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Skeletal Metastatic Disease of the Femur: Results by Management with Intramedullary Nailing

Metastázová choroba femuru: výsledky ošetření nitrodřeňovým hřebem

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ABSTRACT

PURPOSE OF THE STUDY

This study aimed to analyse the outcome following intramedullary nailing for metastases of the femur in a large cohort with special regard to mechanical, implant associated complications and patient survival. Furthermore, we aimed to identify factors influencing the overall survival.

MATERIAL AND METHODS

All patients (n = 74) that underwent intramedullary nailing for metastatic disease of the femur between 2004 and 2008 and were retrospectively reviewed. Data were recorded from the patients' medical record and the outpatients' clinics files. Details about the tumour biology, the surgery performed as well as the postoperative care were documented. Survival data were extracted from patient records or obtained via communication with outpatient oncologists or the community registration office.

RESULTS

74 (28 (37.8%) male, 46 (62.2%) female; p = 0.048) patients with a mean age of 64.4 ± 11.7 years were included. Breast (25, 33.8%), lung (18, 24.3%), bone marrow (7, 9.5%) and kidney (6, 8.1%) were the primary tumours in more than 75% of all patients. The mean overall survival was 17.5 (95% CI: 9.6 – 25.5) months. Patients with osseous metastases had a significant longer survival than patients with visceral and/or cerebral metastases (p = 0.025 and p = 0.032).

CONCLUSION

Intramedullary nailing represents a valuable fixation method for pathologic fractures or impending fractures of the femur in patients with an advanced stage of metastatic disease. It provides adequate stability to outlast the patient s remaining life-span. However, the balance must be found between therapeutic resignation and surgical overtreatment since operative treatment may be accompanied with serious complications.

Key words: bone metastases, intramedullary nailing, metastatic disease, cement augmentation, osteolytic defect.

INTRODUCTION

Skeletal metastases occur in up to 50% of all cancer patients (18, 20-22) and are indicative of advanced stage of disease. When considering certain tumour types (e.g. breast cancer, myeloma, bronchial, prostate, thyroid and kidney) that are known to typically spread to the skeletal system, estimates for evolving distant skeletal lesions even range from 25% to 100% (5). The femur is the most affected long bone with one third of lesions being located in the proximal part after metastases of the spine and pelvis (16). Impending or pathologic fractures of the proximal femur are associated with severe pain and may lead to a dramatic disability of the patients and a decline in quality of life (16, 20). Due to significant advances in tumour therapy resulting in improved survival of the patients, orthopaedic surgeons are more frequently faced with skeletal metastases and pathologic fractures (22). Whereas pathologic fractures represent an absolute indication for surgical treatment, impending fractures alert the orthopaedic surgeon to perform a proper clinical judgement. Beside the clinical aspects and the patients history, valid scores (e.g. Mirels score) have been published to confirm the indication for surgery (13, 19). Because healing of pathologic fractures is expected only in 35% of all pathologic fractures, special considerations have to be made concerning the method of reconstruction (9). Hence, durable reconstitution of the load capacity especially under full weight bearing at the biomechanically critical region of the proximal femur must be provided by the implant itself in many cases (7). Since fractures involving the hip or knee joint are most commonly treated by arthroplasty, fractures to the metaphysis or the shaft can be treated either by nailing or plating (16). Intramedullary nailing has attracted major interest as one treatment method for impending or pathologic fractures due to the minimal invasive implantation technique, the biomechanically favourable advantages (central medullary device) over angular stable plates known from long bone fracture care (10, 14). Although usually closed reduction is performed, intramedullary nailing can be combined with tumour debulking or curettage and additional cement augmentation, depending on the underlying tumour entity, the size and localisation of the metastasis, and the state of disease (16). The choice of implant (cephalomedullary nail versus intramedullary nail without femoral neck fixation) continues to be a controversy (14, 23). However, in our own experience whenever the intramedullary nailing due to metastases is indicated, the entire femur should be stabilised in one procedure to avoid any further risk for the patient (i.e. progressive osteolysis due to advanced metastatic disease impairing stability and increasing periimplant-pathological fracture risk). The increasing life expectancy of patients suffering from malignancies and skeletal lesions with impending or manifest pathological fractures require both, ultimate surgical techniques which are safe, uncomplicated and implants whose stability is sufficient to exceed the patient's life span. A multitude of different studies concerning the treatment of metastatic disease of the femur exist (23-25). Patient cohorts, follow-up rates, tumour biologies, outcome parameter and results are very heterogeneous and incoherent making meaningful conclusions increasingly difficult. However, more detailed analyses of the outcome parameter would only be possible using large registers which also have their known weaknesses and are to date rarely available. Therefore, clinical series with adequate numbers of patients are needed to clarify the outcome and form the base for treatment recommendations.

