ORIGINAL PAPER
PŮVODNÍ PRÁCE

Surgical Management and Outcome of Skeletal Metastatic Disease of the Humerus

Chirurgické léčení metastatického postižení humeru a jeho výsledky

P. SCHWABE, M. RUPPERT, S. TSITSILONIS, I. MELCHER, K.-D. SCHASER, S. MÄRDIAN

Center for Musculoskeletal Surgery, Charité – University Medicine Berlin, Germany

ABSTRACT

PURPOSE OF THE STUDY

Evaluation of outcome after surgical treatment of humerus metastases with a focus on tumour and patient derived factors, timing and strategy of intervention, surgical outcome and complications.

MATERIAL AND METHODS

Sixty-five patients with a mean age of 64.3 years (range 25–89) with 66 metastases of the humerus were surgically treated in a 7-year time-period and retrospectively reviewed.

RESULTS

Renal cell carcinoma and breast cancer were the most abundant types of primary tumour. The mean time from diagnosis of primary tumour to first metastasis was 14.5 months (range 0–173). The mean time from diagnosis of metastasis to surgery was 21.4 months (range 0–173). 38/28 intramedullary nails/locking plates were used for 58/8 manifest/impending pathological fractures. Mean cumulative survival was 16.3 months and implant failure rate was 6.1% with a mean time from initial surgery to revision of 22.2–20.6 months.

CONCLUSIONS

Our data indicate that treatment with intramedullary fixation or cement augmented plate osteosynthesis is successful for the vast majority of patients, but thorough clinical evaluation and precise decision making adapted to the patient's estimated life expectancy must be applied to avoid overtreatment or risk of implant failure.

Key words: bone metastases, skeletal metastatic disease, humerus metastasis, pathologic fracture, impending fracture.

INTRODUCTION

Metastatic tumours as being the most frequent malign lesion of the skeleton may cause a dramatic decline in quality of life due to disabilities, such as pain and reduced function with more than 10% of the patients suffering from pathologic fractures (4). Research efforts and continuous clinical developments of pharmaceutical and radio-oncological treatment strategies can contribute to decrease associated adverse skeletal events. However, in many cases, surgical intervention remains the only treatment modality and an indispensable necessity. Osteosynthetic stabilisation is often required to regain or maintain the function of the skeletal system. The main objective of any surgical treatment should be a reconstruction allowing for an immediate postoperative mobilization with stability spanning over the patient's remaining lifetime. Refined treatment regimes concerning specific primary tumours led to prolonged patient survival in a way that advances in oncosurgical osteosynthetic stabilisation procedures are desirable to meet the increasing demands in terms of enduring mechanical stability and reduced failure rates. Many of the surgical techniques place a greater demand on the orthopaedic surgeon by precisely adapting the surgical plan to the patients general state and requiring angular stable implants preshaped to anatomical sites of impending or manifest pathological fractures.

A common site for bone metastases is the upper extremity with the humerus being the second most affected long bone site after the femur (5, 7). A functionally intact upper limb is crucial for the patient's independence. The focus of treatment is to achieve fast pain relief with only short postoperative immobilisation and regain acceptable function of shoulder and elbow with unrestricted motion of the wrist and fingers. It has been shown that metastases to the shoulder girdle and humerus can be successfully treated with osteosynthetic fixation techniques and patients may return to ambulant care within as little as three days (15).

The present study is aimed to retrospectively analyse over a 7-year time-period the oncosurgical treatment

