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Research Article

Management of Vertebral Metastases in Prostate Cancer: A Retrospective Analysis in 119 Patients Chu hassan II of fez

O,SIYOURI[1*], J,CHOUEF[2], H,EL HILALI[3], S,ELHAKYM[4], C,CHBIHI[5], L,AMAADOUR[6], K,OUALLA[7], Z,BENBRAHIM[8], S,ARIFI[9], N,MELLAS [10]

[*]**Correspondence to**: Siyouri Oumaima, Department of Oncology, Moracco.

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Abstract

The objectives of this study were to define clinical problems and treatment strategies in vertebral metastases of prostate cancer. The clinical files of 634 patients with prostate cancer seen in a comprehensive cancer center during a 5-year period were retrospectively reviewed. One hundred nineteen patients (18.8%) had 212 significant episodes of osseous spinal metastases. Pain was nearly universal (93%), and motor and bladder impairment occurred in 25% and 3.1% of patients, respectively. Bone scan and magnetic resonance imaging (MRI) were performed in 197 and 64 episodes, respectively. Fifteen episodes of spinal cord compression were treated surgically. Other treatments included hormonal therapy (163 episodes), chemotherapy (70 episodes), and radiation therapy (103 episodes). Osteolytic lesions were observed alone and in combination with osteoblastic pattern in 18% and 26% of episodes, respectively. Bone scan was the most effective screening procedure of vertebral involvement, and MRI effectively showed epidural involvement. Overall treatment led to improvements in pain and motor impairment in 77% and 50% of patients, respectively. However, clinical episodes were recurrent (1.78 episodes per patient; range, 1-8). Median survival after vertebral metastasis episode was 14 months compared with only 4 months after surgery for spinal cord compression. Vertebral metastases strongly alter quality of life in patients with prostate cancer. Pain and neurologic complications are the major problems. Careful early screening with bone scan and MRI may help to define better treatment strategy. However, further prospective studies of clinical management are needed to determine the optimal timing of radiation therapy, medical treatments, and surgery.

Introduction

Metastatic prostate cancer, an incurable disease, is a permanent therapeutic challenge because of complications that may arise in the course of its evolution. Prostate cancer is also one of the most frequent cancers in developed countries, including France,1 where this disease and its complications are a significant public health problem. More than 80% of patients with metastatic development will have vertebral metastases during the

course of disease evolution.2

The major problem of osseous vertebral metastases is pain control, but 6.7% of patients will also present with spinal cord compression (SCC).3-7 Consequences are neurologic complications (pain, motor deficit, immobility, sphincter dysfunction) and, eventually, a strong decrease in quality and duration of life. Vertebral metastases of prostate cancer were largely reviewed in the past 10 years.2,3 More specific studies also investigated the biologic and molecular characteristics of metastases and metastatic bone metabolism in this disease.8-10

We designed a retrospective study of patients with prostate cancer and vertebral metastases treated at the hospital of oncology of the CHU HASSAN II, fez, over a 5-year period with the aim of focusing on clinical problems that remain to be solved.

Patients and Methods

We analyzed the clinical records of all consecutive patients with prostate cancer referred to or treated at the hospital of oncology of the CHU HASSAN II, fez, between January 2018 and March 2023, which totaled 634 patients. Each clinical file was reviewed, and those of patients with vertebral metastases were selected (n = 119). All consecutive significant episodes of osseous vertebral problems in this group of patients were analyzed, including episodes that occurred before January 2018 or after March 2023 (212 episodes). We defined episodes as symptomatic or asymptomatic (eg, new symptoms or discovery of new metastases) or requiring new diagnostic investigations or different and specific therapeutic interventions. We did not consider significant episodes that required no further diagnostic investigation or treatment, such as the progression of a known vertebral lesion during treatment. Over this 5-year-period, the hospital database included 634 patients with prostate cancer. We excluded patients with localized cancer as well as patients without vertebral metastases, patients with prostatic cancers of non-adenocarcinoma histology (3 cases of prostatic sarcoma), patients with benign spinal disease (2 patients with osteoporosis), patients referred for a specific diagnostic procedure (52 patients undergoing bone scan only), and patients undergoing punctual treatment with particular techniques (radiopharmaceuticals, radiation therapy) with no long-term follow-up (n = 76). Patients with concurrent prostate adenocarcinoma and other cancer types were also excluded (n = 36), as were 3 patients with incomplete data.

