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Treatment of Bone Metastases in Urologic Malignancies

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Key Words

Bone metastases · Radiotherapy · Stereotactic · Denosumab · Zoledronic acid · Urologic neoplasms

Abstract

The skeletal system is the most common site of metastatic cancer spread. Bone metastases are often associated with severe morbidity, pain and functional impairment. Timely diagnosis and proper treatment may decrease morbidity, improve quality of life and in some cases even improve survival. External beam radiotherapy may effectively give pain relief in patients with painful bone metastases. In bone metastases from castration-resistant prostate cancer or urothelial bladder cancer, treatment with zoledronic acid or denosumab may reduce skeletal-related events. In contrast to castration-resistant prostate cancer, in patients with bone metastases from bladder cancer such treatment may even improve survival. On the other hand, the efficacy of these agents is questionable in patients with bone involvement from metastatic renal cell carcinoma or germ cell tumors. When bisphosphonates or denosumab are considered in such cases, the potential benefits of treatment should be critically weighed against the risk of side effects. In germ cell tumors, bone metastases may be cured by cisplatin-based chemotherapy, however, there are only limited data on the specific management of residual disease. Oligometastases may be treated by stereotactic radiotherapy or – especially in patients with renal cell carcinoma – by surgical resection and endoprosthetic replacement. Limited data are available on the management of bone involvement in germ cell tumors. Decisions on the resection or local radiotherapy of residual disease should be individualized considering the overall response and the feasibility and risks of resection.

Introduction

Of all organ systems, bone is the most common site of metastatic cancer spread [1]. Bone metastases may be associated with severe morbidity, pain and functional impairment. Among urologic cancers, prostate, kidney and bladder cancer are frequently associated with metastatic bone disease. About one third of patients with metastatic kidney or bladder cancer and the majority of patients with castration-resistant prostate cancer develop bone metastases [2, 3]. The incidence of skeletal-related complications may supersede the 50% level in patients with bone metastases from these tumors [2]. In recent years, several new treatment options have become available for patients with metastatic bone disease. In this article, we

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give an overview on the available evidence and discuss recommendations of current guidelines concerning the treatment of metastatic bone disease in urologic malignancies.

Palliative Radiotherapy for Painful Bone Metastases

External beam radiotherapy is an effective option for pain relief in patients with painful bone metastases. It may significantly improve symptoms in up to 80% and completely control pain in about one third of patients [4]. Various schemes of fractionation have been tested. Data from randomized trials showed that 30 Gy in ten fractions, 24 Gy in six fractions, 20 Gy in five fractions or 8 Gy in a single fraction may provide excellent pain relief with minimal toxicity [4]. Also, palliative external beam radiotherapy may be repeatedly applied in case of recurrent pain. In this situation, data from a randomized trial suggested that treatment with 8 Gy in a single fraction is not inferior and less toxic compared to 20 Gy given in multiple fractions [5]. Patients with multiple painful osteoplastic metastases which could not be conveniently and safely treated by external beam radiotherapy are candidates for radionuclide treatment [4].

Radiotherapy of Oligometastases

Traditionally, the metastases of most solid tumors have been treated as systemic disease with palliative intent [6]. In recent years, stereotactic radiotherapy of oligometastases has become a common practice [6]. The prevention of local symptoms and progression is the primary aim of stereotactic radiotherapy for oligometastases. Local control rates of up to 80% may be achieved, but cure is possible only in exceptional cases [6]. It has been hypothesized that the destruction of oligometastases may positively influence the course of the disease since relatively favorable progression-free survival rates have been reported and molecular evidence for a role of oligometastases in the further spread by the accumulation of genetic aberrations has been found [6]. Currently, a randomized trial is planned to evaluate whether stereotactic radiotherapy is actually able to improve progression-free and overall survival [6]. However, since the available evidence is limited, there are still only sparse recommendations on the use of stereotactic radiotherapy for oligometastases in the current clinical guidelines for urologic malignancies. Among the guidelines of the European Association of Urology (EAU), only in the 2014 update of those on renal cell carcinoma stereotactic radiotherapy for the treatment of bone metastases is specifically recommended [7].

