. Psychological symptoms such as helplessness, depression and anxiety were also common. These problems have interfered with the relationships and social activities of patients.

Conclusions: The studies included in the literature review provide an overview of the many important factors involved in affecting the quality of life of oncological patients with bone metastases, including, as well as the presentation of less studied aspects that might have interference with the quality of life of these patients. Also, this literature review provides landmarks to new unexplored directions in order to identify new factors that impact the quality of life of patients with bone metastases.

Keywords: bone metastases, cancer, quality of life, pain, investigations, treatment, factors involved.

Rezumat

Introducere: Metastazele osoase reprezintă o complicație destul de frecventă a unor tipuri de cancer precum cancerul de sân, prostată sau plămân, aceste localizări fiind și cele mai frecvente surse de metastaze osoase, la care se mai alătură și altele precum cancerul tiroidian și renal. Odată cu progresele înregistrate în managementul atât al tumorilor solide, cât și al metastazelor osoase ale acestora, s-a obținut și o îmbunătățire a calității vieții pacienților, cu toate acestea, pacienții cu metastaze osoase prezintă o deteriorare a calității vieții sub impactul anumitor factori care intervin în cursul bolii.

Scopul: Această revizie de literatură își propune să scoată în evidență principalii factori implicați în afectarea calității vieții la pacienții oncologici cu metastaze osoase prin prelucrarea datelor din cele mai relevante publicații, precum și stabilirea unor domenii și aspecte neexplorate în cercetările anterioare.

Materiale și metode: Pentru identificarea publicațiilor relevante au fost utilizate bazele de date PubMed, Google Search Engine (Google Academic), Frontiers, SpringerLink, ResearchGate, BMC Cancer, Elsevier. Au fost stabilite criteriile de includere și excludere a publicațiilor. După identificarea tuturor studiilor prin căutare în bazele de date, acestea au fost incluse în diagrama PRISMA. Din cele 127 de studii identificate, au fost incluse în revizia de literatură 21.

Discuții: Dintre instrumentele de evaluare a calității vieții la pacienții cu metastaze osoase, chestionarul QLQ-C30 s-a dovedit a fi cel mai des utilizat în studii, la care se adaugă chestionarul suplimentar QLQ-BM22, elaborat pentru completarea evaluării. Printre factorii determinanți identificați în studii ca având impact asupra calității vieții au fost: sexul, statusul de performanță și histologia tumorii primare. Alți factori cu impact semnificativ au fost: vârsta, nivel de studii și statusul de angajare în câmpul muncii. Simptomele psihologice, cum ar fi neputința, depresia și anxietatea au fost, de asemenea, frecvente. Aceste probleme au interferat cu relațiile și activitățile sociale ale pacienților.

Concluzii: Studiile incluse în cadrul reviziei de literatură oferă o imagine de ansamblu asupra multiplilor factori importanți implicați în afectarea calității vieții pacienților oncologici cu metastaze osoase, precum și prezentarea unor aspecte mai puțin studiate care ar putea avea interferențe cu calitatea vieții acestor pacienți. De asemenea, această revizie de literatură oferă puncte de reper spre noi direcții neexplorate în vederea identificării unor noi factori cu impact asupra calității vieții pacienților cu metastaze osoase.

Cuvinte cheie: metastaze osoase, cancer, calitatea a vieții, durere, investigații, tratament, factori implicați.

Introduction
Bone metastases are a fairly common complication of cancer. Breast and prostate cancers are the most common cancers to develop bone metastases, with an incidence of 75% and 68% respectively. In addition, lung, thyroid and renal carcinoma develop bone metastases in about 40% of cases. Bone metastases have been reported in 70-85% of cancer patients at autopsy. [1]
With advances in effective systemic treatment, survival of patients with bone metastases has substantially improved. It is estimated that the prevalence of patients with bone metastases has doubled during this time. Certain sub-groups of patients with bone metastases (e.g. breast and prostate cancer with predominantly bone or bone-only metastases) have life expectancies ranging from 2 to 5 years. Successful management of bone metastases in these years is essential to reduce skeletal complications and maximize patients' quality of life (QOL). [2]

Aim of the literature review
- To identify factors influencing quality of life in patients with bone metastases;
- To identify areas unexplored by previous research.

Research question for the literature review
What factors influence quality of life in cancer patients with bone metastases?

