Incidence of atypical femoral fractures in the treatment of bone metastasis: An alert report

Takumi Kakua, Yoto Oh,⁎, Shingo Satoc, Hirotaka Koyanagib, Takashi Hiraia, Masato Yuasa, Toshitaka Yoshiia, Tsuyoshi Nakagawad, Satoshi Miyakec, Atsushi Okawaa

a Department of Orthopaedic and Spinal Surgery, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan
b Department of Orthopaedic and Trauma Research, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan
c Center for Innovative Cancer Treatment, Tokyo Medical and Dental University Medical Hospital, Tokyo, Japan
d Department of Breast Surgery, Tokyo Medical and Dental University Medical Hospital, Tokyo, Japan

ABSTRACT

Background: As the life expectancy of cancer-bearing patients has increased, more patients with bone metastasis are receiving long-term treatment with bone-modifying agents (BMAs; e.g., zoledronate and denosumab), which are a risk factor for developing atypical femoral fracture (AFF). In this study, we surveyed the risk of iatrogenic AFF using a clinical database on treatment of bone metastasis in the past 10 years.

Methods: From April 2011 through October 2019, 721 patients with bone metastasis (436 men, 285 women; mean age, 65.7 ± 12.4 years) were registered under the bone metastasis consultation system, which has been run by orthopaedic surgeons since 2011, at a university hospital in Japan. We retrospectively reviewed the database to identify patients who had received BMAs for treatment of bone metastasis, and we investigated the incidence of critical skeletal-related events (including AFF) which required surgical interventions by orthopaedic surgeons.

Results: BMAs were administered to 529 patients (73.4%). Orthopaedic surgery for the treatment of skeletal-related events was performed in 36 patients (5.0%): femur, 13 (1.8%); others, 23 (3.2%). Eight AFFs in 5 patients (breast cancer, n = 4; prostate cancer, n = 1), who all had prior exposure to zoledronate or denosumab before onset of AFF, were treated with internal fixation using intramedullary nailing. In 192 patients with no BMA exposure, critical (surgically treated) AFF was not detected. In summary, the incidence of critical AFF was 0.9% among 529 patients who received BMAs for treatment of bone metastasis, and the incidence was 6.6% when limited to breast cancer patients (4 of 61).

Conclusion: In treatment of bone metastasis using BMAs, especially for breast cancer patients, attention should be paid to the risk of developing AFFs. Routine radiographic screening for AFF might be necessary in patients with prolonged BMA use for bone metastasis, even if asymptomatic. This report alerts all physicians and surgeons involved in the management of cancer patients, especially those with bone metastasis, regarding the risk of AFF following BMA use.

1. Introduction

Patients with bone metastasis are usually treated with bone-modifying agents (BMAs) such as zoledronate or denosumab to reduce the risk of skeletal-related events (e.g., pathological fracture and spinal cord compression), which require radiation therapy or orthopaedic surgery [1–5]. The life expectancy of cancer-bearing patients, even those with distant metastasis, has increased because of recent advances in cancer treatment [6], and thus the frequency of treating cancer patients with bone metastasis is on the rise. These patients tend to receive long-term treatment with BMAs and are at risk of developing atypical femoral fracture (AFF) [7–10].

AFFs are defined as diaphyseal femoral fractures with specific features, including the following major features: 1. association with low-energy trauma or no trauma; 2. transverse or oblique fractures originating from the lateral cortex; 3. complete fracture extending through both cortices or incomplete fracture involving only the lateral cortex; 4. noncomminuted or minimally comminuted; and 5. periosteal or...
endosteal thickening of the lateral cortex [11]. AFF is considered a multifactorial condition, and its pathogenesis is reported to involve certain drugs (e.g., bisphosphonates, denosumab, proton pump inhibitors, and glucocorticoids) [11–13] as well as certain diseases [14], femoral morphology [15–18], loading stress [17–20], and bone fragility [21,22]. However, prolonged exposure to specific drugs including BMAs, which can suppress bone turnover, could be the most common etiology of AFF worldwide [12,13,23–26].