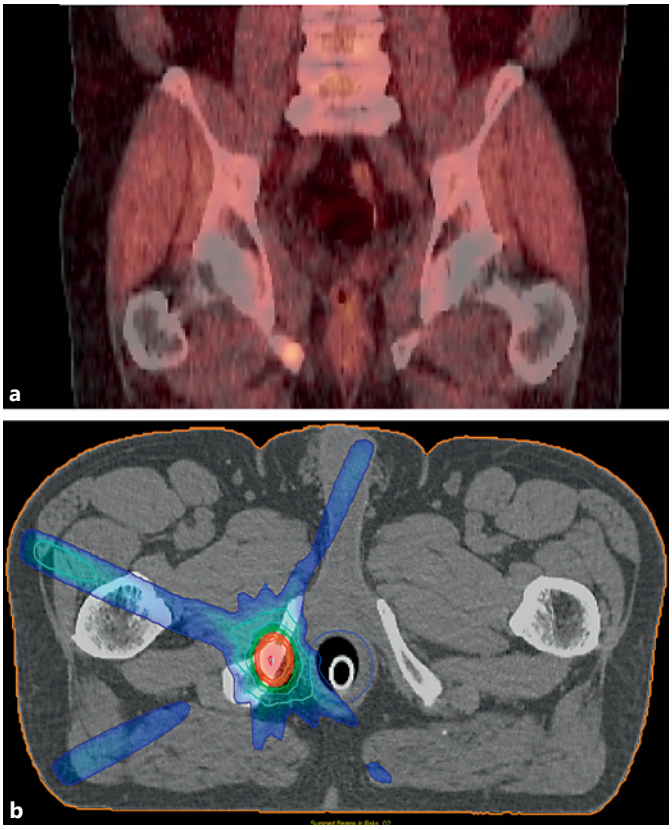

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Fig. 1. Positron emission tomography/computed tomography scan (**a**) and planning computed tomography scan for stereotactic radiotherapy (**b**) in a 49-year-old patient with a solitary bone metastasis diagnosed during workup for prostate-specific antigen persistence after radical prostatectomy for an organ-confined prostate cancer.

Prostate Cancer

The various current guidelines [8–12] give no recommendations on specific treatment of oligometastases in prostate cancer. There are data that conventional radiotherapy may effectively control pain and prevent pathologic fractures in this situation [13, 14]. Stereotactic radiotherapy for oligometastases has been suggested to prolong the time before androgen deprivation treatment needs to be implemented [15] (fig. 1). It is, however, unknown, whether conventional or stereotactic radiothera-

py of oligometastases may improve survival in patients with prostate cancer [13, 16].

Several studies have investigated the systemic treatment of bone metastases in patients with castration-resistant prostate cancer. Zoledronic acid (4 mg given intravenously once every 3 weeks for 20 cycles, i.e. 15 months) has been shown to reduce the incidence of skeletal-related events compared to placebo [17–19]. Compared with zoledronic acid, denosumab, a monoclonal antibody against the receptor activator of nuclear factor κB ligand, was associated with a greater reduction of skeletal-related events without, however, any impact on overall survival [20]. Considering overall adverse events, there was no detectable difference between both treatment arms [20]. Concerning major adverse events (osteonecrosis of the jaw, hypocalcemia, second malignancies), there was a trend towards higher rates in the denosumab arm [20]. Therefore, the choice of the agent (zoledronic acid vs. denosumab) should be carefully made considering the individual risk of severe and difficult-to-treat skeletal-related events such as spinal cord compression (of which 26 events in the denosumab arm compared to 36 events in the zoledronic acid arm were observed in the sample of 1,901 patients). While the current EAU guideline favors denosumab ('denosumab being superior to zoledronic acid' [8]) in patients with bone metastases from castration-resistant prostate cancer, the 2014 update of the German interdisciplinary S3 guideline states no preferences ('denosumab or … zoledronic acid … should be offered' [9]). Recently, an official warning about potential serious side effects (vasculitis and hypocalcemia) associated with the increased use of denosumab has been issued in Germany [21]. Particularly in patients with renal insufficiency, a critical consideration of alternatives and prophylaxis of hypercalcemia is required [21]. Generally, the expected benefit of treatment with denosumab or zoledronic acid has to be weighed against the risk of side effects [9, 22]. Current guidelines recommend prophylactic measures such as calcium and vitamin D supplementation for the prevention of hypocalcemia [8, 9] as well as pretreatment dental evaluation with the elimination of dental risks and consulting on oral hygiene [9] in order to prevent osteonecrosis of the jaw.