Search method (keywords, databases etc)
Keywords: bone metastases, cancer, quality of life, pain, investigations, treatment, factors involved.
Databases: PubMed, Google Search Engine (Google Academic), Frontiers, SpringerLink, ResearchGate, BMC Cancer, Elsevier;
Inclusion criteria:
- Studies evaluating patients with bone metastases;
- Studies available in full text;
- Quality of Life Questionnaire (QOL) was used;
- Investigation and treatment data were available;
- Factors impacting quality of life were uncovered.

Exclusion criteria:
- Studies with incomplete data on extension/confirmation of bone metastases;
- Studies evaluating one type of treatment on bone metastases or comparing different types of therapies;
- Studies in which the QoL questionnaire was not used.

Prisma Diagram

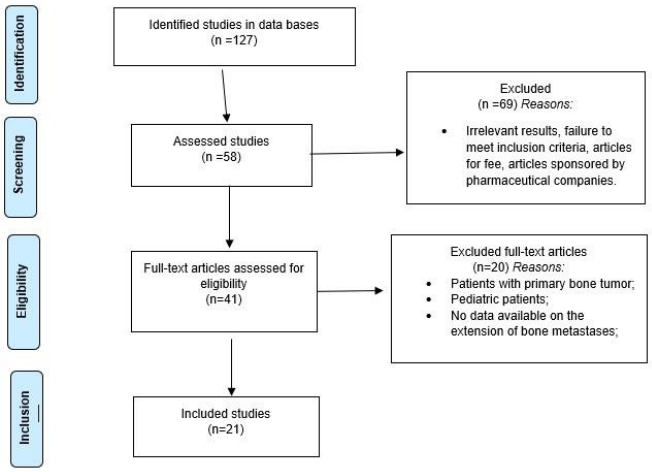

Table with included studies

Author/year	Study type	Aim	Results
Shchelkova et al. 2020	Questionnaire	Identification of psychological factors influencing quality of life (QoL) in patients with bone metastases	Such personality characteristics as a tendency to transfer responsibility, low personal resources, avoidant problem-solving behaviour, low conscientiousness and social dependence decrease QoL in patients with bone tumours.
Wong et al. 2013	Retrospective study	Identification of factors influencing quality of life (QoL) in patients with bone metastasis.	Factors identified were: performance status, sex, age and histology of the primary tumour.
Anwar et al. 2022	Cohort study	Identification of risk factors and predictors of bone metastasis in a population of breast cancer survivors initially diagnosed at advanced stages and at high risk of recurrence.	Bone metastases are relatively high in breast cancer patients diagnosed at advanced stages. Luminal A subtypes with multiple metabolic comorbidities and lobular histology are associated with higher risks of recurrent bone metastases.
Tharmalingam et al. 2022	Literature review	Better understanding of QOL instruments used in bone metastasis studies.	A total of 24 different instruments were used to assess QOL, including pain rating scales, validated QOL instruments and study-designed questionnaires.