Although higher and more frequent doses of BMAs are used in the treatment of bone metastasis in general compared with treatment of osteoporosis or osteopenia [1–5,27], only a few studies have investigated the association between prolonged high-dose BMA use and AFF onset [28–30]. Also, there is inadequate clinical data on the risk of developing AFF in the treatment of bone metastasis using BMAs. In this study, we examined the incidence of AFF using a database for multidisciplinary treatment of bone metastasis in a single institution.

2. Patients and methods

2.1. Study design and setting

This study was conducted at a Japanese national university hospital with an established bone metastasis consultation system run by orthopaedic surgeons since April 2011. In this retrospective observational study, we reviewed the medical records of patients with bone metastasis who had been registered in the above consultation system from April 2011 through October 2019 at one high-volume multidisciplinary cancer research institute in Japan. This institute registers about 2600 new cancer patients annually.

2.2. Patient demographics

During the study period, 721 patients with bone metastasis (436 men, 285 women; age at registration, mean 65.7 ± standard deviation 12.4 years) were entered into the database. Primary cancer types are shown in Table 1. Lung cancer (n = 155, 21.5%) was the most common, followed by breast cancer (n = 78, 10.8%) and prostate cancer (n = 68, 9.4%). Others (n = 31) were uterine cancer, uterine sarcoma, ovarian cancer, testicular cancer, adrenal cancer, malignant pleural mesothelioma, thymic carcinoma, thymic carcinoid, angiosarcoma, hematangiopericytoma, leiomyosarcoma, malignant insulinoma, duodenal cancer, and small intestinal cancer (each <1%). It should be noted that the bone metastasis consultation system in this study has no strict consultation criteria or protocol, and that patients are referred to the orthopaedic department at the discretion of the primary physician after a diagnosis of bone metastasis.

2.3. Bone-modifying agents

Using the pharmacy database at our institution, we examined the administration and type of BMAs used for all 721 registered patients during follow-up for bone metastasis. Receipt of zoledronate and/or denosumab for treatment of bone metastasis according to the judgement of the attending clinician was regarded as BMA use. The administration of these drugs for other purposes (e.g., osteoporosis) was excluded from BMA use.

2.4. Skeletal-related events

From the database of our bone metastasis consultation system, we evaluated patients who underwent orthopaedic surgery for skeletal-related events. To assess the occurrence of AFF, we categorized these surgeries into two: surgery involving the femur and others.

Among patients who required surgical intervention involving the femur, we extracted and investigated patients with AFF. The case definition of AFF was in accordance with the revised diagnostic criteria for AFF published by the American Society for Bone and Mineral Research Task Force in 2014 [11]. Then, we examined the clinical characteristics of patients with AFFs; primary cancer type, sites of bone metastasis, history of BMA use at AFF onset, fracture type using AO Foundation/Orthopaedic Trauma Association (AO/OTA) classification, fracture location, bilaterality, surgical procedure for AFF, and bone healing after surgery.

3. Results

3.1. Bone-modifying agents

Among the registered 721 patients with bone metastasis, 529 patients (73.4%) had received BMAs for treatment of bone metastasis (Table 2). Zoledronate (intravenous; 4 mg) was administered to 199 (27.6%), denosumab (subcutaneous; 120 mg or 60 mg) was administered to 401 (55.6%), and both agents were administered to 73 (10.0%).

![Table 1](data:image/latex-image)

Table 1 Overview of patients.