Therefore, this study aimed to analyse the outcome following intramedullary nailing for metastases of the femur in a large cohort with special regard to mechanical, implant associated complications and patient survival. Furthermore, we aimed to identify factors influencing the overall survival.

MATERIAL AND METHODS

A retrospective review of all patients treated surgically by intramedullary nailing of the femur due to metastases at our institution from January 2004 to September 2008 was conducted. Only patients with multiple metastases were included due to the significant differences in surgical treatment and aftercare for solitary metastases.

Patient management

All patients were evaluated with biplanar radiographs preoperatively to identify the location and evaluate the dimension of the osteolytic lesion in order to select the appropriate implant. Computed tomography (CT) of chest, abdomen and the pelvis were performed dependent on histopathological results for initial imaging (in cases of new diagnosis of malignancy) or restaging in order to assess the status of disease prior to the surgical procedure. Indications for surgery included pathological fractures that were either manifest or impending with a Mirels score of ≥ 9 or intractable pain with loss of function intolerably decreasing patient s quality of life. In cases of unknown primary tumour biology, standard procedures for tumour screening (staging, biopsy etc.) were performed prior to surgery.

Surgical treatment

Throughout the entire study period intramedullary nails of only one manufacturer (Synthes GmbH, Umkirch, Germany) were used. The different nail types used for implantation were the proximal femur nail antirotation (PFN-a), the lateral femur nail (LFN, which were proximally locked with the femoral neck options) as well as the retrograde femur nail (r-AFN). All surgeries were performed in general anaesthesia on a traction table to simplify reduction and intraoperative image intensifier use. Although this was not a single surgeon series, only experienced orthopaedic consultants performed the procedures. All nails were locked in static mode. Whenever the osteolysis led to a circular or semicircular loss of cortical support after reduction of the fracture cement augmentation was indicated during the surgery. In cases of impending fractures the preoperative X-ray diagnostics was reviewed and the same standard was applied.

Data acquisition

All data were extracted from the patient's medical record and the outpatients' clinics files. The surgical details (duration of surgery, type of implant) as well as the implant and surgery associated complications (hardware failure, infection) were recorded. Only complications, which led to another surgical intervention were recorded because these are considered to have a significant negative impact on patients remaining life span. Postoperative oncologic treatment regimens (radiation, chemotherapy, combined, no further therapy) were documented. In cases of no further therapy, the reasons were recorded. Patient's metastatic load was classified according to the last staging available. Metastases were graded into three groups (A: other osseous metastases, B: osseous and visceral/lung metastases and C: osseous, visceral/lung and cerebral metastases). Survival data were extracted from patient records or obtained via communication with outpatient oncologists or the community registration office.

Statistical analysis

All data were recorded and analysed using IBM® SPSS® Statistics Release 22.0 (IBM Corporation, Armonk, New York, United States). The assumption of normality and homogeneity of variance was tested using the Kolmogorov-Smirnov test. The statistical analysis was performed using the t-test for testing numeric matched/unmatched samples. For interval scaled factor analysis an ANOVA was performed. In case of multiple comparisons the post-hoc Bonferroni correction for repeated measurements was applied. To correlate numeric values the Pearson s correlation coefficient was calculated. The Chi-square-test was used for cross table evaluation. To verify predictive factors to the outcome a multiple regression analysis was performed including variables that showed significant correlation to the outcome parameter in a pre-analysis. Differences were considered significant for $p < 0.05$.

