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# Interdisciplinary approach in a patient diagnosed with prostate cancer and spine metastases

## Abstract

Prostate cancer is one of the malignant tumours in which treatment of bone metastases is a significant clinical problem. In this article 66-year-old patient diagnosed with prostate cancer and multiple metastases to all parts of the spine with accompanying neuropathic pain of severe intensity, which disabled self-moving of a patient is presented. The patient was not qualified for surgery during neurosurgeon consultation. During palliative care provision for the patient by an interdisciplinary team of Home Hospice composed pharmacology treatment of pain was introduced using oxycodone/naloxone, ketoprofen and adjuvant analgesics: zoledronate acid with calcium and vitamin D supplementation, pregabalin and dexamethasone. Stability of the spine was provided through high trunk orthosis in order to minimize the risk of spine damage associated with rehabilitation. A significant decrease in pain, constipation and anxiety intensity was achieved with an improvement of overall performance status and quality of life, which enabled a further anticancer treatment and palliative radiotherapy. The submitted case indicates on a necessity of palliative care provided by the interdisciplinary team for patients diagnosed with prostate cancer and dissemination to bones and severe pain intensity, which significantly increases a chance for obtaining satisfactory analgesia, improvement in the quality of life and a possibility of continuing anticancer and symptomatic treatment.

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**Key words:** bone pain, treatment, opioids, pain, bone metastases, prostate cancer

## Introduction

The number of patients diagnosed with malignant tumours continues to rise along with new anticancer treatment possibilities, which together with effective symptomatic management prolong overall survival [1]. Among numerous problems of contemporary oncology, which appear with prolonged survival, one of the most important is the treatment of patients with bone metastases, especially those with spine secondaries. The presence of bone metastases is

usually an evidence of advanced stage of cancer, significantly decrease patients' quality of life (QoL) and render a possibility of the development of potential life-threatening skeletal-related events (SRE), such as pathological bone fractures, including spine, spinal cord compression and hypercalcemia [2].

Bone metastases are present in 30–50% patients diagnosed with malignant tumors [3, 4], most frequently in the course of multiple myeloma (80–100%), prostate (70–75%), breast (65–75%), thyroid (50%), lung (30–40%), malignant melanoma (15–40%) and

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renal cancer (20–25%) [5–7]. Metastases are present 20-times more frequently compared to primary spine tumours [8], and the most frequent location is thoracic spine (70%), and less frequently lumbar and cervical spine [9, 10]. Regarding radiology picture, metastases may be divided into osteolytic and osteoblastic (osteosclerotic). However, due to the reciprocal influence of osteoclasts and osteoblasts bone metastases have no uniform type (i.e. exclusively osteolytic or osteoblastic). It rather may be characterized as bone metastases with predominant osteolytic (multiple myeloma, renal cancer, malignant melanoma) or predominant osteoblastic (prostate and breast cancer) [11].

Spine metastases significantly affect patients' QoL, mainly due to severe pain limiting patients' activity and performance status (PS), hypercalcemia symptoms, and also pathological fractures of vertebral bodies and paralysis induced by spinal cord compression [12, 13]. In the diagnostic process, it is important to find out whether neurology complications are present, such as movement disturbances, dysesthesia and sphincter functions. In case of sudden and recent appearance of these symptoms, it is necessary to conduct diagnostic tests and appropriate therapeutic intervention. In each case, however, in order to diminish the consequences of spine metastases, maximizing patients' PS and QoL, and achieving possible improvement, it is necessary to undertake appropriate diagnostic investigations and treatment. Due to the complexity of problems, most frequently interdisciplinary approach is required [14].

## Case presentation

67-year-old patient, a farmer, fit, professionally active, till 2014 did not need medical care. For 4 years irregularly consulted in urology outpatient clinic due to benign prostate hyperplasia. For 3 years complained about pain localized in a lumbar spine, intensifying during movements, and relieving at rest when lying. In this time patient received PRN doses of over the counter analgesics (paracetamol, ibuprofen, metamizol). In November 2017 due to the intensifying pain patient visited a family physician who diagnosed back pain, probably evoked by spondylarthrosis, and prescribed ketoprofen 100 mg twice a day as intramuscular injections.