In patients with hormone-sensitive prostate cancer and bone metastases, zoledronic acid is probably less effective than in patients with castration-resistant disease [23]. Neither the incidence of skeletal-related events nor progression-free survival was influenced by an early application of zoledronic acid [23]. No prophylactic effect of zoledronic acid on the development of bone metastases was observed either when given to patients with high-risk non-metastatic prostate cancer [24]. In one randomized trial with an earlier bisphosphonate (clodronate), overall survival was longer compared to the placebo arm when patients with hormone-sensitive prostate cancer and bone metastases were treated [25]. This effect, however, was not confirmed in a recent study using zoledronic acid, although a trend to longer overall survival was visible in the zoledronic acid arm despite the absence of a detectable effect on disease progression [23].

There is currently no indication for a prophylactic application of denosumab or zoledronic acid to prevent the occurrence of bone metastases in patients with prostate cancer. Although in patients with castration-resistant disease without known bone metastases denosumab has been shown to delay the manifestation of bone metastases [23], denosumab has not received approval for this indication neither in the US nor in Europe [26, 27].

Treatment with the alpha emitter radium-223 is another option for prostate cancer patients with multiple bone metastases [28]. In patients with castration-resistant disease with two or more bone scan-detected metastases but without evidence of visceral metastases (with or without previous docetaxel treatment), treatment with radium-223 was associated with an improved overall survival and a better quality of life accompanied by a favorable toxicity profile (adverse events were less frequent than in the placebo arm) [28]. The 2014 update of the German interdisciplinary S3 guideline recommends offering radium-223 as a first-line treatment to patients with castration-resistant prostate cancer and bone metastases as well as a second-line treatment to such patients after receiving docetaxel [9]. Even in patients with an impaired general physical status, radium-223 may be considered an option [9]. Somewhat more reluctant statements are given in the 2014 update of the EAU guideline. According to that, the early use of palliative treatments for painful bone metastases, including radionuclide administration, is recommended; the fact that only for this radionuclide a survival advantage has been demonstrated is stressed without, however, giving a special recommendation for the use of this drug [8].

Renal Cell Carcinoma

In the case of oligometastases of renal cell carcinoma, surgical resection and/or stereotactic radiotherapy are recommended if feasible [7] (fig. 2). There is evidence from non-randomized studies that surgical resection of solitary bone metastases may improve survival in patients