RESULTS

A total of 74 (28 (37.8%) male, 46 (62.2%) female; $p = 0.048$) patients with a mean age of 64.4 ± 11.7 years underwent intramedullary nailing for metastatic disease of the femur. Indications for surgery were significant ($p = 0.002$) more manifest pathologic fractures (51, 68.9%) as opposed to impending pathological fractures (23, 31.1%). Of the patients with an impending fracture 18 (78.3%) had a Mirels score of ≥ 9 (9: 21.7%, 10: 4.3%, 11: 47.8%, 12: 34.8%), while in 5 patients (21.7%) severe pain resulting in immobilisation was the indication for surgery. Of these, three had a Mirels score of 8 (13%) and two scored 7 (8.7%).

Tumor biology, metastatic status and postoperative care

A detailed description of the different primary tumour biology is given in Table 1 and Figure 1. In summary breast (25, 33.8%), lung (18, 24.3%), bone marrow (7, 9.5%) and kidney (6, 8.1%) were the primary tumours in more than 75% of all patients. Concerning the status of the disease all (74, 100%) patients had multiple osseous metastases. Additional visceral metastases were found in 45 patients (60.8%) and 13 patients (17.6%) presented with cerebral metastases. We did not find any patients with cerebral metastases that did not have visceral/lung and other osseous metastases. Postoperatively, 14 (18.9%) patients underwent radiation therapy, 18 (24.3%) chemotherapy and 12 (16.2%) were treated with a combined radio-chemotherapy. 30 (40.5%) patients did not receive any further adjuvant therapy. Among those three (10%) patients were stabilised for pain control only and had a survival of less than 12 weeks while 27 (90%) had undergone radiation of the affected femur prior to surgery (no further radiotherapy options as maximum radiation dose was reached).

Surgical details

A cephalomedullary nail (PFN-a) was used in the vast majority of the cases (67, 90.5%). Six patients received a LFN (6, 8.1%) and one patient an r-AFN (1, 1.4%). The mean operating time was 117±62 minutes. Local augmentation with bone cement (Refobacin®, Biomet, Dordrecht, The Netherlands) was performed in 22 (29.7%) of the cases. 5/18 (27.8%) of the impending and 17/34 (50%) of the manifest pathologic fractures underwent cement augmentation. Statistical testing yielded no

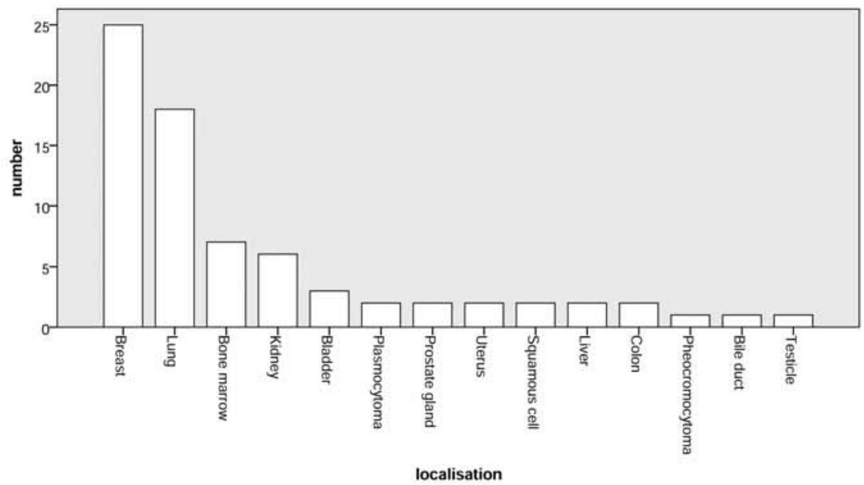

Fig. 1. The absolute numbers of each tumour entity is shown. Breast, lung, bone marrow and kidney were the most abundant.