Due to the lack of analgesic effect and a change of the pain characteristics (radiation to thighs), after 3 weeks the patient was referred to Neurology Department. An MRI (magnetic resonance imaging) scan was conducted with multiple spondylarthrosis in a majority of vertebral bodies with accompanying discopathy on levels Th1/Th2, Th2/Th3, Th8/Th9, Th12/L1, L1/L2,

L2/L3, L3/L4, L5/S1 (without features of disco-radicular conflict) and L4/L5 with narrowing of the right intervertebral foramen and pressure on nerve roots. In all thoracic and lumbar vertebra and in sacral bone multiple foci of different size have been shown, which underwent heterogenous reinforcement after contrast administration – a picture of metastases. The height of the vertebral bodies was preserved.

Additionally, enlarged lymph nodes were demonstrated in the retroperitoneal space. In an X-ray of hips coxarthrosis with both sides sub-cartilage sclerotization and narrowing of a joint aperture at the right side. The chest X-ray was normal. Concurrently PSA (Prostate Specific Antigen) was assayed with significantly risen values (total PSA > 100.0 ng/mL; free PSA > 50.0 ng/mL). Prostate cancer with spine metastases was diagnosed. The patient was consulted by a neurosurgeon who disqualified the patient from a neurosurgical intervention.

The pain was treated with transdermal buprenorphine in the dose of 35 µg/h, every 3 days and PRN 1–3 tablets per day of paracetamol with tramadol (325 mg + 37.5 mg, respectively). Additionally, dexamethasone 4 mg twice daily IV was administered. Patient with a slight improvement in analgesia according to NRS (Numerical Rating Scale) 6–7 was discharged home with a recommendation of continuing analgesic regimen and conducting prostate biopsy in Urology Department and consultation in Oncology Outpatient Clinic.

Due to severe pain, intensifying confusion, and intense constipation patient was again consulted at home by family physician who stopped buprenorphine, and reinstated ketoprofen 100 mg and dexamethasone 4 mg (both drugs administered orally twice daily), increased the dose of tramadol with paracetamol to 3 times daily 75 mg + 650 mg, respectively, and recommended glycerin suppositories PRN rectally and omeprazole 20 mg once daily orally. Due to lack of improvement patient himself increased a dose of ketoprofen till 100 mg 3–4 times a day, and additionally took ibuprofen 200 mg up to 3 times a day, metamizol 500 mg twice a day and paracetamol 500 mg 2–3 times a day orally. In Urology outpatient clinic prostate biopsy was conducted, histopathology: adenocarcinoma (Gleason 4 + 4).

At the time of starting palliative care at home (Home Hospice) the patient in general was in a quite poor condition. Due to severe pain patient's activity was significantly limited: PS according to Karnofsky 40 and ECOG 3–4 [15]. Pain according to NRS (pain right now and average pain within last 2 weeks) 9–10. The pain was localized in lumbar region depicted as burning, radiating to both lower extremities with

characteristics similar to electric shock-like sensations along the spine, which intensified during each activity — the patient was unable to stand up due to the pain. Physical examination showed limited movements of lower extremities induced by pain without radicular symptoms, weakness of proximal muscles and hyperesthesia of the skin of anterior surface of thighs, predominantly at the right side. PainDetect questionnaire result was 30/38, which confirmed a neuropathic pain component [16]. HADS–M (Hospital Anxiety and Depression Scale — Modified Version) result: depression 6/21, anxiety 15/21 — anxiety disorders [17].