| Primary cancer | Number of patients (%) | Age (years) ± standard deviation | Sex, male (%) |
|----------------|------------------------|---------------------------------|--------------|
| Total          | 721                    | 65.7 ± 12.4                     | 436 (60.4)   |
| Lung cancer    | 155 (21.5)             | 69.3 ± 10.0                     | 94 (60.6)    |
| Breast cancer  | 78 (10.8)              | 59.0 ± 12.2                     | 0 (0)        |
| Prostate cancer| 68 (9.4)               | 73.4 ± 10.4                     | 68 (100)     |
| Colorectal cancer| 65 (9.0)           | 64.2 ± 10.5                     | 41 (63.1)    |
| Head and neck cancer| 61 (8.5)       | 61.9 ± 11.2                     | 45 (73.8)    |
| Renal cell carcinoma| 42 (5.8)        | 67.5 ± 12.8                     | 32 (76.2)    |
| Hepatobiliary cancer| 39 (5.4)     | 68.2 ± 12.2                     | 32 (82.1)    |
| Esophageal cancer| 31 (4.3)             | 67.9 ± 9.3                      | 24 (77.4)    |
| Urothelial cancer| 26 (3.6)             | 71.6 ± 10.2                     | 21 (80.8)    |
| Neuroendocrine tumor| 21 (2.9)          | 56.8 ± 12.9                     | 11 (52.4)    |
| Multiple myeloma| 20 (2.8)             | 64.7 ± 6.8                      | 8 (40.0)     |
| Malignant lymphoma| 19 (2.6)             | 51.5 ± 21.9                     | 13 (63.2)    |
| Gastric cancer  | 18 (2.5)               | 61.7 ± 12.2                     | 13 (72.2)    |
| Pancreatic cancer| 18 (2.5)             | 70.4 ± 7.2                      | 11 (61.1)    |
| Melanoma       | 11 (1.5)               | 66.5 ± 15.1                     | 4 (36.4)     |
| Cancer of unknown primary| 10 (1.4)       | 59.3 ± 14.8                     | 3 (30.0)     |
| Thyroid cancer | 8 (1.1)                | 71.0 ± 14.4                     | 4 (50.0)     |
| Others         | 31 (4.3)               | 61.8 ± 11.0                     | 13 (41.9)    |

* Data are expressed as the mean ± standard deviation.
patients. In most patients who had been exposed to both drugs, BMA use was switched from zoledronate to denosumab. No patient received zoledronate for purposes other than treatment of bone metastasis, and only 2 of all 721 patients received a single dose of low-dose (60 mg) denosumab for other therapeutic indications, such as osteoporosis. In 401 patients who received denosumab for treatment of bone metastasis, high-dose (120 mg) denosumab was generally injected every 4 weeks.

3.2. Skeletal-related events

Among all 721 patients registered in our bone metastasis consultation system, orthopaedic surgery for skeletal-related events was performed in 36 patients (5.0%): femur, 13 (1.8%) and others, 23 (3.2%). Surgical sites other than the femur were the spine (n = 17, 2.4%), humerus (n = 4, 0.6%), and pelvis (n = 2, 0.3%).

3.3. Incidence and clinical characteristics of AFF

Among 13 patients who underwent surgical intervention involving the femur, 5 patients (1 man and 4 women) had 8 AFFs (Table 3). Primary cancer type was breast cancer in all 4 female patients, and prostate cancer in the 1 male patient. All 5 patients with AFF had a history of BMA use (>6 years, n = 3; 4.5 years, n = 1; 1.5 years, n = 1) for treatment of bone metastasis. In 192 patients who had not been exposed to BMAs in this survey, critical (surgically treated) AFF was not detected. Thus, the incidence of critical AFF was 0.9% in 529 patients who received BMAs for bone metastasis. Notably, the incidence was 6.6% in BMA-exposed patients with breast cancer (4 of 61). Surgical treatment using anterograde intramedullary nailing was required for all 8 AFFs (complete, 5; incomplete, 3) in the 5 patients (Figs. 1 and 2). All 5 complete AFFs were definitively classified as simple fracture (AO/OTA classification 32A), and clinical bone union was achieved in all cases. No implant breakage was seen in any of the 8 AFFs during follow-up.