Liu et al. 2022	Cross-sectional study	Investigation of quality of life and mental health status and identification of relevant risk factors among patients with advanced cancer with spinal metastases.	Patients with advanced cancer with spinal metastases suffer from poor quality of life and severe anxiety and depression, particularly among patients aged 60 years or older and younger than 70 years. Early mental health care and effective measures should be performed in patients with advanced cancer with vertebral metastases, and more attention should be paid to the care of patients aged 60 years or older and <70 years in terms of quality of life and mental health status.
Wolf et al. 2016	Retrospective study	Overall survival (OS), bone survival (BS - time from first diagnosis of bone metastases to death) and prognostic factors in patients with stable and unstable spinal bone metastases from solid tumours were assessed	This study found no difference in SB or OS between patients with stable and unstable bone metastases in different cancer types. However, prognostic factors differ between the two groups, and stability should be taken into account in treatment decisions.
Knapp et al. 2023	Descriptive study	The incidence and predictive factors for bone metastases by demographic and tumour characteristics were calculated	Approximately 5% of patients with solid tumours have bone metastases at presentation. In addition to T and N stage, there are several risk factors for bone metastases depending on the site of the primary tumour.
Yucel et al. 2015	Retrospective study	Demonstration of the negative impact of a tumour mass in a large cohort of patients with metastatic bone cancer	According to multivariate analysis, the presence of bone metastases with a tumour mass was found to be an independent prognostic factor (p =0. 011, hazard ratio: 1.62, 95 confidence interval: 1.11-1.76). Bone metastases with a tumour mass were more strongly associated with osteolytic lesions, other primary diseases (except primary breast and prostate cancers) and spinal cord compression
Bollen et al. 2014	Cohort study	The objective of the study was to identify prognostic factors associated with survival in patients with symptomatic spinal bone metastasis (SBM) and to create a validated risk stratification model	A total of 1043 patients were studied. The most prevalent tumours were breast (n = 299), lung (n = 250) and prostate (n = 215). The median follow-up duration was 6.6 years and 6 patients were lost to follow-up. Based on the results of the uni- and multivariate analyses, 4 categories were created. Median survival in category A was 31.2 months (95% CI, 25.2-37.3 months), 15.4 months (95% CI, 11.9-18.2 months) for category B, 4.8 months the same (95% CI, 4.1-5.4 months) for category C, and 1.6 months (95% CI, 1.4-1.9 months) for category D. Harrell's C-statistics were calculated after the model was applied to an external data set, yielding a result of 0.69
Akezaki et al. 2021	Retrospective, observational study	This study examined changes in quality life (QOL), as well as factors affecting QOL, among patients with painful spinal metastases without paralysis for 1 month after radiotherapy	An unstable SINS score was a positive factor for global health status ($p < 0.05$). Improvement in daily activities and pain response were positive factors for physical function ($p < 0.05$). A positive effect on emotional function was was confirmed among female patients ($p < 0.05$).
Rajeswaran et al. 2023	Literature Review	The primary objective of this systematic review was to compile a list of QoL issues relevant to BM (bone metastases) and its interventions. The secondary objective was to identify common tools used to assess QoL in patients with BM and the QoL problems they fail to address.	Physical and functional problems observed in patients included pain, interference with ambulation and daily activities, and fatigue. Psychological symptoms such as helplessness, depression and anxiety were also common. These problems interfered with patients' relationships and social activities. Items not mentioned in existing QoL instruments were related to newer BM treatments, such as onset of pain, flu-like symptoms and jaw pain due to osteonecrosis.
Rustøen et al. 2005	Randomized clinical trial	The aim was to determine the extent to which pain characteristics (e.g.,	Pain severity was significantly correlated with all other variables, especially pain intensity and

		pain severity, duration, pain significance, and perceived availability and effectiveness of pain relief), psychological distress (e.g., depression), physical functioning, social functioning, and QOL are intercorrelated and to determine which of these variables are important predictors of QOL in patients with bone metastases.	duration. The most important predictors of QOL were depression, social functioning and physical functioning. Depression was found to be the most important predictor of QOL.
Coleman et al. 2014	Guideline	Providing a framework for maintaining bone health in cancer patients.	Establishing the algorithm for diagnosis and treatment of bone metastases.
Von Moos et al. 2016	Literature review	This assessment considers how the management of metastatic bone pain could be optimized in order to limit the considerable burden it can impose on affected patients	The treatment should combine antitumor therapy with BTA and analgesia. Because of their proven efficacy in improving pain, QoL and skeletal outcomes, BTA should be initiated as soon as bone metastases are diagnosed and the duration of treatment should be tailored to the benefit-risk profile of each patient. As part of a holistic approach to pain management, the complementary short- and long-term effects of these agents should be harnessed to help optimize the quality of life of these patients
Ignat et al. 2021	Cohort study	Identification of prognostic factors for overall survival and analysis of palliative radiotherapy treatment patterns (proportion of SFRT prescription and predictors of radiotherapy regimen) for bone metastases	Overall survival at 3 years was 15%. The prognostic factors associated with poor overall survival were multiple bone metastases [hazard ratio (HR = 5.4)], poor performance status (HR = 1.5), and brain metastases (HR = 1.37). SFRT prescription increased from 41% in 2017 to 51% in 2017. Predictors of SFRT prescription were poor performance status [odds ratio (OR = 0.55)], lung (OR = 0.49) and urologic primaries (OR = 0.33) and lower midbody irradiation lower body area (OR = 0.59). Spinal metastases were more likely to receive MFRT (OR = 2.09).
Lam et al. 2013	Questionnaire	The current study examines the relationships between baseline social determinants of health and medical factors and self-reported HRQOL in patients with bone metastases receiving palliative radiotherapy	Karnofsky performance status (KPS) was correlated with better physical ($p = 0.0002$), role ($p < 0.0001$), emotional ($p < 0.0001$), and social ($p < 0.0001$) functioning, and global health scores ($p = 0.0015$) and lower predicted symptom scores for fatigue ($p < 0.0001$), pain ($p < 0.0001$), appetite loss ($p < 0.0001$), and constipation ($p < 0.0001$). Increased age was predictive of better social functioning ($p < 0.0001$) and less insomnia ($p = 0.0036$), higher education correlated with better global health ($p = 0.0043$), and patients who were employed or retired had improved physical functioning ($p = 0.0004$ and $p = 0.0030$, respectively) and fewer financial challenges compared to patients who were unemployed ($p = 0.0005$).
Janssen et al. 2019	Questionnaire	To assess which factors are independently associated with physical function and pain intensity in patients with bone metastases	Patients with bone metastases have poor physical function. Physical function and pain intensity depend on tumor histology but also on potentially modifiable factors such as other disabling conditions.