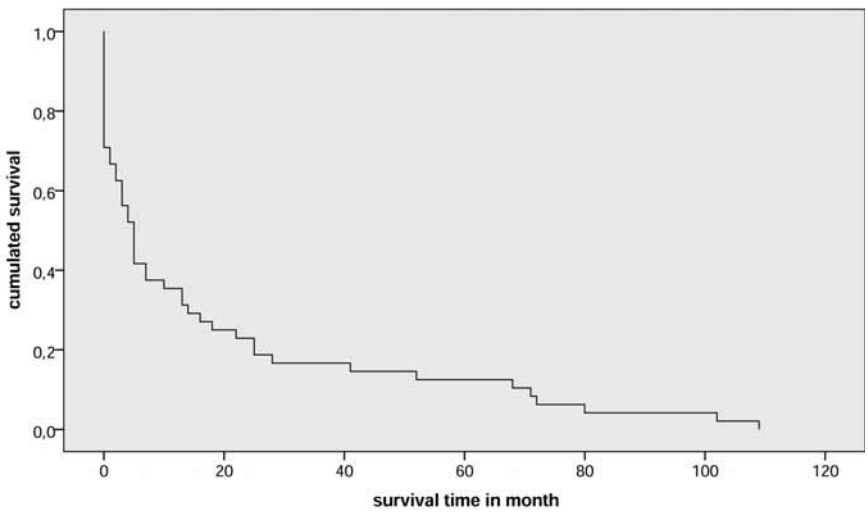

Fig. 2. The overall survival in our cohort independent from the underlying tumour entity revealed 17.5 (95% CI: 9.6–25.5) months. More than 50% died within the first two years after surgical intervention.

significant difference (p = 0.313). The documentation of mechanical complications revealed a total of 4 (5.4%) implant failures (one proximal cut out, one nail breakage and two cases of loosening). Although not significant (p = 0.085) those patients had a longer mean survival compared to the ones without failure (40.8 ± 46.6 versus 15.4 ± 25.7 months). Considering the degree of disease categorized by the locations of metastases, two of the patients (50%) with hardware failure were metastasized to the bone only whereas one patient showed additional visceral metastases and the other one additional cerebral metastases. The underlying tumour biologies were one case of lung cancer (survival: 2 months), one of bile duct cancer (survival: 7 months) and two cases of breast cancer (survival: 52 and 102 months). The hardware failures occurred one, six, nine and fifty-two months after treatment. Interestingly, the implant breakage and cut out occurred in the two patients with longer survival. We did not find a relation between the use of cement and the occurrence of hardware failure (p = 0.831). Concerning additional complications we found one case (1.4%) of a postoperative infection.

Table 1. The recorded tumour biologies are listed in detail. The absolute number, percentage and the cumulative numbers and percentages of our cohort are shown. Breast, lung, bone marrow and kidney represent more than 75% of all patients

Tumour entity	Number	Percentage (percentage)	Cumlative number
Breast cancer	25	33.8	25 (33.8)
Lung cancer	18	24.3	43 (58.1)
Bone marrow	7	9.5	50 (67.6)
Kidney cancer	6	8.1	56 (75.7)
Bladder	3	4.1	59 (79.7)
Plasmocytoma	2	2.7	61 (82.4)
Prostate gland cancer	2	2.7	63 (85.1)
Uterus cancer	2	2.7	65 (87.8)
Squamous cell cancer	2	2.7	67 (90.5)
Liver cancer	2	2.7	69 (93.2)
Colon cancer	2	2.7	71 (95.9)
Pheocromocytoma	1	1.4	72 (97.3)
Bile duct cancer	1	1.4	73 (98.6)
Testicular cancer	1	1.4	74 (100)

