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Short-term outcomes of en bloc resection of solitary bone metastases in limbs

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
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Summary

Background: To evaluate the pain, quality of life (QOL), and limb function of patients after en bloc resection of solitary metastatic bone cancer in the limbs.

Material/Methods: A total of 27 patients with solitary metastatic bone cancer in the limbs were recruited. All these patients underwent limb-salvage surgery with en bloc resection of the metastatic tumor. Pain and QOL were evaluated before and after surgery. Pain was assessed with a 10-point scale before and 1 month after surgery. The QOL was evaluated with the SF-30 scale before and 3 months after surgery. Limb function was evaluated with the Musculoskeletal Tumor Society scale (MSTS) 3 months after surgery. Follow-up was performed for 6~31 months (mean: 16.15±7.47 months).

Results: All procedures were successfully performed. Post-operative complications were found in 6 patients, including incision infection, prosthesis dislocation, deep vein thrombosis, and pulmonary infection. The pain score before and 1 month after surgery was 6.85±3.11 and 1.26±0.81, respectively, indicating obvious improvement (t=9.978, $P<0.001$). The QOL score before and 3 months after surgery was 38.30±13.05 and 65.78±10.65, respectively, indicating pronounced improvement (t=–18.550, $P<0.001$). The mean post-operative MSTS score was 23±3 (range: 17–30) (t=–1.450, $P=0.016$). No local recurrence was observed in any patient during the follow-up.

Conclusions: Limb salvage surgery with wide or marginal resection for solitary metastatic bone cancer may significantly improve the pain, QOL, and limb function, but there is no difference in local control between wide and marginal resection.

key words: **metastatic bone cancer • en bloc resection • limb function • quality of life • local recurrence**

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Background

Metastatic cancer is usually found in the bone, which is the third most common site of cancer metastasis [1]. Metastatic bone cancer often occurs in the axial skeleton such as pelvis, ribs, skull, and vertebrae [2]. Metastatic cancer of the limbs is frequently found at the proximal end of long bones such as the proximal end of the humerus and femurs [3]. Metastatic cancer of the limbs inevitably causes pain, limb dysfunction and formation of a bump, or even results in pathological fracture. These complications significantly influence the quality of life (QOL) and affect the performance of adjunctive therapies, including chemotherapy and radiotherapy, which may further influence the survival time and the prognosis of these patients [4–6].

Non-surgical treatment is a major strategy for the treatment of multiple metastatic bone cancers of limbs, and, in addition to radiation (external beam radiation, radiopharmaceuticals), adjunctive therapies include bisphosphonates and chemotherapeutic agents, ablative techniques (radiofrequency ablation [RFA] and cryoablation), inhibitors of RANK-RANKL interaction (eg, denosumab), hormonal therapies, and interventional techniques (eg, kyphoplasty) [7,8]. For patients developing pathological fracture at the limbs, palliative surgical treatment is frequently adopted in which the lesions are removed completely, followed by filling of bone cement and fixation with plates and screws or intramedullary nails [9–11]. These treatments may relieve the pain, but are less beneficial for the recovery of limb function, and weight-bearing walking is usually not possible using a crutch or a walker, so these patients often have poor QOL [12–14]. For patients with solitary metastatic bone cancer of the limbs, palliative surgical treatment is often clinically preferred [15]. In the present study, solitary metastatic bone cancer of the limbs was treated according to the principles for the treatment of primary bone cancer. En bloc resection was performed, followed by limb-salvage reconstruction of bone defects and limb function. To analyze the effectiveness of this strategy, the pain, QOL, limb function, tumor-free survival and operative complications were evaluated.