Results presented narratively by themes

Bone metastases - incidence, risk factors, investigations and scores

Metastatic bone disease is most commonly seen with specific types of cancer, especially breast, prostate, lung and kidney cancers, as well as multiple myeloma (MM). The most common sites of bone metastases are throughout the axial skeleton. Bone metastases affect many patients with advanced disease and, whether lytic or blastic, often lead to skeletal complications, commonly referred to as skeletal-related events (SREs). This term (SREs) usually refers to five major objective

complications of tumour bone disease: pathologic fracture, the need for bone radiotherapy, the need for bone surgery, spinal cord compression and hypercalcemia, although the latter is often of para-neoplasic origin, especially in the absence of bone metastases. The need for radiotherapy and pathologic fractures are the most common skeletal events, reflecting the burden of bone pain and structural damage caused by metastatic involvement. These complications are associated with life-altering morbidity and can reduce overall survival (OS). In a population-based cohort study of nearly 36 000 newly diagnosed breast cancer patients followed for up to 9 years, median survival for breast cancer patients with bone metastases was 16 months, but was only 7 months for patients with bone metastases and SRE. Typically, bone events are associated with a loss of mobility and social functioning, a decrease in quality of life (QoL) and a substantial increase in healthcare costs.

Among all tumour types, breast cancer patients have the highest incidence of bone complications. In the absence of bone-targeted therapies, the mean skeletal morbidity rate, i.e. the mean number of SREs per year, in breast cancer patients with bone metastases ranged from 2.2 to 4.0.7. [3] Approximately 5% of patients with solid tumours have bone metastases at presentation. In addition to T and N stage, there are several risk factors for bone metastasis depending on the site of the primary tumour [4]. Bone metastasis as a tumour mass comparative to the disseminated form is a strong and independent negative prognostic factor for survival of cancer patients [5]. Site-based analysis has identified a high risk of bone metastases and SREs in breast cancer patients diagnosed at advanced stages, associated with luminal subtypes, multiple metabolic comorbidities and lobular histology with higher risks of recurrent bone metastases [6].

Mirel proposed a scoring system based on four characteristics: (1) lesion site; (2) lesion nature; (3) lesion size; and (4) pain. All characteristics were assigned progressive scores ranging from 1 to 3 Pathological fracture risk (Mirels classification) | Radiology Reference Article | Radiopaedia.org

Injury site includes three categories: upper extremity, lower extremity, and peritrochanteric area of the femur (peritrochanteric). These sites received increasing scores from 1 to 3, respectively. It is commonly believed that injuries in the peritrochanteric area are at high risk of fracture. It is also believed that the chances of pathologic fractures are higher for weight-bearing bones than for non-weight-bearing bones. The nature of the lesion is also subdivided into three categories with increasing scores (1-3): blast, mixed and lytic. In Mirel's initial investigation, fracture rates in the three categories were 0%, 32% and 48%, respectively. [7]

Lesion size is expressed as a fraction of cortical thickness. Progressively increasing scores (1-3) are assigned to lesion-to-cortex ratios of < 1/3, 1/3 to 2/3, and > 2/3. At baseline assessment, the rate of pathologic fractures was 0% for lesions less than 1/3 of the size of the cortex, 5% for lesions between 1/3 and 2/3 of the size of the cortex, and 81% for lesions occupying more than 2/3 of the cortex.