The date of study entry was the date of first manifestation, or first evidence, of vertebral metastasis. The date of last consultation or the date of death was considered for the calculation of follow-up and survival. We did

not review radiologic images but took radiologic reports into account. Clinical files were reviewed for the presence of symptoms: somatic pain, pain at nervous roots, defective sensibility, impaired motility, and bladder dysfunction. Patients with SCC were those with most specific clinical symptoms such as sensory or motor deficit and urinary dysfunction, or with minimal symptoms but with radiologic evidence of epidural compression. The effect of treatment was considered as a whole (eg, relief of both symptoms and disease). It included pain control, neurologic symptom improvement, and, in some instances, objective response on imaging. Pain improvement was assessed from significant bone pain reduction (2/10 degrees on visual analogue scale), decrease of analgesic drug dosages, and increase of Karnofsky score by ≥ 20%.

Results

One hundred nineteen (18.8%) of the 634 patients with prostate cancer were included in the study. Median patient age was 66 years (range, 49-86 years). Median Karnofsky perform ance status score was 70 (range, 30-100). The 119 patients had 212 significant episodes of osseous spinal metastases (median, 1.78 episodes per patient; range, 1-8). The interval between episodes ranged from 1 month (5 episodes) to a maximum of 69 months, with a median of 7 months. The diagnoses of prostate cancer and vertebral metastases were concomitant in 17 patients. Biologic data, including evaluation of prostate-specific antigen and markers of bone metabolism. One hundred sixteen patients (97.5%) had bone lesions outside the spine during disease evolution, and 46 (38.7%) of them had other nonosseous lesions. We screened spinal segments involved in each episode. One hundred ninety-eight significant episodes were symptomatic. Symptoms revealed vertebral metastases in 102 patients in whom they were markers of disease progression. Twenty-nine episodes of motor impairment occurred in 24 patients: paraplegia, paraparesis, and different combinations of paresis in 5, 14, and 10 patients, respectively. Ten patients were eventually bedridden. Spinal cord compression was more likely to occur in the upper vertebral bone spine: the incidences of SCC in the lumbar, cervical, and thoracic segments were 10.6% (17 of 161 patients), 14.9% (11 of 74 patients), and 15.7% (26 of 166 patients), respectively. Among the 5 patients with paraplegia, 4 had SCC of the thoracic segments and 1 had SCC of the cervical segments. The effect of each treatment may be difficult to differentiate because treatments were often combined. Chemotherapy was used in 70 episodes in 61 patients. In the 29 episodes with improvement, the duration of response was estimated at a median of 6 months (range, 3 to > 51 months). There was no toxic death, and side effects were moderate. The most important adverse events were neutropenic fever in 2 episodes and cardiac insufficiency in 5 patients. Radiopharmaceuticals were used in 21 episodes even though their effect was limited and short-lived (median, 2 months). External radiation therapy was delivered in 103

episodes in 72 patients. Total dose and fractionation varied depending on the patient history, the clinical situation, and the daily practice. The most common schedule was 30 Gy given in 10 fractions (53 episodes). Side effects of radiation therapy were mild. Fourteen patients had surgical treatment, 1 of whom had 2 operations. Indication of surgery was based on either clinical neurologic deficit or severe risk of neurologic impairment by SCC evaluated on magnetic resonance imaging (MRI). Finally, 6 patients had exclusive symptomatic therapy. When all treatments are combined, there were 77% and 50% episodes with pain and motor deficit improvement, respectively. However, 10 patients had permanent neurologic impairment (lasting until last followup or death). Median follow-up was 11 months for the 119 patients (range, 1-86 months). Thirty-one were lost to follow-up. Sixty-seven have died, with a median survival time of 14 months (range, 1-86 months).