4. Discussion

In the treatment of patients with bone metastasis, especially those with longer life expectancy who are receiving BMAs, AFF can occur and the incidence cannot be ignored. In this study, we reviewed over 500 cancer patients with BMA use for bone metastasis treatment and demonstrated a high incidence of critical (surgically treated) AFF: 0.9%. The annual incidence rate (in 2012) of hip fracture in Japan was reported as 6.10 per 10,000 population [31], and the incidence of AFF accounted for 0.5% of all hip fractures [32]. In the context of AFF in patients with bone metastasis, some reports have described varying incidence. Puhaïndran et al. reviewed 327 patients with intravenous bisphosphonate use (>24 doses) for bone metastasis and reported the incidence of subtrochanteric AFF as 1.2% (4/327) [33]. Edwards et al. reported 23 AFF cases (clinical, 14; subclinical, 9) out of 10,587 patients who had been exposed to bisphosphonates for bone metastasis (total dosing period, 4482 years), and estimated the incidence as 0.05 per 100,000 person-years [34]. In recent years, several studies have focused on the association between denosumab use and AFF in patients with bone metastasis. A multi-center retrospective study conducted in Japan revealed 5 clinical AFF cases among 277 patients with denosumab use for bone metastasis (incidence, 1.8%) [28]. In that report, 4 of the patients with AFF had primary breast cancer and been exposed to zoledronate and subsequent denosumab (>45 doses) [28]. In a retrospective imaging review, the incidence of AFF associated with denosumab use for treatment of bone metastasis was reported as 0.4% (clinical, 1/253) and 4.5% (subclinical, 3/66) [29]. Although there was selection bias because of the retrospective analysis using available images in only 66 patients [29], the high incidence of asymptomatic AFF (4.5%) suggests that more patients with subclinical AFF might be

| Case | Site of bone metastasis | Side | Condition of AFF | Age at AFF onset (years) | Zoledronate use | Denosumab use | AO/OTA classification |
|------|-------------------------|------|------------------|--------------------------|----------------|---------------|----------------------|
| 1    | Lumbar spine, pelvis    | Lt   | Complete         | 57                       | 19 M           | -             | 32A2                 |
| 2    | Lumbar spine            | Lt   | Complete         | 62                       | 56 M           | -             | 32B3                 |
| 3    | Lumbar spine, pelvis    | Lt   | Incomplete       | 65                       | 56 M           | -             | 32A2                 |
| 4    | Lumbar spine, pelvis    | Lt   | Complete         | 65                       | 56 M           | -             | 32A2                 |
| 5    | Sternum, lumbar spine, pelvis | Lt   | Complete         | 72                       | 56 M           | -             | 32A2                 |
missed in daily practice for bone metastasis.

In this study, we identified critical (surgically treated) AFF in 4 of 61 patients with breast cancer who received BMAs (incidence of critical AFF, 6.6%). Previous reports indicated that most patients with AFF had breast cancer; followed by prostate cancer, myeloma, and other cancer [28,29,33,34], consistent with our results. In contrast, none of the 155 patients with lung cancer, the most common cancer type in this study, developed AFF. Although AFF has been reported in 2 patients with non-small cell lung carcinoma, both were cases of double cancers, namely, breast cancer and non-small cell lung carcinoma; one had a prior history of bisphosphonate use for osteoporosis and the other had bone metastasis from primary breast cancer [29,35]. Thus, to our knowledge, there has been no report of AFF in patients with single primary lung cancer. A population-based registry of cancer statistics in Japan reports the 5-year survival rate (initial diagnosis, 2006–2008) of lung cancer to be 31.9%, whereas that of breast and prostate cancer was 91.1% and 97.5%, respectively [6]. Furthermore, when limited to patients with distant metastasis, the 5-year survival rate of lung cancer was 4.9%, whereas that of breast and prostate cancer was 33.7% and 49.1%, respectively [6]. These data demonstrate that patients with breast or

Fig. 1. Case 4. (A) Impending atypical subtrochanteric femoral fracture of the right femur in a 74-year-old man with prostate cancer. He complained of severe pain in the right thigh, and radiograph revealed an apparent focally thickened lateral cortex with an incomplete fracture line toward the medial cortex in the subtrochanteric region (arrowhead). Several minor focal thickenings of the lateral cortex were seen also in the mid-shaft (small arrows). (B) He had no complaints of pain in the contralateral left thigh, but radiograph revealed a distinct thickened lateral cortex with no fracture line (big arrow), associated with numerous minimal focal thickenings (small arrows). (C) Prophylactic internal fixation was performed for both femurs with long anterograde reamed intramedullary nailing. This surgery contributed to his early recovery. He was able to go home and return to original daily life with no difficulties or symptoms at just 10 days after surgery.