Pain was managed with oxycodone/naloxone, starting from a dose of 10 mg + 5 mg, every 12 h, subsequently with good treatment tolerance the dose was increased, every few days in the following order: 20 mg + 10 mg, every 12 h → 30 mg + 15 mg, every 12 h → 40 mg + 20 mg, every 12 h. Ketoprofen administered orally at a dose of 100 mg was continued. Concurrently, pregabalin as a co-analgesic was introduced in the form of capsules, starting at 75 mg before sleep for 7 days, increasing the dose, every 7 days by 75 mg (75 mg/at night → 75 mg twice daily → 75 mg in the morning; 150 mg at night → 150 mg twice daily). Morphine sulfate immediate – release (IR) orally was used as a rescue analgesic, starting with a dose of 10 mg, increased to 20 mg, most often 60 minutes before planned hygienic procedures and rehabilitation. Dexamethasone was continued with tapering the dose to 2 mg twice daily, omeprazole was substituted with esomeprazole at a dose of 40 mg once daily (both drugs administered orally). Constipation was additionally treated with lactulose 20 ml three times daily. A significant improvement in analgesia and PS was achieved and after 2 weeks the pain intensity right now and pain on average according to NRS equaled 3–4, and the patient was able to walk without assistance at his house, using PRN 1–2 tablets of 20 mg of IR morphine sulphate per day, with improvement in anxiety. The patient had spontaneous bowel movements every 2 days.

Concurrently, zoledronic acid was introduced at a dose of 4 mg every 21 days intravenously with vitamin D (2000 U per day) and calcium (400 mg calcium carbonate daily) supplementation, with surveillance of creatinine and ionized calcium concentrations in the blood serum. The first administration of the drug-induced para-flu symptoms – treatment comprised oral administration of paracetamol 500 mg 3 times daily for 2 days with good effect. After achieving satisfactory analgesia, dexamethasone was tapered to 2 mg in the morning. The patient was referred for a consultation to Radiotherapy Unit for palliative radiotherapy of the lumbar spine.

## Discussion

The presented patient was a farmer, working on his own farm, and interpreted the occurrence of his pain as a consequence of straining associated with physical effort, as the pain intensified during movement and relieved at rest. Until the pain was not too severe and limited to a spine area, the patient took over the counter analgesics and when lacking their efficacy at a next stage — drugs prescribed by a family physician. Only the appearance of severe pain disabling movements with radiation to lower extremities and accompanying weakness of muscle strength of lower extremities was a reason for hospital admission and conducting MRI scan. A weakness of muscle strength is the second most frequent symptom present in 35–75% of patients diagnosed with spine metastases at the moment of diagnosis [18]. Usually, patients complain about a feeling of heaviness in extremities, and in physical examination motor deficits are found which may be accompanied with dysesthesia, although a function of sphincters may still be preserved in earlier stages of spinal cord compression [19].

Pain may have different characteristics, but is one of the most frequent symptoms of spine metastases and is present in approximately 90% of patients [20]. Pain usually intensifies during palpation and percussion, and it may also resemble radicular pain induced by pressure on spinal nerve roots, or it may display pain exacerbated by movement and alleviated by rest [21, 22]. Such diversity of pain characteristics is often the reason that patients are for a long time treated by family physicians, orthopedists, or neurologists with an assumption that a cause of a back pain is spondylarthrosis or discopathy, especially if in the medical history cancer was not diagnosed and patient is an active person who matches symptoms with excessive physical straining.

Diagnosis of bone metastases is possible with using several methods of imaging. X-ray is often a preliminary screening test because of common availability and low cost. A negative result, however, does not exclude the presence of bone metastases, which are clearly visible just after the destruction of nearly half of vertebral body [23]. Computed tomography (CT) is useful in the assessment of bone elements of the spine, including osteolytic or osteosclerotic changes, also a compressive fracture of the vertebral body. Main disadvantages of CT refer to the inability of differentiation of soft tissues and the necessity of contrast administration in the technic of myelography to show subarachnoid space; it is the reason why it is possible to show only 50% of changes in epidural space and in soft tissues [24]. A precise method of

spine metastases diagnosis is MRI, which allows on multidimensional imaging in high fidelity of all spine elements, including bone structures and also for the differentiation of soft tissues, which enables to show the spinal cord, radicular nerves, intervertebral discs and paravertebral muscles. Bone scintigraphy and other isotope investigations such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) in imaging of bone metastases [25] should be also mentioned, although these are less available in Poland. After diagnosing of multiple spine metastases in case of presence of neurology symptoms urgent neurosurgeon consultation is recommended [26]. The depicted patient was disqualified from a neurosurgical intervention.