Table 1. Implant failures

Patient	Primary	Primary tumor treatment	Localisation	Initial surgery	Postop. tretment metastasis	Time until failure (d)	First failure	First revision	Postop. treatment metastasis	Second failure	Time to 2nd revision (d)	Second revision
Case 1 male, 75 years	prostate	chemotherapy	metaphysis distal	conventional plate osteosynthesis (DCP) (external hospital)	none	22	screw loosening, omplete plate dislocation	LCP plates + cement	radiotherapy	instability of proximal plate part, progressive peri-implant lysis	28	long LCP plate
Case 2 male, 79 years	kidney	nephrectomy	diaphysis	IM nail (Seidel-Nail) (external hospital)	none	345	nail loosening distal	IM nail (EHM)	radiochemotherapy			
Case 3 male, 69 years	kidney	none	metaphysis proximal	LCP + cement	radiotherapy	867	distal screw breakage, slight plate dislocation	patient refused any further treatment				
Case 4 female, 68 years	uterus	hysterectomy	metaphysis proximal	LCP + cement	radiochemotherapy	1429	distal screw breakage	long LCP	patient refused chemotherapy	partial screw loosening, impaired healing, subsequent plate dislocation	168	revision to proximal humerus replacement

results of a consecutive patient series with humerus metastases of a single institution. Special emphasis is laid on the timing of surgery, indications for prophylactic surgery in impending pathologic fractures, the type of fixation and the rationale for additional use of cement augmentation.

MATERIAL AND METHODS

Patients

Upon local ethics committee approval, the physical and electronic medical records including radiographs as well as office charts of 65 patients who underwent surgical intervention for 66 bone metastases of the humerus between July 2003 and December 2009 were retrospectively reviewed. Patients with solitary metastases were excluded due to significant differences in oncological concepts and surgical procedures. Pre- and post-operative treatment regimens, as well as surgical technique, intra- and post-operative complications and duration of surgery were recorded. All patients were evaluated pre-operatively with biplanar radiographs. As a surrogate parameter for the volume of the metastases (assuming ellipsoid volume) the size of the osteolytic lesion was measured in both planes.

Computed tomography (CT) scans of chest/abdomen/pelvis and entire body scinitigraphic bone scans were performed dependent on histopathological results for initial imaging (new diagnosis of neoplastic disease) or re-staging. Indications for surgery included pathological fracture, signs of impending fracture according to Mirels' score (dependent on localisation, size and type of the lesion) (11), as well as intractable pain with loss of function affecting quality of life. In case of unknown primary tumour, standard procedures for tumour screening (staging, biopsy etc.) were performed prior to surgical intervention.

Evaluation included treatment regimes concerning the primary tumour and the metastases. Methods of stabilisation, complications of those and adjuvant therapies were retrospectively assessed. Survival data were extracted from patient records or obtained via communication with outpatient oncologists or the community registration office.

Statistics

All data were recorded and analysed using IBM® SPSS® Statistics Release 22.0 (IBM Corporation, 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 Mann Whitney U test for comparison of unmatched nonparametric samples as well as the t-test for testing numeric samples. Survival analysis was conducted using the Kaplan-Meier-algorithm. For testing of significance within the Kaplan-Meier-analysis the log rank (Mantel-Haenszel) test was performed. A multiple regression analysis was performed to identify prognostic factors (gender, primary tumour, adjuvant treatment of primary tumour, impending/ pathologic fracture, implant

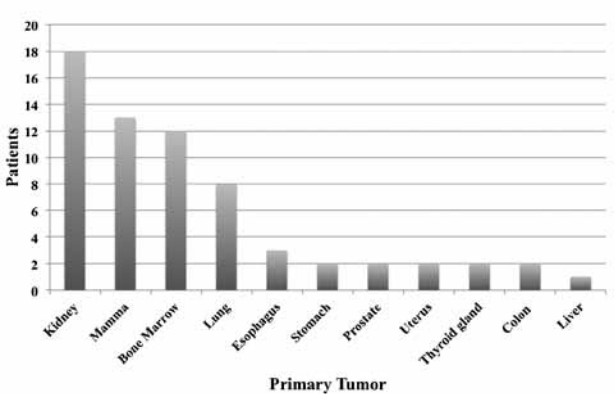

Fig. 1. Primary tumour biology.

type, cement augmentation) influencing the cumulative survival. Descriptive analyses of patients and characteristics were reported using means and standard deviations for continuous and median as well as confident intervals for discrete variables. Differences in statistical analysis were considered significant for $p<0.05$.