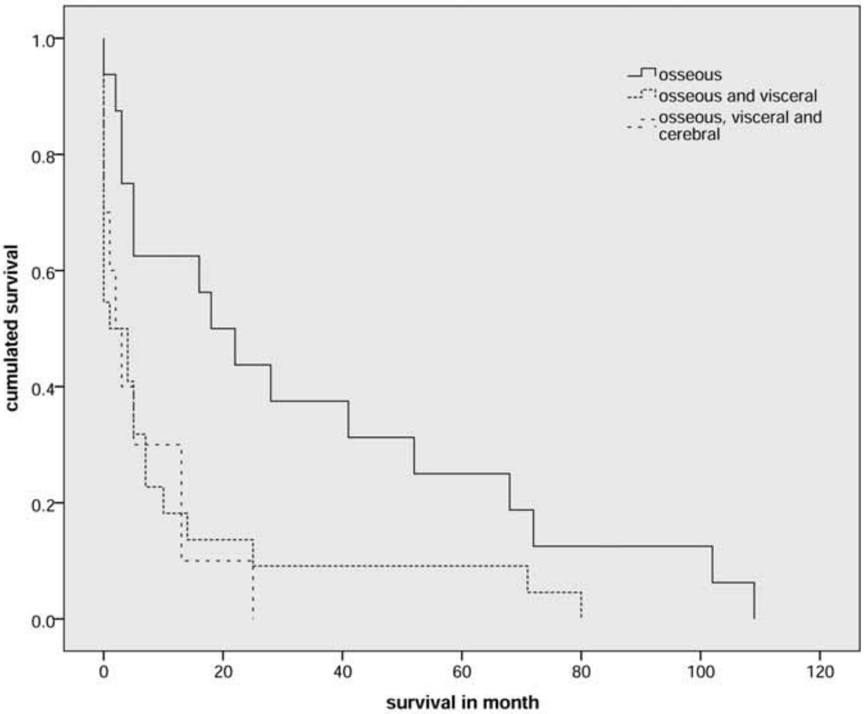

Fig. 3. The cumulative survival as a function of the different metastatic groups showed a significant (p = 0.025) longer survival in group A (osseous metastases) as compared to group B (osseous and visceral) and group C (osseous, visceral and cerebral). Comparison of group B and C yielded no significant difference.

Survival analysis

The mean overall survival was 17.5 (95% CI: 9.6–25.5) months (Fig. 2). We could not detect significant differences in the mean survival regarding the four leading (Table 1) primary tumour entities (p = 0.083). Data showed no difference in the survival of pathologic fractures as opposed to impending fractures (p = 0.266). Analysis of the postoperative treatment regime (no adjuvant therapy versus radiation versus chemotherapy versus combined) revealed no significant influence on survival (p = 0.708). Regarding the defined metastatic groups (A–C) our data revealed a significant longer survival in group A compared to group B (p = 0.025) and group C (p = 0.032, Fig. 3), however, no difference between group B and C (p = 1.000) was found (Figure 3). Additionally, survival time was negatively correlated with the metastatic load (increasing from group A to C; r = –0.390, p = 0.006). Patients that received additional cement augmentation had a significant lower survival than patients that were not augmented (0.6 ± 1.1 versus 22 ± 30, p < 0.001, Fig. 4). The cumulative survival within the first year after surgical intervention was 35%. After the second year 23% were still alive and only 17% after the third year.

DISCUSSION

Published data estimate that about 10% of all patients with metastatic disease suffer from a pathologic fracture. More than 60% of these patients subsequently require surgical therapy by internal fixation (16). Primary tumours from the breast, kidney and prostate followed by lung, colon and thyroid gland typically show a osseous spread to the skeleton with the femur as the most frequently affected long bone (16). The endpoint of surgical intervention must provide stability that outlasts the remaining life-span of the patient and allow for a direct mobilisation under full weight bearing. The procedure should be as less invasive as possible, fast and ultimate and associated with a low rate of complications (16, 20).