During the patient's stay in a hospital, pain was treated with buprenorphine and a composite product containing tramadol and paracetamol without any effect. Such treatment with concurrent use of analgesics from all steps of the WHO analgesic ladder (paracetamol, NSAIDs, tramadol and buprenorphine), usually is not practised [27]. In the depicted patient, these drugs induced adverse effects (AE): confusion and constipation. Despite the fact that buprenorphine belongs to the strong opioids preferred in older patients as well as in the treatment of neuropathic pain [28], due to lack of satisfactory analgesia and appearance of AE the treatment was terminated. Another strong opioid which possesses evidenced efficacy in the treatment of chronic pain in cancer patients with neuropathic pain component is oxycodone [29]. However, due to the history of chronic constipation, oxycodone was used with naloxone [30], which allowed to relieve both pain and constipation. Treatment with ketoprofen was continued, and due to neuropathic pain component, pregabalin was added as a co-analgesic recommended in the management of this type of pain by the Polish Association for the Study of Pain and the Polish Association of Neurology [31, 32]. Due to the age of the patient the dose of pregabalin was carefully titrated with increments in doses every 7 days, which allowed avoiding AE.

Further improvement in analgesia with a decrease of intensity of concurrent generalized anxiety, which may be matched with an additional anxiolytic effect of pregabalin, was observed [33]. In connection with an improvement and lack of symptoms of depression in HADS-M, antidepressants (venlafaxine, duloxetine) were not used, which are also recommended in the treatment of patients diagnosed with neuropathic pain [31, 34]. Dexamethasone which was instituted at Neurology Department was continued with a gradual decrease of the dose. Such an approach was supported by a high probability of local activation of

spinal nerve roots by metastases to vertebral bodies, which was based on symptoms and results of imaging investigations [35]. Because dexamethasone was co-administered with ketoprofen, prophylaxis was instituted with proton pump inhibitor (omeprazole, which was due to a lower risk of drug interactions subsequently substituted with esomeprazole) [36].

Bone metastases increase the risk of appearance of SRE [37]. SRE in the course of prostate cancer appear with the following frequency: radiotherapy 33%, pathological fractures 25%, hypercalcemia 25%, spinal cord compression 8% and the necessity of surgical intervention 4% (combined frequency of SRE equals 49%) [38]. Bisphosphonates display anticancer properties through blocking signal transmission between cancer cells and bone cells [39]. Bisphosphonates also prolong TTSRE (time to skeletal-related event) and prevent the appearance of SRE [40]. In the depicted patient a treatment with zoledronic acid was instituted intravenously and supplementation with calcium and vitamin D given by oral route. Additionally, due to a rehabilitation of the patient, high trunk orthosis was used to decrease the risk of SRE.

In a study that was a base for registration of zoledronic acid for the treatment of patients diagnosed with prostate cancer and bone metastases, apart from anticancer treatment, zoledronate was administered intravenously at a dose of 4 mg or placebo every 21 days [40]. The primary outcome of the study was the frequency ratio of SRE in both patient groups during 15 months of the treatment. Significantly less SRE were found in the group of patients treated with zoledronate compared to those receiving placebo (33% vs. 44%). Similarly, patients treated with zoledronate had significantly longer time (median) to the first SRE (488 days vs. 321 days). Apart from the aforementioned benefits the use of zoledronate was associated with less pain intensity as well as counteracted the development of osteoporosis, already present or induced by corticosteroids and hormone manipulations [41].