RESULTS

A total of 65 patients (30 males, 35 females; mean age 64.3 years, range 25–89) with 66 humerus metastases met the inclusion criteria and were included for analysis.

Primary tumour

The site of the primary tumour (Fig. 1) was kidney (n=18; 27.7%), breast (n=13; 20%), bone marrow (n=12; 18.5%), lung (n=8; 12.3%), esophagus (n=3; 4.6%), stomach (n=2; 3.1%), colon (n=2; 3.1%), prostate gland (n=2; 3.1%), uterus (n=2; 3.1%), thyroid gland (n=2; 3.1%) and liver (n=1; 1.5%).

The primary tumour had been resected before treatment of the metastasis in 27 cases (41.5%). Of those, 9 patients received adjuvant therapy in terms of chemotherapy (n=6), radiotherapy (n=2) or combined radiochemotherapy (n=1). A total of 15 patients without resection of the primary tumour (23.1%) were treated with chemotherapy, one patient underwent radiotherapy (1.5%) and another one received combined radiochemotherapy (1.5%). Twenty patients did not receive any previous treatment (30.8%).

Metastases

The metastases were located in the diaphysis (n=28; 42.4%), metaphysis (n=24; 36.4%), or in both, meta- and diaphysis (n=14; 21.2%). All metastases were of osteolytic nature. However, osteoblastic portions were observed in three patients. The average bony volume of the metastases was 36.8 mm^3 (range 1.5–156.0 mm^3). In 20 (31%) cases the metastasis led to the first diagnosis of a neoplastic disease. In this group lung cancer (n=5) and multiple myeloma (n=4) were the leading entities, followed by breast (n=3), kidney (n=3), stomach (n=2), esophagus (n=1), prostate (n=1) and liver (n=1). In 31 (48%) patients metastases were limited to the skeleton, whereas 34 (52%) patients showed additional non-osseous metastatic dissemination. The mean time from diagnosis of the primary tumour to first metastasis (metastasis-free-interval) was 14.5 months (range 0–173). Since some of the metastases received previous treatment the mean time to surgery was 21.4 months (range 0–173).

Surgical intervention

Surgical procedures were carried out with locking-compression plates (LCP) in 38 cases and intramedullary nails in 28 cases. All implants were manufactured by the same company (Synthes GmbH, Umkirch, Germany). In patients with diaphyseal metastasis two plates and 26 nails were used. For metastasis in the metaphysis, only plates have been utilized (n=24). For the cases in which metastases affected both dia- and metaphysis, 12 plates and two nails were used for osteosynthesis. Intralesional curettage and defect filling with bone cement (Refobacin R ®, Biomet GmbH, Berlin, Germany) was additionally performed in 38 cases (35 plates; 3 nails). If patients presented with a pathologic fracture and a neoplastic disease was not yet diagnosed a biopsy and staging was performed prior to stabilisation. If metastatic disease of the primary tumour was obvious a tissue specimen for histology was taken during the stabilisation procedure. Fifty-eight patients were treated for a pathologic fracture whereas 8 patients presented with an impending fracture with a mean Mirels Score of 9 (range 8–10). Twenty-two patients had initial non-operative treatment of the metastasis (chemotherapy n=10; clinical observation n=8; radiotherapy n=3; radiochemotherapy n=3) before surgical treatment became necessary. For these, the mean time period from detection of metastasis until operation was 17.6 months (range 2–74). Average duration of surgery was 97.8 minutes (range 32–176) and lengths of total hospitalisation (including oncologic and radiotherapeutic treatment) was 20.5 days on average (range 5–66).

Complications

We observed no systemic and five (7.6%) procedure-related complications. These included one patient that suffered from a temporary radial nerve palsy following plate ostesynthesis of a pathologic fracture and four (6.1%) implant failures (Table 1). One of these failures was caused by initial treatment being technically insufficient (single conventional plate) needing revision to an adequate (double plate) and angular stable plate system (Fig. 2). The other reason for failure was progressive peri-implant osteolysis with drawing the basis for stable implant fixation or fatigue failure of the implant in longer-term survival patients due to impaired biology restricting from adequate fracture healing needing revision to a new osteosynthesis or tumour prosthesis (Fig. 3). The mean time from initial surgery to revision was 22.2–20.6 months. There was no correlation between implant failure and bony volume of the metastasis or type of implant used.