Fig. 2. Case 5. (A) Complete atypical femoral fracture in the mid-shaft of the right femur (AO/OTA classification, 32A3). No radiographic signs suspected to be atypical femoral fracture were seen in the left femur. (B) Internal fixation using anterograde intramedullary nailing was performed. (C) Radiographs show good external callus at 3 months after surgery. Clinical bone union was achieved, and she can walk pain-free.
prostate cancer tend to have longer life expectancy, and thus more prolonged exposure to BMAs, than those with lung cancer. This might result in higher incidence of AFF in patients with breast or prostate cancer. However, because the 5-year survival rate in almost all cancer types including lung cancer is gradually improving in recent years [6], it might be necessary to pay more attention to the development of AFF in patients with other cancer previously regarded as low risk. Thus, routine radiographic screening for the development of AFF might be necessary in patients with long-term (e.g., >2–3 years) exposure to BMAs for bone metastasis, even if asymptomatic.

AFF in patients with bone metastasis may not be complicated by nonunion. AFF is often reported to be at high risk of delayed bone healing [11,36–41], especially in cases with subtrochanteric AFF associated with bone turnover suppression due to specific drugs (e.g., bisphosphonates) [42]. Meanwhile, this report has some discrepancies associated with bone turnover suppression due to specific drugs (e.g., zoledronate) could reduce the rate of skeletal-related events by 39% [2]. Furthermore, Martin et al. [3] and Henry et al. [5] reported that, compared with zoledronate, denosumab had significantly greater therapeutic effects on skeletal-related events in patients with bone metastases. In addition, regarding bisphosphonate use in the treatment of osteoporosis, the benefits of preventing fragility hip fractures far outweigh the risk of developing AFF [43]. Although bisphosphonates are predominantly used at higher doses for the treatment of bone metastasis than that for the treatment of osteoporosis, Puhaindran et al. demonstrated no significant difference in drug dose or duration between cancer patients who had subtrochanteric AFFs and those who did not [33]. However, the unexpected onset of complete AFF undoubtedly causes drastically diminished activities of daily living (ADL). In this study, case 4 involved impending AFF with an ideal surgical intervention by the orthopaedic surgeon, which contributed to maintaining ADL and quality of life (QOL) in this patient. Further analyses with a larger number of patients is required in order to devise a protocol for monitoring and detecting asymptomatic incomplete AFF in the early stage and for determining the optimal surgical treatment to prevent complete AFF in multidisciplinary treatment of bone metastasis.

This study has several limitations. First, this is a retrospective study and the regimen of BMAs for treatment of bone metastasis was not standardized. There was also selection bias at registration in this bone metastasis consultation system. Not all cancer patients with bone metastasis were registered throughout the study period. Second, we were unable to carry out a detailed review of the duration and timing of BMA use. Also, we were unable to investigate the administration of other bisphosphonates (for purposes other than treatment of bone metastasis) except zoledronate. Third, we could not review the follow-up period of registered patients, so we did not investigate differences in life expectancy for each primary cancer. Fourth, we were able to extract only those patients who underwent orthopaedic surgery at our hospital and it is possible that asymptomatic AFF cases could have been missed or that some patients might have undergone internal fixation for AFF at local hospitals other than our institution.

5. Conclusions

In this study, we demonstrated the credible incidence of critical (surgically treated) AFF in the context of a multidisciplinary bone metastasis consultation system in a Japanese national university hospital, and this frequency cannot be ignored. The current prolonged life expectancy of cancer patients is associated with a marked increase of BMA use. AFF should be recognized as a side effect of BMA use, and more attention should be paid to the risk of developing AFF especially in BMA-exposed patients with breast cancer. Early diagnosis and surgical treatment of AFF is important for preventing diminished ADL and QOL. Therefore, routine radiographic screening for the development of AFF should be considered in patients with long-term exposure to BMAs for bone metastasis, even if asymptomatic.