Discussion

This retrospective study is based on a series of patients with vertebral metastases related to advanced prostate cancer. Published series generally refer to patients with SCC from a wide variety of cancers.10-16 The median ages of patients included in these series are similar to that presented here. We observed that vertebral involvement is a recurring complication in patients with prostate cancer, with a mean of 1.78 episodes per patient and as many as 8 different episodes in 1 patient in our series. This may be favored by prolonged evolution with several lines of treatment (2 or 3 lines of hormone therapy and chemotherapy, ≥ 2 courses of radiation therapy, as well as other palliative treatments). The rate of initial prostate cancer diagnosis (14.3%) associated with the diagnosis of vertebral metastases in our series is similar to the 12% rate published in other series.4

All published studies of SCC related to prostate cancer that included. The results in patients included in our series are also given under 2 categories: the whole patient population and the subgroup of patients with surgical treatment. Of note, the 3 series published in the literature concern exclusively patients with clinical SCC.5-7 The distribution of spinal lesions in our group of patients is similar to that of other series. The affinity of prostate cancer for the axial skeleton has been well described; sites most often involved are, in descending order of frequency, the pelvis, the thoracolumbar spine, and cervical areas.15,17 This specific distribution of bone metastases may be explained by the existence of paravertebral Batson venous plexus18 and the retrograde deposit of prostatic cells in lumbar and sacral bones. Other authors have favored an arterial distribution of metastases.19 Anatomic considerations are insufficient to account for a biologic mechanism that was first conceptualized by surgeon Stephen Paget in the “seed and soil theory”20 and then documented in more recent

studies.21 The diagnostic procedures used in our study were mostly conventional osseous radiography and bone scan. However, MRI was the most useful technique for investigating SCC, more precisely epidural involvement. We have found MRI particularly useful because it allows a more precise anatomic diagnosis, and it makes it possible to noninvasively visualize the whole spinal cord and signs of compression.22-25 Coletti et al have demonstrated that MRI modified treatment choice in 62% of cases of patients with metastatic prostate cancer.26 Besides, as recently pointed out by Berruti et al,27 MRI is a useful tool to make differential diagnosis with other disease.28 This was the case for 2 patients we excluded from the study because MRI revealed that they had spinal complications of osteoporosis, not of prostate cancer. Questions arise about the best strategy to be used to manage patients with prostate cancer with bone metastases. Bone scan is a good tool for screening bone metastases,22,23 but it is not known whether new techniques such as single photon emission computed tomography may improve its specificity.29 Magnetic resonance imaging may be used for screening spinal bone metastases, but this is not a validated strategy.26 Because all segments of the rachis may be involved, all should be studied.30 There are arguments in favor of screening even asymptomatic segments31 because multiple involvement is frequent.32 It is important to use well-defined diagnostic and therapeutic strategies for reducing risks and costs.22,33 However. invasive explorations such as myelography may sometimes have a role to play when MRI is contraindicated.34 Back pain is the most frequent symptom in vertebral metastatic involvement, but it is not disease-specific.13 Symptoms such as nerve root pain, sensory deficit, motor impairment, and sphincter dysfunction (bladder) are more specific to neurologic compression. However, considering the diagnosis of bladder dysfunction in a group of patients with genitourinary cancer remains difficult. More than 85% of episodes included back pain, 65% included nerve root pain, and 25% included motor deficit. The incidence of motor deficit is generally reported to be < 20%.3,35,36 Overall, we found 5.2% of patients with SCC as reported by Kuban et al.4 However, we observed that 41 of 212 of significant episodes of osseous spinal involvement (19.3%) were clinically associated with SCC. Typically, there is a major risk of compression of neurologic structures at the thoracic level mostly caused by natural kyphosis and the shrinkage of the medullary canal at this level.4 It is important to underline that vertebral lesions can produce asymptomatic SCC.31 Results of medical treatments in this series were evaluated retrospectively, reflecting general routine practice; yet, several of the patients were included in prospective trials. In spite of important biases in the report of treatment effects, results are on the order of those published in the literature. Only 18% of the patients had clinical improvement with hormone therapy, whereas a majority actually had hormone-refractory disease. Approximately 40% of the patients had symptom improvement with chemotherapy, which is on the order of results obtained in the Canadian randomized trial, which demonstrated