Material and Methods

General data

From 2007 to 2010, a total of 27 patients with solitary metastatic bone cancer were treated in our department, including 15 males and 12 females, with a mean age of 58±8.58 years (range: 43–75 years). Follow-up was carried out for 16.15±7.47 months (range: 6–31) (t=1.073, P=0.294). The primary cancers included lung cancer in 7 patients, renal carcinoma in 6, breast cancer in 5, prostate cancer in 2, endometrial carcinoma in 1, thyroid cancer in 1, colon cancer in 1, rectal cancer in 1, liver cancer in 1, glioma in 1, and gastric cancer in 1 patient. Metastatic bone cancer was detected 8~123 months (mean: 42.20±33.61 months) after diagnosis of primary cancers in 20 patients, but metastatic bone cancer as the first sign facilitating the diagnosis of primary cancers was detected in 7 patients. The cancer metastasis sites included the proximal end of the femur in 11 patients, proximal end of the humerus in 6, middle part of the humerus in 3, scapula in 2, middle part of the femur in 2, distal end of the femur in 1, middle part of the ulna in 1, and proximal end of the tibia in 1 patient. The complaints included simple pain in 10 patients, pain and bump in 6, and pathological fracture in 7 patients. Four patients had no complaints and metastatic bone cancer was identified by routine ECT or PET. All data are shown in Table 1.

Surgical procedures

Limb-salvage surgery was performed in all patients according to the principles for the treatment of primary bone cancer. Artificial prosthetic replacement was performed in 21 patients, simple resection in 2, reconstruction with allogeneic bones in 2, inactivated bone replantation in 1, and removal of hemi-cortex of the bone, filling of bone cerement, and internal fixation in 1 patient. In 7 patients, primary cancer and metastatic bone cancer were identified simultaneously and then a one-stage operation was carried out for resection of primary cancer and metastatic cancer simultaneously. According to the Enneking's Staging System, wide resection was done in 19 patients and marginal resection in 8 patients. In 21 patients, post-operative systemic chemotherapy and/or local radiotherapy were performed, of whom 7 patients receiving marginal resection underwent local radiotherapy post-operatively. Six patients received surgical intervention alone and no adjunctive therapy was carried out.

Post-operative evaluation

QOL and pain were evaluated before and after surgery in 21 patients. Pain was assessed with the 10-point scale before and 1 month after surgery. The QOL was assessed with the SF-36 scale [14] before and 3 months after surgery. Scoring was done by the same physician. Post-operative limb function was evaluated with the American Musculoskeletal Tumor Society (MSTS) system 3 months after surgery.

Statistical analysis

Statistical analysis was performed with SPSS version 14.0. Quantitative data with normal distribution were expressed as mean ± standard deviation to describe the central tendency or discrete tendency. The scores of pain, QOL, and limb function were compared with the t test. Long rank test was employed for survival analysis between groups. Tumor-free survival was defined as the time from the end of surgery to the presence of new lesions. A value of $P<0.05$ was considered statistically significant.

Results

Postoperative complications

All procedures were performed successfully, and no patient died during the follow-up period. Superficial incision infection was found in 2 patients and resolved after debridement. Post-operative prosthesis dislocation occurred in 1 patient and closed reduction was successfully carried out. Deep venous thrombosis was found in 3 patients of whom inferior vena cava filter was placed in 2 and systemic anti-coagulation therapy done in 1 patient. Pulmonary infection was controlled following anti-infection therapy in 1 patient.

Table 1. Patient date of all 27 patients.