Pain is the only subjective variable in this classification system. Mild, moderate or functional pain are assigned scores from 1 to 3, respectively. The fracture rate was only 10% among patients with mild to moderate pain. However, all patients with functional pain progressed to a fracture. Mirel's score also reported an association between pain and lesion size.

Based on an overall score, a recommendation is given for or against prophylactic fixation of a lesion. According to Mirel's recommendation, prophylactic fixation is highly indicated for a lesion with an overall score of 9 or higher. A lesion with an overall score of 7 or less can be managed using radiotherapy and drugs. An overall score of 8 presents a clinical dilemma. The probability of fracture is only 15% and it is recommended to use clinical judgment in such cases and consider prophylactic fixation. [7]

For patients with certain types of primary tumours that are asymptomatic, but have a moderate to high risk of metastasis, skeletal scintigraphy detects metastases with high sensitivity, especially if SPECT or SPECT-CT is performed in addition.

Projectional radiography is the diagnostic method of choice to evaluate symptomatic bone lesions, to assess fracture risk, to investigate suspicious scintigraphy findings and to monitor treatment effects. If scintigraphy is positive, but plain films are negative, CT or MRI should be performed.

CT is useful if the results of other imagistic techniques are unclear (e.g., pathologic vs. non-pathologic rib fracture) and is an important means of assessing the stability of bony lesions. CT combined with SPECT enhances the specificity of scintigraphy by revealing degenerative changes.

Whole-body MRI and PET-CT are now the most sensitive and specific methods for detecting skeletal metastases. Whole body MRI is becoming increasingly available; it allows the most sensitive detection of bone marrow metastases and extraosseous tumour extension. For certain primary tumour types, PET-CT is often sufficient as the sole imaging method for staging. [8]

Assessment and factors that influence quality of life in cancer patients with bone metastases

Quality of life in patients with bone metastases is increasingly considered an essential outcome for clinical trials and patient management, and therefore good assessment tools are of growing importance. In recent years, a large number of QOL tools have been developed, including several tools for the general cancer population, among them the QLQ-C30 and QLQ-BM22 questionnaires. However, none are specific to issues associated with bone metastases. Research in the field of bone metastases has focused on pain and its associated outcomes. However, QOL is affected by many factors other than pain, including limited mobility, reduced performance, side effects and impaired functionality. [9,10] The three most important variables: depression, physical functionality and social functionality have been identified as important domains of QOL. [11,12]

Metastatic bone pain has a marked negative impact on patients' quality of life and, despite numerous therapeutic options, remains undertreated. Treatment should combine antitumor therapy with BTAs (bone-targeted agents) and analgesia. Because of their proven efficacy in improving pain, quality of life and skeletal outcomes, BTAs should be initiated as soon as bone metastases are diagnosed, and the duration of treatment should be tailored to the benefit-risk profile of each patient. As part of a holistic approach to pain management, the short- and long-term complementary effects of these agents should be harnessed to help optimize the quality of life of these patients. [13] Others characteristics such as personality have been shown to impact quality of life, such characteristics as personalities as high degree of self-awareness, personal resourcefulness, cooperation and willingness for positive reappraisal in difficult situations correspond to higher quality of life. At the other extreme, patients with low personal resources, low self-awareness, and high social dependence correspond

to decreased quality of life in patients with bone tumours. [14] Patients with advanced cancer with metastases of the spine suffer from poor quality of life and severe anxiety and depression, especially among patients aged 60 or older but less than 70 years old. [15]

The results of radiotherapy appear to be positive on the improvement of quality of life. The QOL of patients with painful spinal bone metastases showed a significant improvement in overall health and physical function at 1 and 3 months after RT, respectively. At 1 month after RT, improvements in pain relief and ADL (activities of daily living) increased QOL. Engaging in rehabilitation along with RT leads to improvements in QOL for patients with spinal bone metastases. [16,17] Also, prognostic factors of overall survival have been established for the prescription of palliative radiotherapy in spinal bone metastases, among these factors are: multiple bone metastases, brain metastases, low performance index. [17]

Factors associated with decline of quality of life in patients with bone metastases