the efficacy of mitoxantrone for palliation.37 Results of radiopharmaceutical therapy were worse than reported in the literature,38,39 which might be because our patients were treated very late, generally after chemotherapy. We found that external radiation therapy had an excellent palliative effect for controlling localized bone pain; our results were comparable to those published in the literature.40,41 It is difficult to assess the role of radiation therapy for the prevention of local disease progression in relationship to both epidural involvement and osteolytic lesions. Homogenous series of patients with prostate cancer are not numerous. It shows the results of 1 surgical series,5 2 radiation therapy series,6,7 and our own series of patients. Surgery has been widely studied in SCC consecutive to vertebral metastases, but patient populations considered are heterogeneous, with different primary cancers and clinical symptoms. Generally, indication and type of surgery are analyzed on a caseby-case basis, according to the clinical characteristics of disease and patients.42 In our series, motor improvement was obtained in 5 of 9 of the whole patient population and in 1 of 5 nonambulatory patients, which is worse than results reported by Shoskes and Perrin5: 82% and 62%, respectively. The optimal surgical approach is a subject of controversy. There is no evidence of the superiority of other techniques over laminectomy.42 In our series, 10 episodes were treated by laminectomy only; 4 patients had additional stabilization, and 1 patient had corporectomy and stabilization. It is noteworthy that, on 9 occasions, radiation therapy was performed after surgery, whereas it was performed 3 times before surgery, and wound-infection complications occurred in 1 patient. Percutaneous vertebroplasty was not used in our series.43 As a whole, a good palliative effect was achieved in this patient group, with 77% pain control improvement and 50% motor function improvement. The median survival was 14 months, which is similar to durations reported in the literature.3,5-7 Evaluation of treatment results is difficult,44 but the most important issues are pain control and quality of life. However, objective response is important7 and may prevent recurrence, which is characteristic of this clinical situation.32 Because metastatic prostate cancer remains an incurable disease, symptom care and quality of life are the most important issues to consider in this patient population.37,45-47 However, these are difficult to assess in the retrospective setting and would be better measured prospectively in the course of patient management. Biologic variables indicative of disease evolution, malnutrition, and bone metabolism were also investigated. We observed wide variations of alkaline phosphatase and prostate-specific antigen serum levels, revealing different biologic behaviors of the tumor. A majority of patients had hypoproteinemia, which is in relation with malnutrition. Although bone metabolism markers were not specifically studied in this retrospective series, 19.4% of the patients had hypocalcemia, which was certainly related to hypoproteinemia, and 12% and 9.7% had hyper- or hypophosphatemia, respectively. The 2 major metabolic disorders observed in prostate cancer are osteomalacia and osteoporosis.

Osteomalacia is frequent,48 but the most important bone disorder is osteoporosis, which induces a decrease in bone density49 and secondary bone fractures.50 The use of bisphosphonates for osteoporosis prevention and treatment is under evaluation.51 However, the effect of bisphosphonates on quality of life has not yet been demonstrated in this disease.

Conclusion

Vertebral metastases are a major problem in the evolution of prostate cancer. They induce quality of life impairment and are often a major factor of dependence. Pain is the most frequent symptom, which, by itself, requires a specific treatment. But behind the symptom, it can indicate severe complications such as SCC, which is caused by osteolytic lesions of the vertebra or epidural involvement by the tumor. It is thus highly recommended to screen vertebral metastases as early as possible using a radionuclide bone scan and to precisely study bone involvement by MRI. However, it is not well known whether early radiation therapy on involved sites has a preventive effect on further neurologic complications even though it is very active on pain. Thus, the exact timing of screening imaging techniques, in-depth study of bone involvement, and local treatments (eg, radiation therapy or surgery) is not known.

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