6. Ethics

This study was approved by the institutional review board, and opt-out consent was obtained from patients involved in this study. All procedures involving human participants were performed in accordance with the ethical standards of the relevant institutional and/or national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The data were fully anonymized, thereby protecting the patients’ privacy and dignity.

Conflicts of interest

The department to which the corresponding (YO) and fourth author (HK) belong has received funding for operating costs from Saku Central Hospital of the Nagano Prefectural Federation of Agricultural Cooperatives for Health and Welfare, Suwa Central Hospital, Doujin Hospital, Medtronic Sofamor Danek Co., Ltd., Stryker Japan Co. Ltd., and HOYA Technosurgical Co., Ltd. The other authors declare that they have no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Takumi Kaku: Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing - original draft, Writing - review & editing. Yoto Oh: Conceptualization, Data curation, Investigation, Methodology, Project administration, Validation, Visualization, Writing - original draft, Writing - review & editing. Shingo Sato: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing. Hirotaka Koyanagi: Conceptualization, Data curation, Investigation, Writing - review & editing. Takashi Hirai: Conceptualization, Investigation, Writing - review & editing. Masato Yuasa: Conceptualization, Investigation, Writing - review & editing. Toshitaka Yoshii: Conceptualization, Supervision, Writing - review & editing. Tsuyoshi Nakagawa: Conceptualization, Investigation, Resources. Satoshi Miyake: Conceptualization, Project administration, Resources, Supervision. Atsushi Okawa: Conceptualization, Methodology, Project administration, Resources, Supervision, Writing - review & editing.

References

[1] L.S. Rosen, D. Gordon, M. Kaminski, A. Howell, A. Belch, J. Mackey, J. Appelbaert, M.A. Hussein, R.E. Coleman, D.J. Reitsma, B.-L. Chen, J.J. Seaman, Long-term efficacy and safety of zolendronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma, Cancer 98 (2003) 1735–1744.
[2] N. Kohno, K. Aogi, H. Minami, S. Nakamura, T. Asaga, Y. Iino, T. Watanabe, C. Goesl, Y. Ohishi, S. Takashina, Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial, J. Clin. Oncol. 23 (2005) 3314–3321.
[3] M. Martin, R. Bell, H. Bourgeois, A. Bruzsky, I. Diel, A. Eini, L. Fallowfield,
A. Tano, Y. Oh, K. Fukushima, Y. Kurosa, Y. Wakabayashi, K. Fujita, T. Yoshii, I.T. Haider, P. Schneider, A. Michalski, W.B. Edwards, Influence of geometry on Y.Oh,K.Fujita,Y.Wakabayashi,Y.Kurosa,A.Okawa,Location of a typical femoral bone in patients with metastatic breast cancer treated with zoledronic acid, J. Breast Cancer 15 (2012) 261–264.

K. Ishizuma, D. Ota, A. Fukuchuki, M. Teraoka, A. Fujii, M. Mori, T. Nishi, A case of femoral diaphyseal fracture after long-term treatment with zoledronic acid, Breast Cancer 22 (2015) 90–94.

D. Tateiwa, H. Outani, S. Iwasa, Y. Imura, T. Tanaka, K. Oshima, N. Naka, N. Araki, A typical femoral fracture associated with bone-modifying agent for bone metastasis of breast cancer: a report of two cases, J. Orthop. Surg. 25 (2017) 1–4.

T. Sogahara, M. Koizumi, K. Hayakawa, Y. Ino, N. Sata, Impending atypical femoral fracture in a patient of breast cancer with bone metastases receiving long-term denosumab, Clin. Nucl. Med. 43 (2018) 365–366.