We found a mean survival of 17.5 months and 35% of the patients survived for more than one year after the operative intervention. This rate was reported to be markedly lower in different reports, although survival data vary in literature (16, 20). Furthermore, our data show that the metastatic load significantly influences the survival of patients which is in concordance to the results of Bohm *et al.* (4). Many authors described the positive effect of adjuvant radiation in the treatment of metastases of the long bones (i.e. pain relief, local tumour control) (11, 15). In our analysis we could not identify a postoperative treatment regime that influences the survival of our patients, however, the sample size of our subgroup analysis is too small for valid interpretation. Considering the above mentioned prerequisites of treatment, our data clearly demonstrate that intramedullary nailing is a safe and fast procedure with a low overall complication rate (6.6%). Nevertheless, some authors have questioned the use of intramedullary nailing for the treatment of metastases due to the risk for dissemination of tumour cells, emboli and pulmonary compromise (16). However, plate osteosyntheses have been shown to be associated with high rates of mechanical failures which led to a shift in treatment algorithms towards the use of intramedullary implants known to be biomechanically superior (6, 16, 23, 25). Different studies demonstrated that the estimated survival time is considered the most important risk factor for implant failure, underscored by data that showed a higher mechanical complication rate in patients with a survival of more than three years (12, 16, 26). The mean survival in our cohort was 17.5 months (95% CI 9.6–25.5), indicating that most of our patients did not reach this critical survival time. This disease specific survival may also explain the relatively low complication rate (1.4% infection, 5.4% hardware failure) in a patient cohort which is subjected to have a serious risk profile. However, the four patients who sustained a hardware failure had a mean survival of 40.8±46.6 months (which is outside of our 95% confident interval) as compared to 15.4±25.7 months of patients without any hardware problems. Although we could not identify an influence of cement augmentation to the incidence of hardware failure, different authors emphasized the positive role of cement when increased construct stability is desired (8, 27). However, our subcohort of patients with hardware failures is too small to formulate general recommendations, we feel that additional stabilisation (e.g. additional cement augmentation) should be evaluated in cases with large size metastases including extensive osteolysis and segmental loss of cortical bone to avoid hardware complications. Nevertheless, identification and proper clinical judgement of patients that would benefit from cement augmentation should take place prior to surgery. Useful scoring systems aiming to that have been proposed but not validated yet (17). Future research effort should further focus on this issue in order to increase the quality and long lasting performance of surgical care.

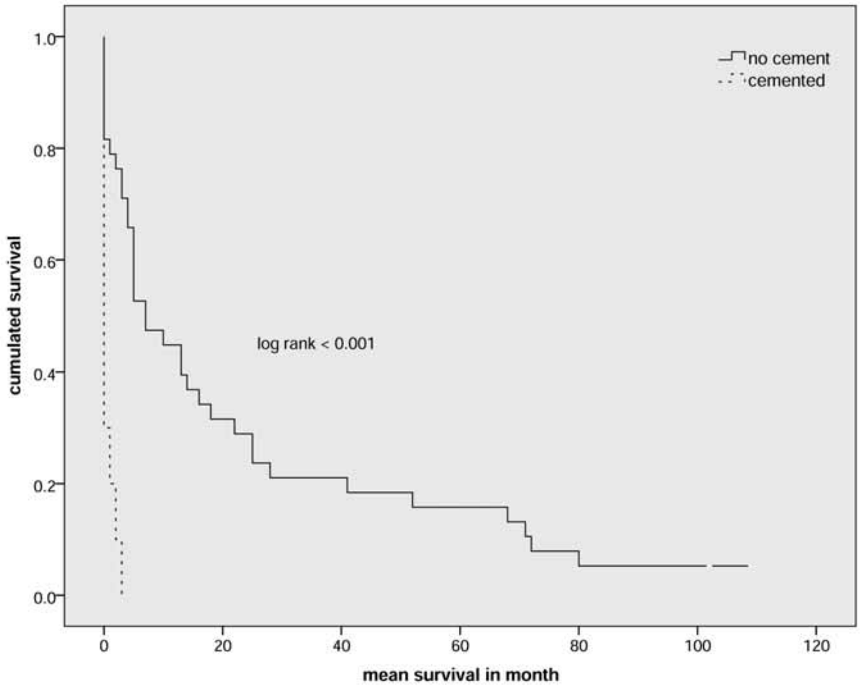

Fig. 4. Patients that were augmented with additional cement during the procedure had a significant shorter survival (log rank < 0.0001) indicating that these patients were in an advanced stage of metastatic disease.