Among AE of bisphosphonates administered through intravenous route should be listed electrolyte imbalance (most frequently hypocalcemia), renal function disturbances, jaws necrosis, and transient flu-like symptoms, which appear most often after the first administration of the drug. During the treatment with bisphosphonates should be conducted appropriate fluid supply, supplementation with vitamin D and calcium, and assays of electrolytes, especially ionized calcium and eGFR before each bisphosphonate administration [42–44]. Before starting treatment with bisphosphonates a dentist consultation is required, and any necessary stomatology treatment should be

instituted. During bisphosphonates treatment teeth extraction, implants institution, and other stomatology and facial–jaw surgical interventions should be avoided. Regular dental control every 3–4 months is recommended during bisphosphonate therapy [45].

Radiotherapy (RT) is deemed method of treatment of patients diagnosed with spine metastases. The aim of RT is to decrease pain intensity, improvement of patients' QoL and maintaining or improvement of bone system function. RT benefits concerning pain relief may be observed within a period of a few days to a few weeks, which should be considered in optimizing pharmacology treatment [46]. Apart from bone pain, other indications for RT in patients diagnosed with spine metastases comprise imminent or symptoms of spinal cord compression, threat or appearance of pathological fracture after surgical treatment. In the case of spine metastases transdermal vertebroplasty combined with complementary RT seems to be more beneficial compared to RT used alone in order to relieve pain, maintain the stability of the spine and improving patients' QoL [47]. Contraindications to RT are associated with a dose of former irradiation tolerated by critical organs, and in consequence lack of the possibility to repeat irradiation of a given location, which mainly refers to the spinal cord, guts, urinary bladder and very short (few days) predicted survival time [48].

In numerous randomized studies, similar analgesic efficacy of a single fraction (6–8 Gy) or multiple fractions (30 Gy in 10 fractions, 24 Gy in 6 fraction and 20 Gy in 5 fractions) was demonstrated [49,50]. Analgesic effect of RT regardless of fractionation method is observed in approximately 50–85% treated patients and in 30% of treated patients pain completely disappears [51]. A complete or partial analgesic effect of RT in patients diagnosed with bone metastases usually appears in the period of 4 weeks since RT and the mean time of remission lasts for approximately 19 weeks [52]. The response rate is higher, and the remission period is longer in patients diagnosed with breast and prostate cancer compared to those diagnosed with lung and other primary tumour locations [53].

Another treatment method that is used independently or in combination with local RT and other types of treatment in patients diagnosed with multiple spine metastases in the course of prostate cancer are radioisotopes. This treatment method is used in patients with osteoblastic or mixed metastases, sometimes before the clinical symptoms appear, which decrease the number of new pain areas and risk of pathological fractures. The use of radioisotopes decreases pain intensity and number of SRE and improves patients' QoL [54].

The treatment used improved overall PS and QoL and regained the patient self–care, which allowed to refer the patient for consultations and further treatment to Radiotherapy Unit and Urology Outpatient Clinic.

## Conclusions

Cancer patients with spine metastases often visit physicians with numerous and complex diagnostic and/or therapeutic problems that require integrated care. Diagnostic and therapeutic management requires cooperation between different specialists, including orthopedist, neurologist, neurosurgeon, radiotherapist, nuclear medicine and palliative medicine specialist, and also specialists for the treatment of cancer: urologist — prostate and renal cancer, pulmonologist — lung cancer, haematologist — multiple myeloma, oncologist — other tumours. Such physicians team should additionally cooperate with a nurse, physiotherapist, psychologist, social worker, medical career and a chaplain. The additional condition that is necessary to improve patients' QoL, independent from a prognosis, is a provision of appropriate coordination of care and integration of proposed treatment. Such an interdisciplinary approach gives a chance for better care for a patient in a difficult clinical situation as the presence of multiple spine metastases is.

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