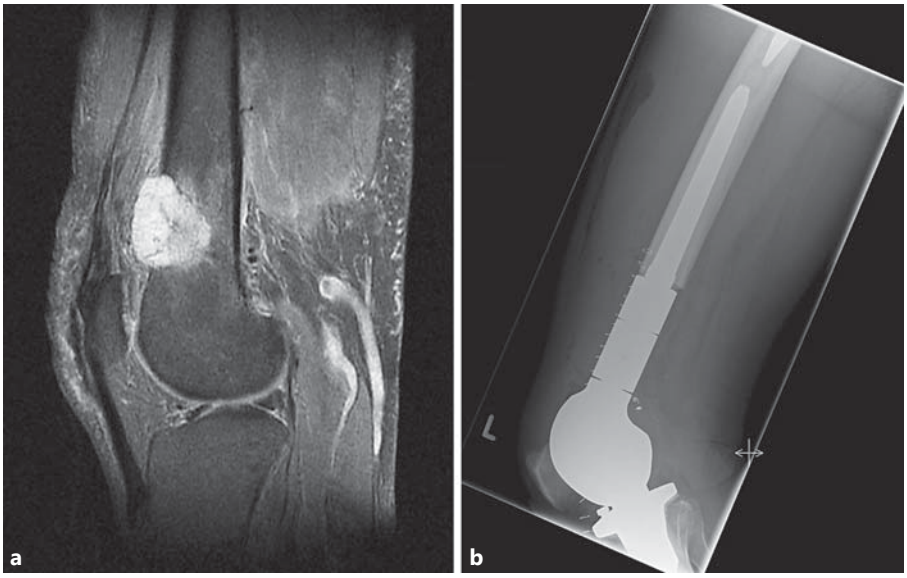

Fig. 2. Surgical resection and endoprosthetic replacement of a solitary left-sided femoral metastasis of a renal cell carcinoma 6 months after removal of the primary tumor in a 78-year-old male patient. **a** Magnetic resonance image of the femoral metastasis. **b** Plain X-ray after complete resection of the metastasis and endoprosthetic replacement. By courtesy of Dr. Christine Hofbauer.

with renal cell carcinoma [29]. Among patients who underwent endoprosthetic replacement for bone metastases from renal cell carcinoma, multiple skeletal metastases, concomitant visceral metastases and local recurrence were predictors of poor survival [30]. Despite the overall shorter survival, these factors should not preclude endoprosthetic replacement in order not to miss the chance of functional improvement since survival rates of more than 1 year may still be expected [30].

While evidence supports the surgical and/or radiotherapeutic treatment of bone metastases in renal cell carcinoma, the role of systemic bone-seeking treatment is less well defined. An early subgroup analysis of 46 patients with renal cell carcinoma enrolled in a phase III trial suggested a reduction of skeletal-related events and a trend towards improved overall survival with zoledronic acid compared to placebo [31]. This finding has been questioned by a recent pooled analysis of data from 2,749 patients with bone metastases from eight phase II or phase III trials in whom bisphosphonate treatment was not associated with improved progression-free or overall survival [32]. In the current EAU guideline on renal cell carcinoma, no recommendation for the use of bisphosphonates in patients with bone metastases is given [7].

Bladder Cancer

Bone involvement is common in patients with metastatic bladder cancer (30–40%) [33] (fig. 3). In a small randomized trial enrolling 40 patients with bone metastases from bladder cancer, patients receiving zoledronic acid had a significantly reduced risk of developing a bone-related complication and improved overall survival [34]. Furthermore, the pain score was significantly improved by treatment with zoledronic acid compared to placebo. In this small study, there was no increased incidence of side effects in the zoledronic acid arm. The current EAU guideline on muscle-invasive and metastatic bladder cancer recommends zoledronic acid or denosumab for the treatment of bone metastases of urothelial carcinoma [33]. Patients should be informed about the potential side effects and receive prophylactic treatment against osteonecrosis of the jaw and hypocalcaemia with supplementation of calcium and vitamin D [33].

Germ Cell Tumors

Patients with germ cell tumors and bone metastases belong to the International Germ Cell Cancer Collaborative Group intermediate prognosis (seminomas) or poor prognosis groups (non-seminomas) [35]. The current EAU guideline gives no specific recommendation for the management of bone metastases in germ cell tumors [35]. Bone involvement is a rare event in patients with germ cell tumors (incidence approximately 0.5% at primary diagnosis [36]) and only a few studies on the clinical management have been published. In one series including 19 patients with bone involvement (13 primary and 6 relapsed tumors) treated by conventional chemotherapy, no information on the further management of the bone