Baseline factors such as gender, performance status and primary histology have been identified as determinant factors of QOL impairment in patients with bone metastases. Further studies that focus on current treatment (chemotherapy, bisphosphonates and radiotherapy) and spiritual well-being may identify additional factors affecting QOL. [18] The Karnofsky Index has been shown to have the greatest influence on EORTC QLQ-C30 domain scores. Age, education level and employment status had a significant impact, although on fewer domains. [19] Physical and functional problems observed in patients included pain, interference with movement, activities of daily living and fatigue. Psychological symptoms such as helplessness, depression and anxiety were also common. These problems interfered with patients' relationships and social activities. Another aspect thought influencing quality of life is related to the specificity of bone metastases as unstable or stable, with a better prognosis for the stable one. [20]

Discussions

Quality of life assessment tools are essential elements in the evaluation of patients with bone metastases, however, they are not perfect and are not able to encompass the multitude of factors involved in affecting quality of life. [9] In this context, a correlation of other variables (age, gender, comorbidities, primary tumour, extent of bone metastases, treatment, etc.) and their correlation with the results of the quality-of-life questionnaire are required to identify impact factors. [9,10,21]

Conclusions

The results of the reviewed studies provide an overview of the directions needed to determine the factors that influence the quality of life in patients with bone metastases, however, many factors remain unexplored, whose correlation with the degradation of quality of life is still not established, offering new directions for research.

References

1. Von Moos, R., Costa, L., Ripamonti, C., Niepel, D., & Santini, D. (2017). Improving quality of life in patients with advanced cancer: Targeting metastatic bone pain. *European Journal of Cancer, 71*, 80–94. https://doi.org/10.1016/j.ejca.2016.10.021
2. Jawad, M. U., & Scully, S. P. (2010). In brief: Classifications in brief. *Clinical Orthopaedics and Related Research, 468*(10), 2825–2827. https://doi.org/10.1007/s11999-010-1326-4
3. Wolf, R., Forster, R. E., Brückner, T., Bostel, T., Schlampp, I., Debus, J., & Rief, H. (2016). Survival and prognostic factors in patients with stable and unstable spinal bone metastases from solid tumors: a retrospective analysis of 915 cases. *BMC Cancer, 16*(1). https://doi.org/10.1186/s12885-016-2571-z
4. Bollen, L., Van Der Linden, Y. M., Pondaag, W., Fiocco, M., Pattynama, B. P., Marijnen, C. A., Nelissen, R. G. H. H., Peul, W. C., & Dijkstra, P. D. S. (2014). Prognostic factors associated with survival in patients with symptomatic spinal bone metastases: a retrospective cohort study of 1 043 patients. *Neuro-Oncology, 16*(7), 991–998. https://doi.org/10.1093/neuonc/not318
5. Ignat, P., Todor, N., Ignat, R., & Șuteu, O. (2021). Prognostic Factors Influencing Survival and a Treatment Pattern Analysis of Conventional Palliative Radiotherapy for Patients with Bone Metastases. *Current Oncology, 28*(5), 3876–3890. https://doi.org/10.3390/curroncol28050331
6. Chow, E., Hird, A., Velikova, G., Johnson, C., Dewolf, L., Bezjak, A., Wu, J., Shafiq, J., Sezer, O., Kardamakis, D., Van Der Linden, Y., Ma, B., Castro, M., Arnalot, P. F., Ahmedzai, S., Clemons, M., Hoskin, P., Yee, A., Brundage, M., & Bottomley, A. (2009). The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for patients with Bone Metastases: The EORTC QLQ-BM22. *European Journal of Cancer*, *45*(7), 1146–1152. https://doi.org/10.1016/j.ejca.2008.11.013
7. Tharmalingam, S., Chow, E., Harris, K., Hird, A., & Sinclair, E. (2008). Quality of life measurement in bone metastases: A literature review. *Journal of Pain Research, 49*. https://doi.org/10.2147/jpr.s4572
8. Liu, Y., Cao, X., Zhao, X., Shi, X., Lei, M., & Qin, H. (2022). Quality of life and mental health status among cancer patients with metastatic spinal disease. *Frontiers in Public Health, 10*. https://doi.org/10.3389/fpubh.2022.916004
9. Akezaki, Y., Nakata, E., Kikuuchi, M., Sugihara, S., Katayama, Y., Katayama, H., Hamada, M., & Ozaki, T. (2021b). Factors Affecting the Quality of Life of Patients with Painful Spinal Bone Metastases. *Healthcare, 9*(11), 1499. https://doi.org/10.3390/healthcare9111499
10. Lam, K., Chow, E., Zhang, L., Wong, E., Bedard, G., Fairchild, A., Vassiliou, V., El-Din, M. a. A., Filho, R. J. G., Kumar, A., Forges, F., Tseng, L., Hou, M., Chie, W., & Bottomley, A. (2013). Determinants of quality of life in advanced cancer patients with bone metastases undergoing palliative radiation treatment. *Supportive Care in Cancer, 21*(11), 3021–3030. https://doi.org/10.1007/s00520-013-1876-6
11. Macedo, F., Ladeira, K., Pinho, F., Saraiva, N., Bonito, N., Pinto, L., & Gonçalves, F. (2017). Bone metastases: an overview. Oncology Reviews. https://doi.org/10.4081/oncol.2017.321
12. Rajeswaran, T., Wong, H. C. Y., Zhang, E., Kennedy, S., Gojsevic, M., Soliman, H., Vassiliou, V., Rades, D., Bonomo, P., Lee, S. F., Chan, A. W., Rembielak, A., Oldenburger, E., Maranzano, E., Pergolizzi, S., Finkelstein, J., Larouche, J., Zhang, N., Zhang, X., . . . Chow, E. (2023). Quality of life issues in patients with bone metastases: A systematic review. *Supportive Care in Cancer, 32*(1). https://doi.org/10.1007/s00520-023-08241-0
13. Anwar, S. L., Avanti, W. S., Dwianingsih, E. K., Cahyono, R., & Suwardjo, S. (2022). Risk factors, patterns, and distribution of bone metastases and Skeletal-Related events in High-Risk Breast Cancer patients. *Asian Pacific Journal of Cancer Prevention,* 23(12), 4109–4117. https://doi.org/10.31557/apjcp.2022.23.12.4109
14. Coleman, R. E., Body, J., Aapro, M., Hadji, P., & Herrstedt, J. (2014). Bone health in cancer patients: ESMO Clinical Practice Guidelines. *Annals of Oncology, 25*, iii124–iii137. https://doi.org/10.1093/annonc/mdu103
15. Janssen, S. J., Pereira, N. R. P., Thio, Q. C. B. S., Raskin, K. A., Bramer, J. a. M., Lozano-Calderón, S., & Schwab, J. H. (2019). Physical function and pain intensity in patients with metastatic bone disease. *Journal of Surgical Oncology, 120*(3), 376–381. https://doi.org/10.1002/jso.25510
16. Heindel, W., Gübitz, R., Vieth, V., Weckesser, M., Schober, O., & Schäfers, M. (2014). The diagnostic imaging of bone metastases.