Although the majority of authors recommend the additional stabilisation of the femoral neck, others have questioned this traditional concept (1–3, 14). From our point of view, the advantage of inclusion of the femoral neck into the osteosynthetic construct is the integral and complete stabilisation of the femur within one procedure. Thus, the need for additional surgery in case of progression of the metastasis into the proximal part of the femur can be avoided, especially since modern implant technology with available aiming devices for femoral neck screw fixation does not lead to a prolongation of surgery or a higher risk for intraoperative complications.

Apart from its retrospective design, the heterogeneity of our patient cohort regarding the tumour biology is a major limitation when interpreting the presented results. Future research endeavours based on prospective studies with larger cohorts of these entities have to be performed in order to confirm our data and expand them to further increase the quality of surgical intervention due to metastases of the femur.

CONCLUSION

The present study provides evidence that intramedullary nailing represents a valuable fixation method for pathologic fractures or impending fractures of the femur in patients with an advanced stage of metastatic disease. This standard surgical technique provides adequate stability to outlast the patient s remaining life-span. However, the balance must be found between therapeutic resignation and surgical overtreatment since operative treatment may be accompanied with serious complications.

References

1. BAUER, H. C.: Controversies in the surgical management of skeletal metastases. J. Bone Jt Surg., 87-B: 608–617, 2005.
2. BICKELS, J., DADIA, S., LIDAR, Z.: Surgical management of metastatic bone disease. J. Bone Jt Surg., 91-A: 1503–1516, 2009.
3. BIERMANN, J. S., HOLT, G. E., LEWIS, V. O., SCHWARTZ, H. S., YASZENSKI, M. J.: Metastatic bone disease: diagnosis, evaluation, and treatment. J. Bone Jt Surg., 91-A: 1518–1530, 2009.
4. BOHM, P., HUBER, J.: The surgical treatment of bony metastases of the spine and limbs. J. Bone Jt Surg., 84-B: 521–529, 2002.
5. COLEMAN, R. E.: Skeletal complications of malignancy. Cancer, 80 (8 Suppl.): 1588-1594, 1997.
6. DIJSTRA, S., WIGGERS, T., VAN GEEL, B. N., BOXMA, H.: Impending and actual pathological fractures in patients with bone metastases of the long bones. A retrospective study of 233 surgically treated fractures. Eur. J. Surg., 160: 535–542, 1994.
7. FAKLER, J. K.VM., HASE, F., BÖSE, J., JOSTEN, C.: Safety aspects in surgical treatment of pathological fractures of the proximal femur – modular endoprosthetic replacement vs. intramedullary nailing. Patient Saf. Surg., 7: 37, 2013.
8. FENSKY, F., NUCHTERN, J. V., KOLB, J. P., HUBER, S., RUPPRECHT, M., JAUCH, S. Y.: Cement augmentation of the proximal femoral nail antirotation for the treatment of osteoporotic pertrochanteric fractures – a biomechanical cadaver study. Injury, 44: 802–807, 2013.
9. GAINOR, B. J., BUCHERT, P.: Fracture healing in metastatic bone disease. Clin. Orthop. Relat. Res., 178: 297–302, 1983.