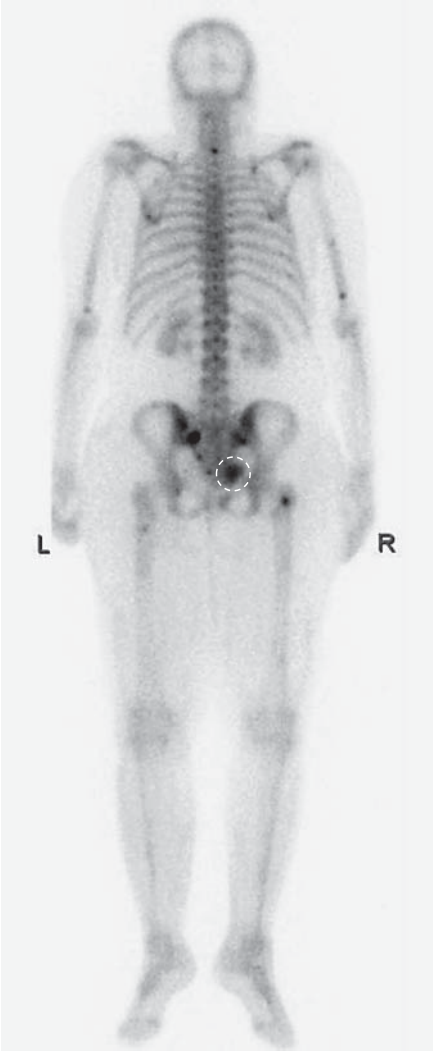

Fig. 3. Bone metastases in a 47-year-old female patient 39 months after radical cystectomy and orthotopic ileal neobladder for locally advanced node-negative bladder cancer (the circle indicates the activity accumulation in the neobladder). Treatment consisted of chemotherapy with gemcitabine and cisplatin and infusions of zoledronic acid. By courtesy of Dr. Klaus Zoephel.

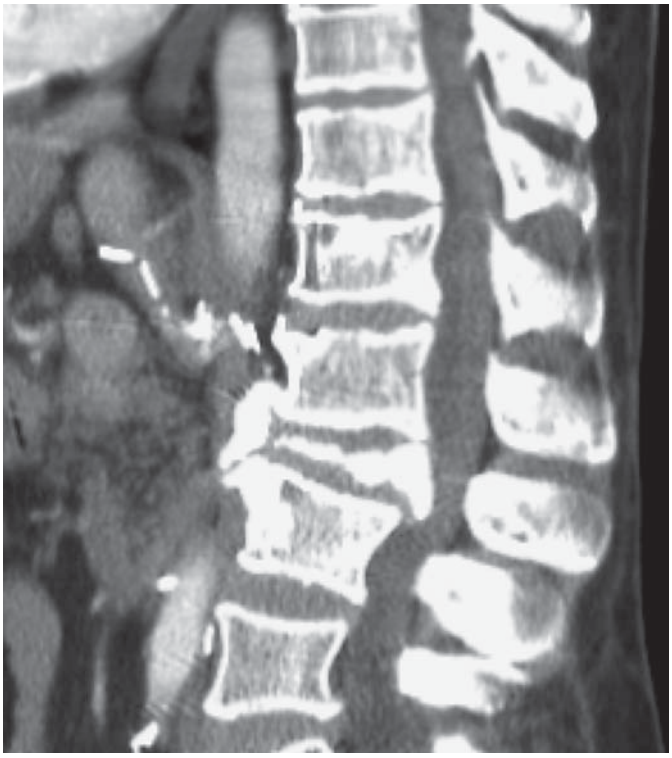

Fig. 4. Computed tomography scan of the spine 93 months after the beginning of emergency simultaneously given radiochemotherapy for extensive spine involvement by a metastatic extragonadal nonseminomatous germ cell tumor causing paraplegia. The patient experienced full functional recovery and was free of disease at the last contact 131 months after primary diagnosis (patient 2 in table 1).

lesions after initial chemotherapy was given [36]. In the largest series available which included 40 patients with primary bone metastases from germ cell tumors (all had non-seminomas) who underwent primary high-dose chemotherapy, long-term progression-free survival was achieved in 63% of patients [37]. In this study, the overall treatment response rate (85%) was identical in patients with and without metastatic bone involvement. Of the 40 patients, 8 (20%) underwent radiotherapy for selected bone metastases and only 4 (10%) underwent post-chemotherapy resection of bone lesions revealing necrosis in all cases. Four patients with primary bone metastases relapsed with the tumor recurrence involving bone in all cases. All four patients died of their recurrent disease despite salvage treatment. None of these patients had symptomatic extraosseous disease at relapse and none had undergone additional local treatment for bone metastases after primary high-dose chemotherapy. In this series, no patient without primary bone involvement (out of 434 poor-risk patients) experienced recurrence in bone. It is unknown to which degree these data may also apply to patients with bone metastases treated with conventional first-line chemotherapy, a population for which few outcome data are available [37]. Since only patients without additional treatment of bone metastases after initial high-dose chemotherapy experienced bone relapse, the authors speculated on the usefulness of a more aggressive approach to bone metastases. On the other hand, all patients with resected residual bone disease after primary