E. Shane, D. Burr, B. Abrahamsen, R.A. Adler, T.D. Brown, A.M. Cheung, F. Cosman, J.R. Curtis, B. Dell, D.W. Dempster, P.R. Ethling, T.A. Einhorn, H.K. Genant, P. Geusens, K. Klaushofer, J.M. Lane, F. McKiernan, R. McKinney, A. Ng, J. Nieves, R. O'Keefe, S. Papapoulos, T.S. Howe, M.C.H. van der Meulen, R.S. Weinstein, M.P. Whyte, Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research, J. Bone Miner. Res. 29 (2014) 1–23.

C.V. Ovadia, J.E. Zerwekh, D.S. Rao, N. Maalouf, F.A. Gottschalk, C.Y.C. Pak, Severely suppressed bone turnover: a potential complication of alendronate therapy, J. Clin. Endocrinol. Metab. 90 (2005) 1294–1301.

A.S. Nevisar, J.M. Lane, B.A. Lenart, F. Edobor-Osula, D.G. Lorich, Low-energy femoral shaft fractures associated with alendronate use, J. Orthop. Trauma 22 (2008) 346–350.

C. Lin, S.Y. Huang, G.A. Lee, S. Kandewalle, J. Provus, B. Ettinger, J.R. Gonzalez, R.L. Hui, C.D. Grimsrud, Clinical correlates of atypical femoral fracture, Bone 51 (2012) 181–184.

Y. Oh, Y. Wakabayashi, Y. Kurosa, M. Ishizaki, A. Okawa, Stress fracture of the bowed femoral shaft is another cause of atypical femoral fracture in elderly Japanese: a case series, J. Orthop. Sci. 19 (2014) 579–586.

E. Hagen, A.N. Miller, S.M. Ott, M. Gardner, S. Morshed, K. Jeray, T.B. Alton, D. Ren, W.P. Abblitt, J.C. Krieg, Association of atypical femoral fractures with bisphosphonate use by patients with varus hip geometry, J. Bone Joint Surg. Am. 96 (2014) 1905–1909.

Y. Oh, Y. Wakabayashi, Y. Kurosa, K. Fujita, A. Okawa, Potential pathogenic mechanism for stress fractures of the bowed femoral shaft in the elderly: mechanical analysis by a CT-based nonlinear finite element method, Injury 50 (2019) 1876–1882.

J.W. Kim, J.I. Kim, Y.-S. Byun, O.-J. Shin, H.K. Oh, K.C. Park, J.-W. Kim, C.-W. Oh, Factors affecting fracture location in atypical femoral fractures: a cross-sectional study with 147 patients, Injury 48 (2017) 1570–1574.

J.H. Koh, J.P. Myong, J. Yoo, Y.-W. Lim, J. Lee, S.-K. Kwok, S.-H. Park, J.H. Ju, Pre-disposing factors associated with atypical femur fracture among postmenopausal Korean women receiving bisphosphonate therapy: 8 years’ experience in a single center, Osteoporos. Int. 28 (2017) 3251–3259.

S.P. Khow, T.Y. Yung, Atypical femoral fracture in a patient treated with denosumab, J. Bone Miner. Metab. 33 (2015) 355–358.

J. Schilcher, P. Aspenberg, Atypical fracture of the femur in a patient using denosumab—a case report, Acta Orthop. 85 (2014) 6–7.

R.N. Thompson, C.L. Armstrong, G. Heyburn, Bilateral atypical femoral fractures in a patient prescribed denosumab — a case report, Bone 61 (2014) 44–47.

R.E. Coleman, E.V. McCloskey, Bisphosphonates in oncology, Bone 49 (2011) 71–76.

M. Takahashi, Y. Ozaki, R. Kizawa, J. Manoda, K. Sakamaki, K. Kinowski, T. Umeru, C. Kondoh, Y. Tanabe, N. Tamura, Y. Miura, T. Shigekawa, K. Kawahata, N. Baba, H. Iuchi, T. Takano, Atypical femoral fracture in patients with bone metastasis receiving denosumab therapy: a retrospective study and systematic review, BMC Cancer 19 (2019) 980.

S.P. Yang, T.W.B. Kim, P.J. Boland, A. Farooki, Retrospective review of atypical femoral fracture in metastatic bone disease patients receiving denosumab therapy, Oncologist 22 (2017) 438–444.