Fig. 2. Implant failure after insufficient stabilisation with single conventional plate (DCP); a) postop. X-ray after 22 days showing pullout of screws and dislocation of the plate; b) postop. X-ray 28 days after revision (double LCP plate + cement) showing progressive lysis leading to instability; c) postop. X-ray after 2nd revision with long LCP.

The cumulative disease specific survival rate of all patients was 16.3 months (Fig. 4). The steepest decline was observed in the first twelve months. Patients showed a cumulative survival of 36% after 1 year, 26% after 2 years, 13% after 3 years and 4% after 5 years. The cumulative mean survival of patients with and without pathological fractures, application of cement, as well as patients treated with plate or nail fixation did not show a significant difference between the groups as illustrated in figure 5. Multiple regression analysis did not reveal any significant prognostic factors affecting cumulative survival.

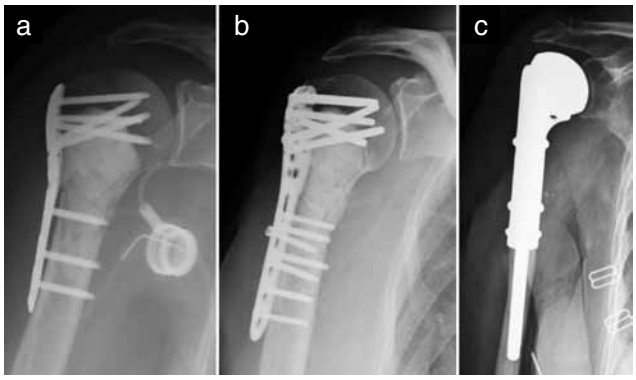

Fig. 3. Implant failure after compound osteosynthesis of proximal humerus; a) initial postop. X-ray, distal screw breakage after 4 years. required revision to a longer plate system (postop. image not displayed) ; b) postop. X-ray 5 months after revision again showing srew loosening and plate dislocation with beginning varus collapse; c) postop. X-ray after 2 revision to a proximal humerus replacement.

DISCUSSION

Due to their high incidence, the most frequent tumours metastasizing to the skeletal system are prostate and breast cancer (1, 12, 15), but in our cohort the most abundant type of primary was renal cell carcinoma. This is in accordance to the distribution of primary tumours in other studies focusing on metastatic dissemination to the humerus (16) and may explain the prolonged mean survival in our cohort with 16.3 month, whereas other authors report about survival being less than 4 months (13, 14). The variety in survival, reported to range from 16% to 88% after one year (2, 5, 15, 16) may be explained by the different composition of primary tumours, metastasis load (stage of disease), bone localisation and rate of impending/pathologic fractures.

There is a paucity of literature regarding the appropriate time-point for intervention. Our data suggest that prophylactic surgery in impending fractures does not improve survival, which is in accordance to other reports (5). In contrast Katzer et al. showed, that patients with stabilisation of impending fracture had a nearly 6-month longer survival than those with pathologic fracture (10). But an improved survival may not be misinterpreted as surgery bringing the cure to the patient with an impending fracture. It is rather the less advanced stage of neoplastic disease which leads to a longer survival compared to those with pathologic fracture. In our series 8 patients (12.1%) received prophylactic surgical fixation for an impending fracture, which is rather low in contrast to 18.9–39% in other studies (12, 15). Different biomechanical conditions at the humerus when compared to femur or tibia (less axial but increased torsional loading) may complicate anticipation and prediction of pathological fracture. Mirels suggested a scoring system two decades ago (11), that was recently shown to