Case	Gender	Age	Lesion site	Primary cancer	Diagnostic time to primary onset (m)	Complaints	Surgical methods	Resection method	Post-operative adjunctive therapy	Follow up (m)	Tumor free survival (m)
1	Male	43	Proximal end of femur	Lung cancer	Simultaneous	Pain and bump	Radical resection for lung cancer + Prosthetic replacement	Marginal	Chemotherapy/ local radiotherapy	13	9
2	Male	56	Proximal end of bilateral femurs	Prostate cancer	Simultaneous	Bilateral pathological fracture	Bilateral Prosthetic replacement	Wide	Chemotherapy	26	19
3	Male	62	Middle part of femur	Lung cancer	28	Identification by ECT	Resection of hemi-cortex +bone cerement filling and fixation	Wide	Chemotherapy	8	5
4	Female	45	Proximal end of humerus	Renal carcinoma	Simultaneous	Pathological fracture	Radical nephrectomy + Prosthetic replacement	Wide	Chemotherapy	30	30
5	Female	58	Subscapular angle	Breast cancer	97	Pain and bump	Subscapular resection	Wide	Chemotherapy	15	15
6	Male	68	Proximal end of femur	Lung cancer	12	Pain and bump	Prosthetic replacement	Marginal	Chemotherapy/ local radiotherapy	9	7
7	Female	64	Proximal end of femur	Endometrial cancer	8	Pathological fracture	Prosthetic replacement	Wide	Chemotherapy	11	9
8	Female	55	Middle part of humerus	Lung cancer	15	Pain	Implantation of allogeneic bone and fixation with plates	Wide	Chemotherapy	6	5
9	Female	48	Proximal end of humerus	Breast cancer	22	Identification by PET	Prosthetic replacement	Wide	Chemotherapy	19	19
10	Male	59	Proximal end of femur	Prostate cancer	64	Pain	Prosthetic replacement	Wide	No	14	11
11	Male	67	Proximal end of femur	Glioma	15	Pain	Prosthetic replacement	Wide	Chemotherapy	7	4
12	Male	58	Proximal end of tibia	Renal carcinoma	Simultaneous	Pathological fracture	Radical nephrectomy + Prosthetic replacement	Marginal	Chemotherapy/ local radiotherapy	17	12
13	Male	49	Glenoid fossa	Liver cancer	8	Pain	Resection of scapula	Wide	Chemotherapy	6	3
14	Female	70	Proximal end of femur	Breast cancer	123	Pain	Prosthetic replacement	Wide	No	25	21
15	Male	57	Distal end of femur	Renal carcinoma	24	Pain	Prosthetic replacement	Wide	Chemotherapy	21	16
16	Male	45	Middle part of humerus	Lung cancer	Simultaneous	Pathological fracture	Radical resection + Prosthetic replacement	Marginal	Chemotherapy/ local radiotherapy	14	10
17	Male	62	Middle part of ulna	Rectal cancer	37	Pain and bump	Implantation of inactivated bone and fixation with plates	Marginal	Local radiotherapy	23	23

Table 1 continued. Patient date of all 27 patients.

Case	Gender	Age	Lesion site	Primary cancer	Diagnostic time to primary onset (m)	Complaints	Surgical methods	Resection method	Post-operative adjunctive therapy	Follow up (m)	Tumor free survival (m)
18	Female	54	Proximal end of femur	Thyroid cancer	51	Pain	Prosthetic replacement	Wide	No	14	14
19	Male	65	Proximal end of femur	Gastric cancer	18	Identification by ECT	Prosthetic replacement	Wide	No	10	8
20	Male	71	Proximal end of humerus	Renal carcinoma	71	Pathological fracture	Prosthetic replacement	Marginal	Local radiotherapy	29	25
21	Male	55	Middle part of humerus	Lung cancer	Simultaneous	Pain	Radical resection + Prosthetic replacement	Wide	Chemotherapy	12	10
22	Female	56	Proximal end of femur	Breast cancer	11	Pathological fracture	Prosthetic replacement	Wide	No	8	8
23	Female	75	Proximal end of humerus	Renal carcinoma	62	Pain and bump	Prosthetic replacement	Marginal	Local radiotherapy	22	20
24	Male	57	Middle part of femur	Renal carcinoma	95	Pain	Implantation of allogeneic bone and fixation	Wide	Chemotherapy	31	31
25	Female	46	Proximal end of humerus	Lung cancer	Simultaneous	Pain	Prosthetic replacement	Wide	Chemotherapy	16	13
26	Female	67	Proximal end of humerus	Breast cancer	49	Identification by PET	Prosthetic replacement	Wide	No	16	16
27	Female	58	Proximal end of femur	Colon cancer	34	Pain and bump	Prosthetic replacement	Marginal	Chemotherapy/local radiotherapy	14	10

Table 2. Scores of pain and QOL before and after surgery.

	Before surgery	After surgery	t	P
Score of pain	6.85±3.11	1.26±0.81	9.978	0.000
Score of quality of life	38.30±13.05	65.78±10.65	–18.550	0.000

Evaluation of pain, QOL and limb function

As shown in Table 2, the score of pain was 6.85±3.11 and 1.26±0.81 before and 1 month after surgery, respectively, indicating that the post-operative pain was markedly improved (t=9.978, $P<0.001$). The QOL score was 38.30±13.05 and 65.78±10.65 before and 3 months after surgery, respectively, revealing the quality of life was dramatically improved following surgery (t=–18.550, $P<0.001$). The post-operative score of limb function ranged from 17 to 30 (mean: 23±3) (t=–1.450, $P=0.016$). Activities of daily living recovered in all patients. For patients with metastatic bone cancer in lower limbs, they could walk with or without a walker.