Deutsches Arzteblatt International. https://doi.org/10.3238/arztebl.2014.0741
17. Rustøen, T., Moum, T., Padilla, G., Paul, S. M., & Miaskowski, C. (2005). Predictors of Quality of Life in Oncology Outpatients with Pain from Bone Metastasis. *Journal of Pain and Symptom Management, 30*(3), 234–242. https://doi.org/10.1016/j.jpainsymman.2005.04.002
18. Knapp, B., Flanagan, M. E., Grandhi, N., Ganesh, B., Santos, G. F. C., Gao, F., Samson, P., Govindan, R., & Morgensztern, D. (2023). The incidence and risk factors predictive of bone metastases at initial diagnosis of malignancy. *Journal of Clinical Oncology, 41*(16_suppl), e18816. https://doi.org/10.1200/jco.2023.41.16_suppl.e18816
19. Yücel, B., Celasun, M. G., Öztoprak, B., Hasbek, Z., Bahar, S., Kaçan, T., Bahçeci, A., & Şeker, M. (2015). The negative prognostic impact of bone metastasis with a tumor mass. *Clinics, 70*(8), 535–540. https://doi.org/10.6061/clinics/2015(08)01
20. Olga Yu. Shchelkova et al./ 2. Personality and quality of life in patients with bone tumors *International Journal of Surgery and Medicine (2020)* 6(2):16-21 https://www.ejos.org/fulltext/136-1522315482.pdf?1706563115
21. Wong, E., Chow, E., Zhang, L., Bedard, G., Lam, K., Fairchild, A., Vassiliou, V., El-Din, M. a. A., Filho, R. J. G., Kumar, A., Forges, F., Tseng, L., Hou, M., Chie, W., & Bottomley, A. (2013). Factors Influencing Health Related Quality of Life in Cancer Patients with Bone Metastases. *Journal of Palliative Medicine,* 16(8), 915–921. https://doi.org/10.1089/jpm.2012.0623