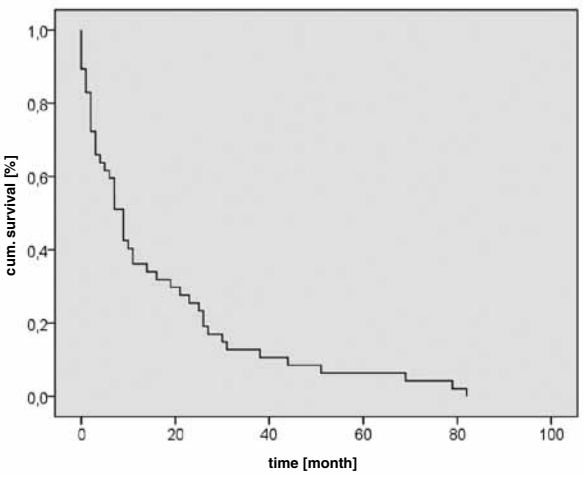

Fig. 4. Kaplan-Meier analysis of cumulative survival.

be reproducible and valid also for humeral lesions (6). Reaching a Mirels score of 8 underlines the importance of additional clinical judgment as the risk for pathological fractures markedly increases. In total, 22 patients of our series with initial presentation of a humeral metastasis were followed for a mean of 17.6 months before intervention became necessary due to pain or functional decrease. Since the cumulative survival of our cohort was relevantly surpassed, thorough clinical judgment with restricted and well defined indication for surgical intervention is essential, in order to prevent unnecessarily performed surgeries with the risk for intra- or postoperative complications in these palliative patients with limited life expectancy.

Surgical intervention prior to fracture is technically less demanding and is associated with decreased blood loss and a lower complication rate (5, 8). However, up to a 4-fold higher number of systemic complications was reported by a recent study with fatal embolisms after treating impending fractures (12). Scoring systems for survival prediction to avoid overtreatment in patients with low life expectancy have been proposed (9, 12). However, they have limited value since they have not been prospectively validated (1).

Generally, surgical treatment of humerus metastases is associated with advantages such as early mobilization and preservation or recovery of function (5, 8, 15). However, skeletal complications in patients with bone metastases are common as progressive osteolysis result in fracture and/or implant loosening and the bone healing response following radiation and/or chemotherapy is decreased. In the past years, substantial progress has been made in decreasing implant related failures by development of angular stable implants, but indeed, effective prevention of these adverse events by developing new implant fixation concepts and surgical technique remains to be a future perspective. The overall complication rate (7.6%) observed in our series compares favorably to reports in literature (2, 16). While transient nerve palsy was observed in one patient (1.5%) following compound plate osteosynthesis for a diaphyseal fracture, rate of radial nerve palsy for similar indications is reported to be up to 5.5 or 5.8% (13, 15). Implants failed and needed revision in four patients of our series (Table 1). There was one early implant failure (22 days), which was related to a technical error. The plate was too short, did not offer angular stable locking options and no curettage and cement augmentation was performed (Fig. 2). The other failures were either due to progressive osteolytic destruction with loss of bone stock around the implant resulting in instability 1 year after initial surgery or to fatigue failure of hardware, which occured 2 and 4 years (Fig. 3) after initial surgery. In these patient tumours with favorable biology, including 2 renal cell carcinoma and 1 sarcoma, were the primary malignancies. Long survival time caused outlasting/ fatigue of the implants, underscoring the fact that surgical treatment needs to be adapted to estimated survival of the patients. These observations highlight the fact that as more individuals