10. GÄNSSLEN, A., GÖSLING, T., HILDEBRAND, F., PAPE, H. C., OESTERN, H. J.: Femoral shaft fractures in adults: treatment options and controversies. Acta Chir. orthop. Traum. čech., 81: 108-117, 2014.
11. KELLY, C. M., WILKINS, R. M., ECKARDT, J. J., WARD, W. G.: Treatment of metastatic disease of the tibia. Clin. Orthop. Relat. Res., (415 Suppl.): S219–229, 2003.
12. MILLER, B. J., SONI, E. E., GIBBS, C. P., SCARBOROUGH, M. T.: Intramedullary nails for long bone metastases: why do they fail? Orthopedics, 34(4), 2011.
13. MIRELS, H.: Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. Clin. Orthop. Relat. Res., 249: 256–264, 1989.
14. MOON, B., LIN, P., SATCHER, R., BIRD, J., LEWIS, V.: Intramedullary Nailing of Femoral Diaphyseal Metastases: Is it Necessary to Protect the Femoral Neck? Clin. Orthop. Relat. Res., (e-pub 2014) 473: 1499–1502, 2015.
15. PEREZ, C. A., BRADFIELD, J. S., MORGAN, H. C.: Management of pathologic fractures. Cancer, 29: 684–693, 1972.
16. PICCIOLI, A., ROSSI, B., SCARAMUZZO, L., SPINELLI, M. S., YANG, Z., MACCAURO, G.: Intramedullary nailing for treatment of pathologic femoral fractures due to metastases. Injury, 45: 412–417, 2014.
17. RATASVUORI, M., WEDIN, R., KELLER, J., NOTTROTT, M., ZAIKOVA, O., BERGH, P., KALEN, A., NILSSON, J., JONSSON, H., LAITINEN, M.: Insight opinion to surgically treated metastatic bone disease: Scandinavian Sarcoma Group Skeletal Metastasis Registry report of 1195 operated skeletal metastasis. Surg. Oncol., 22: 132–138, 2013.
18. RICCIO, A. I., WODAJO, F. M., MALAWER, M.: Metastatic carcinoma of the long bones. Am. Fam. Physician, 76: 1489–1494, 2007.
19. SABO, D., BERND, L.: [Surgical management of skeletal metastases of the extremities]. Orthopade, 27: 274–281, 1998.
20. SARAHRUDI, K., GREITBAUER, M., PLATZER, P., HAUSMANN, J. T., HEINZ, T., VÉCSEI, V.: Surgical treatment of metastatic fractures of the femur: a retrospective analysis of 142 patients. J. Trauma, 66: 1158–1163, 2009.
21. SILVERBERG, E.: Cancer statistics, 1986. CA Cancer. J. Clin., 36: 9-25, 1986.
22. SWANSON, K. C., PRITCHARD, D. J., SIM, F. H.: Surgical treatment of metastatic disease of the femur. J. Am. Acad. Orthop. Surg., 8: 56–65, 2000.
23. VAN DER HULST, R. R., VAN DEN WILDENBERG, F. A., VROEMEN, J. P., GREVE, J. W.: Intramedullary nailing of (impending) pathologic fractures. J. Trauma, 36: 211–215, 1994.
24. WEBER, K. L., RANDALL, R. L., GROSSMAN, S., PARVIZI, J.: Management of lower-extremity bone metastasis. J. Bone Jt Surg., 88-A (Suppl. 4): 11–19, 2006.
25. YAZAWA, Y., FRASSICA, F. J., CHAO, E. Y., PRITCHARD, D. J., SIM, F. H., SHIVES, T. C.: Metastatic bone disease. A study of the surgical treatment of 166 pathologic humeral and femoral fractures. Clin. Orthop. Relat. Res., 251: 213–219, 1990.
26. ZACHERL, M., GRUBER, G., GLEHR, M., OFNER-KOPEINIG, P., RADL, R., GREITBAUER, M., VECSEI, V., WINDHAGER, R.: Surgery for pathological proximal femoral fractures, excluding femoral head and neck fractures: resection vs. stabilisation. Int. Orthop., 35: 1537–1543, 2011.
27. ZORE, Z., FILIPOVIĆ ZORE, I., MATEJCIĆ, A., KAMAL, M., ARSLANI, N., KNEZOVIĆ ZLATARIĆ, D.: Surgical treatment of pathologic fractures in patients with metastatic tumors. Coll. Antropol., 33: 1383–1386, 2009.

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