M. Lockwood, R. Bandeurarapagiri, L.J. Suva, I. Makhoul, Atypical femoral fractures from bisphosphonate in cancer patients — review, J. Bone Oncol. 18 (2019) 100259.

H. Orimo, Y. Yaegashi, T. Hosoi, Y. Fukushima, T. Onda, T. Hashimoto, K. Sakata, Hip fracture incidence in Japan: estimates of new patients in 2012 and 25-year trends, Osteoporos. Int. 27 (2016) 1777–1784.

H. Hagino, N. Endo, T. Yamamoto, A. Harada, J. Iwamoto, N. Kondo, T. Mabisa, S. Mori, J. Nakamura, S. Ohito, A. Sakai, J. Takada, Y. Kato, Treatment status and radiographic features of patients with atypical femoral fractures, J. Orthop. Sci. 23 (2018) 316–320.

M.E. Puhaindran, A. Farooki, M.R. Steensma, M. Hameed, J.H. Healey, P.J. Boland, Atypical subtrochanteric femoral fractures in patients with skeletal malignant involvement treated with intravenous bisphosphonates, J. Bone Joint Surg. Am. 93 (2011) 1235–1242.

B.J. Edwards, M. Sun, D.P. West, M. Guindani, Y.H. Lin, H. Lu, M. Hu, C. Barcenes, J. Bird, C. Feng, S. Saraykar, D. Tripathy, G.N. Hortobagyi, R. Gagel, W.A. Murphy Jr., Incidence of atypical femur fractures in cancer patients: the MD Anderson Cancer Center experience, J. Bone Miner. Res. 31 (2016) 1569–1576.

D.C. Austin, M.T. Torchia, C.M. Klare, R.V. Cantu, Atypical femoral fractures mimicking metastatic lesions in 2 patients taking denosumab, Acta Orthop. 88 (2017) 351–353.

M.L. Prasam, J. Ahn, D.L. Helfet, J.M. Lane, D.G. Lorich, Bisphosphonate-associated femur fractures have high complication rates with operative fixation, Clin. Orthop. Relat. Res. 470 (2012) 2295–2301.

Y.A. Weil, G. Rivkin, O. Safran, M. Liebergall, A.J. Fodles, The outcome of surgically treated femur fractures associated with long-term bisphosphonate use, J. Trauma 71 (2011) 186–190.

R. Bogdan, Atypical femoral fractures: inc., P. Tornetta III, W.M. Ricci, R.F. Ostrum, M. M. McQueen, M.D. McKee, C.M. Court-Brown (Eds.), Rockwood and Green’s fractures in adults, 9th ed., Wolters Kluwer, Alphen aan den Rijn, 2019, 2341–2355.

B.J.X. Teo, J.S.B. Koh, S.K. Goh, M.A. Pug, D.T.C. Chua, T.S. Howe, Post-operative outcomes of atypical femoral subtrochanteric fracture in patients on bisphosphonate therapy, Bone Joint J. 96-B (2014) 658–664.

J. Schilcher, High revision rate but good healing capacity of atypical femoral fractures. A comparison with common shaft fractures, Injury 46 (2015) 2468–2473.

A. Koh, E. Guerino, P.V. Giannoudis, Atypical femoral fractures related to bisphosphonate treatment: issues and controversies related to their surgical management, Bone Joint J. 99-B (2017) 295–302.

Y. Oh, K. Yamamoto, J. Hashimoto, K. Fujita, T. Yoshii, K. Fukushima, Y. Kurosa, Y. Wakabayashi, M. Kitagawa, A. Okawa, Biological activity is not suppressed in a patient prescribed denosumab — a case report, Bone 61 (2014) 44–47.

T. Sugihara, M.Koizumi, K.Hayakawa, Y.Ito, N.Sata, Impending atypical femoral fracture in a patient with metastatic breast cancer receiving denosumab therapy: a retrospective study and systematic review, BMC Cancer 19 (2019) 980.