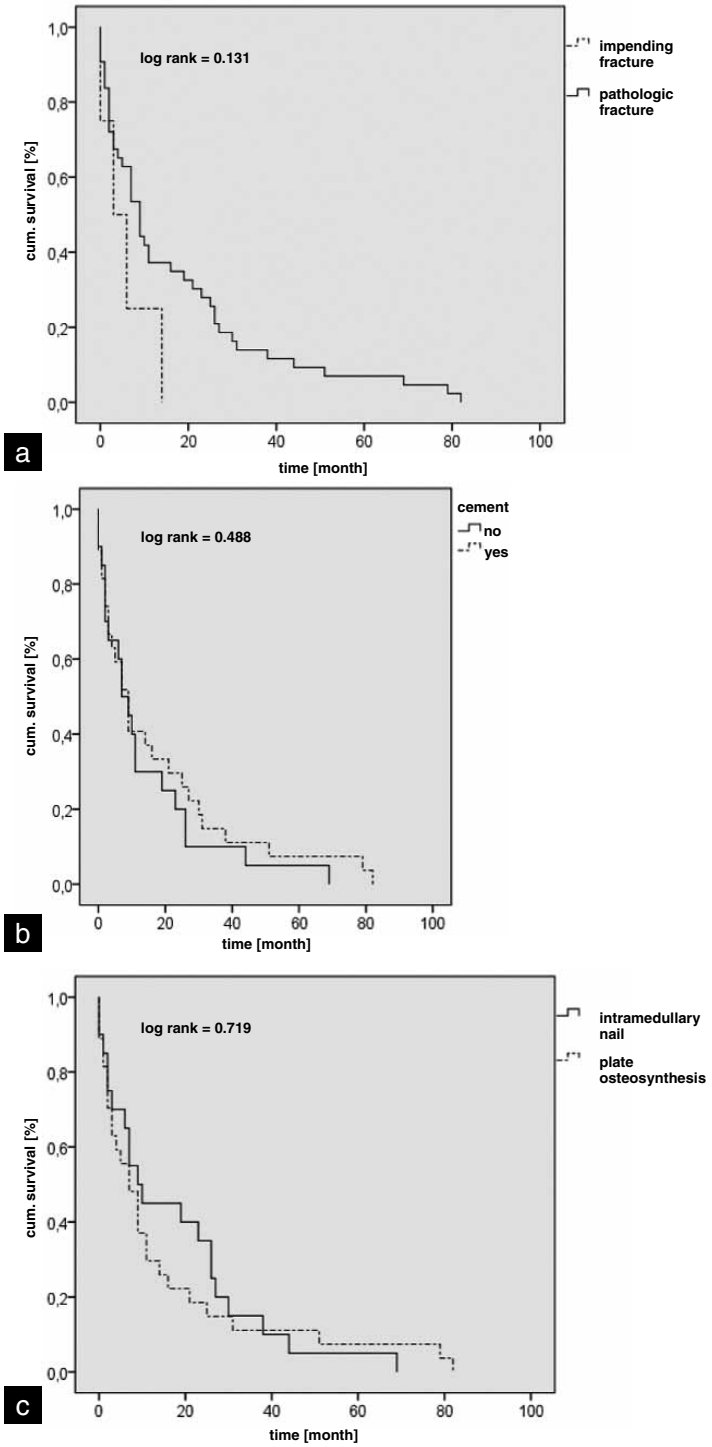

Fig. 5. Kaplan-Meier analysis of survival of patients with a) impending vs. pathologic fracture, b) cement augmentation and c) nail vs. plate fixation.

become long-term survivors of their primary malignancies, surgeons will need to focus on definitive initial surgical solutions and the early detection of implant failures.

In accordance to other authors (3, 5, 13, 16), we prefer the utilization of bone cement with plate osteosynthesis (35/38 cases) after intralesional curettage in order to achieve instant primary stability mostly in the metaphys-

eal areas. The additional curettage and cementation with nailing in diaphyseal fractures seems to be contradictive to the idea of managing pathologic fractures with the lowest surgical risk for collateral damage. However, in presence of extensive osteolysis and cortical bone loss this option appears valid, which has already been stated by others (16).

Apart from the retrospective design, the heterogeneous composition of primary tumour biology in our cohort is a major limitation when interpreting the results. Future research endeavors in the form of multi-center, prospective studies within a larger cohort have the theoretical potential to confirm our findings and expand them to further increase our knowledge regarding the treatment of humeral metastases. Unanswered questions regarding superiority of specific techniques and the optimum timing for surgical intervention need to be addressed by such studies aimed to increase quality of life and prevent surgery-associated complications in patients suffering from humerus metastases.