Table 1. Treatment details and outcome parameters in six unselected patients with bone metastases from non-seminomatous germ cell tumors treated at the University Hospital Dresden (updated and supplemented from [38])

Patient No.	Age, years	Location	Histology	AFP, ng/ml	β-HCG, U/l	Treatment for bone metastases after first-line chemotherapy	Histopathology, residual tumor	Follow-up[a], months	Outcome
1	25	spine	chorionic carcinoma, embryonal carcinoma, teratoma	normal	>200,000	none	necrosis (lung), no biopsy of spine lesions done	112	ANED
2	32	spine	NA[b]	>12,000	normal	none	necrosis (retroperitoneal nodes, biopsy of spine)	131	ANED
3	19	thigh, ribs	yolk sac tumor	1,518	normal	none	complete remission (lung), no biopsy of bone metastasis done	114	ANED
4	31	spine	NA[c]	14	504,440	none	necrosis (retroperitoneal nodes), no biopsy of spine lesion done	80	ANED
5	32	spine	unclassified, probably yolk sac tumor	99,000	normal	none	mature teratoma (pelvic nodes), no biopsy of spine lesion done	8	ANED
6	42	spine	embryonal carcinoma, teratoma, yolk sac tumor	>35,000	731	none (primary progression)	NA (primary progression)	8	DOD

AFP = Alpha-fetoprotein; ANED = alive, no evidence of disease; β-HCG = β-human chorionic gonadotropin; DOD = dead of disease; NA = not available. [a] Measured from the date of initial diagnosis. [b] Extragonadal germ cell tumor, immediate simultaneous radiochemotherapy. [c] Post-chemotherapy orchiectomy: mature teratoma.

high-dose therapy had necrosis in the specimen. Therefore, it seems reasonable to individualize the management of residual bone lesions after primary chemotherapy considering the overall response and the feasibility and risks of resection of post-chemotherapy residual bone lesions. Our own experience with six unselected patients with bone metastases from non-seminomatous germ cell tumors present at primary diagnosis is shown in table 1. Altogether, the outcome was determined by the overall response of the metastatic foci to chemotherapy and was favorable in the long run, although no specific treatment was given to the sites of primary bone involvement after completion of first-line chemotherapy and in some cases removal of retroperitoneal residual tumor.

The decision on supplementary treatment for bone lesions after induction chemotherapy could be easier in patients with seminoma in whom residual bone disease is more susceptible to radiotherapy. Nevertheless, a critical appraisal of the overall response and possibly performing biopsies of suspicious residual bone lesions after completion of standard chemotherapy appears reasonable in order to avoid overtreatment. The follow-up of bone metastases after successful chemotherapy in germ cell tumors may be challenging and should consider the clinical course, tumor markers and previous imaging. Morphologic changes may persist after successful treatment [38] (fig. 4). Since the primary aim in patients with bone metastases is cure by cisplatin-based chemotherapy, there is probably no role for bisphosphonates or denosumab in most of these cases, although almost no data are available concerning this question [36].

Penile Cancer

Very few data are available on the management of bone metastases in penile cancer. The current EAU guideline does not provide a specific recommendation [39], whereas the 2014 version of the National Comprehensive Cancer Network guideline gives a rather general recommendation on palliative radiotherapy to painful metastases after chemotherapy [40]. Bisphosphonate (or denosumab) treatment appears to be a reasonable option in analogy to other squamous cell cancers as well as lung cancer [41].

Conclusion

In patients with bone metastases from castration-resistant prostate cancer or bladder cancer, treatment with zoledronic acid or denosumab may reduce skeletal-relat-

ed events. In contrast to patients with castration-resistant prostate cancer, in patients with bone metastases from bladder cancer, such treatment may even improve survival. The efficacy of such treatment is questionable, however, in patients with metastatic bone involvement from renal cell carcinoma or germ cell tumors. Oligometastases may be treated by stereotactic radiotherapy – especially in patients with renal cell carcinoma – or by surgical resection and endoprosthetic replacement. External beam radiotherapy (given in single or multiple fractions or as repeated treatment) may effectively control pain in patients with bone metastases. Few data are available on the management of residual bone disease after cisplatin-based chemotherapy in patients with germ cell tumors.

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