Conflict of interest: *The authors have no conflict of interest related to the present study.*

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., KOLLENDER, Y., WITTIG, J. C.: Function after resection of humeral metastases: analysis of 59 consecutive patients. Clin. Orthop. Relat. Res., 437: 201–208, 2005.
3. CAPANNA, R., CAMPANACCI, D. A.: The treatment of metastases in the appendicular skeleton. J. Bone Jt Surg., 83-B: 471–481, 2001.
4. COLEMAN, R. E.: Skeletal complications of malignancy. Cancer, 80(8 Suppl.): 1588–1594, 1997.
5. DIJKSTRA, S., STAPERT, J, BOXMA, H, WIGGERS, T.: Treatment of pathological fractures of the humeral shaft due to bone metastases: a comparison of intramedullary locking nail and plate osteosynthesis with adjunctive bone cement. Eur. J. Surg. Oncol., 22: 621–626, 1996.
6. EVANS, A. R., BOTTROS, J., GRANT, W., CHEN, B. Y., DAMRON, T. A.: Mirels‘ rating for humerus lesions is both reproducible and valid. Clin. Orthop. Relat. Res., 466: 1279–1284, 2008.
7. FRASSICA, F. J., FRASSICA, D. A.: Evaluation and treatment of metastases to the humerus. Clin. Orthop. Relat. Res., (415 Suppl.): S212–218, 2003.
8. GEBHART, M., DEQUANTER, D., VANDEWEYER, E.: Metastatic involvement of the humerus: a retrospective study of 51 cases. Acta Orthop. Belg., 67: 456–463, 2001.
9. HANSEN, B. H., KELLER, J., LAITINEN, M., BERG, P., SKJELDAL, S., TROVIK C., NILSSON, J., WALLOE, A., KALÉN, A., WEDIN, R.: The Scandinavian Sarcoma Group Skeletal Metastasis Register. Survival after surgery for bone metastases in the pelvis and extremities. Acta Orthop. Scand. Suppl., 75(311): 11–15, 2004.
10. KATZER, A., MEENEN, N. M., GRABBE, F., RUEGER, J. M.: Surgery of skeletal metastases. Arch. Orthop. Trauma Surg., 122: 251–258, 2002.
11. MIRELS, H.: Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. Clin. Orthop. Relat. Res., 249: 256–264, 1989.
12. RATASVUORI, M., WEDIN, R., 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., 2013. 22: 132–138, 2013.
13. SARAHRUDI, K., HORA, K., HEINZ, T., MILLINGTON, S., VÉCSEI, V.: Treatment results of pathological fractures of the long bones: a retrospective analysis of 88 patients. Int. Orthop., 30: 519–524, 2006.
14. SARAHRUDI, K., WOLF, H., PAJENDA, G., HAUSMANN, J. T., VÉCSEI, V.: Surgical treatment of pathological fractures of the shaft of the humerus. J. Trauma, 66: 789–794, 2009.
15. THAI, D. M., Y. KITAGAWA, CHOONG, P. F.: Outcome of surgical management of bony metastases to the humerus and shoulder girdle: a retrospective analysis of 93 patients. International seminars in surgical oncology : ISSO, 3: 5, 2006.
16. WEDIN, R., HANSEN, B. H., LAITINEN, M., TROVIK, C., ZAIKOVA, O., BERGH, P., KALÉN, A., SCHWARZ-LAUSTEN, G., VULT VON STEYERN, F., WALLOE, A., KELLER, J., WEISS, R. J.: Complications and survival after surgical treatment of 214 metastatic lesions of the humerus. J. Shoulder Elbow Surg., 21: 1049–1055, 2012.

Corresponding author:
Philipp Schwabe, MD
Center for Musculoskeletal Surgery
Charité - University Medicine Berlin
Augustenburger Platz 1
13353 Berlin, Germany
E-mail: philipp.schwabe@charite.de