Local recurrence

Regarding cancer control, no local recurrence occurred in these 27 patients during the follow-up period. As shown in Figure 1, log rank testing revealed there was no significant difference in the tumor-free survival between patients receiving wide resection and marginal resection ($\chi^2=0.121$, $P=0.728$).

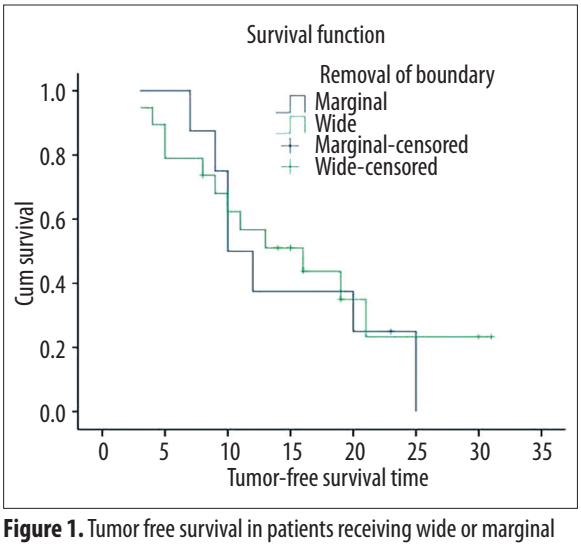

Figure 1. Tumor free survival in patients receiving wide or marginal resection.

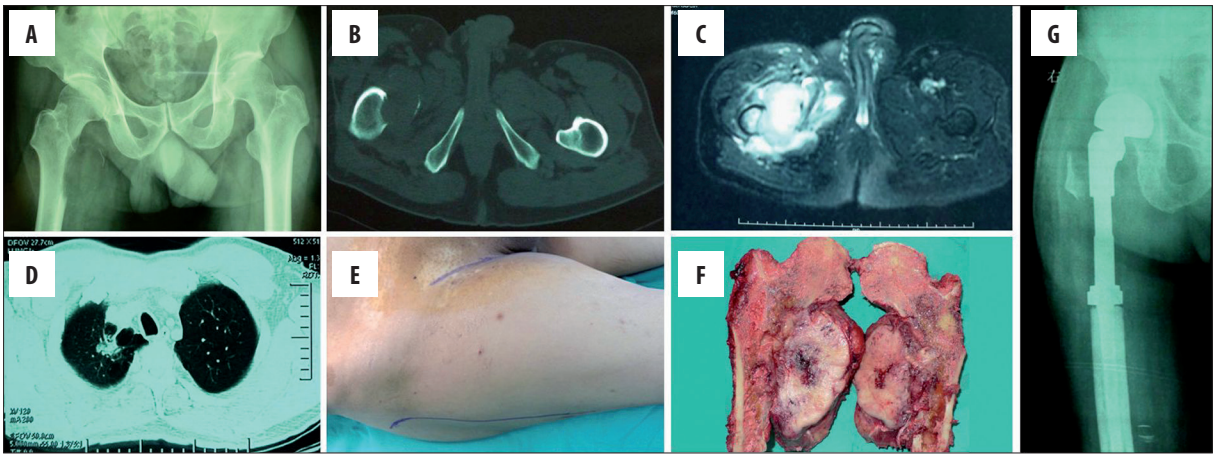

Figure 2. Metastatic bone cancer in the right femur. (**A**) X-ray revealed bone destruction and a tumor at the lesser trochanter of the right femur; (**B**) CT revealed bone destruction and a tumor at the internal side of the affected bone; (**C**) MRI revealed hypertense in T2 weighted images accompanied by edema of surrounding tissues; (**D**) CT revealed right lung cancer; (**E**) gross observation demonstrated a soft tissue mass at the incision site; (**F**) longitudinal section of the cancer; (**G**) post-operative X-ray.

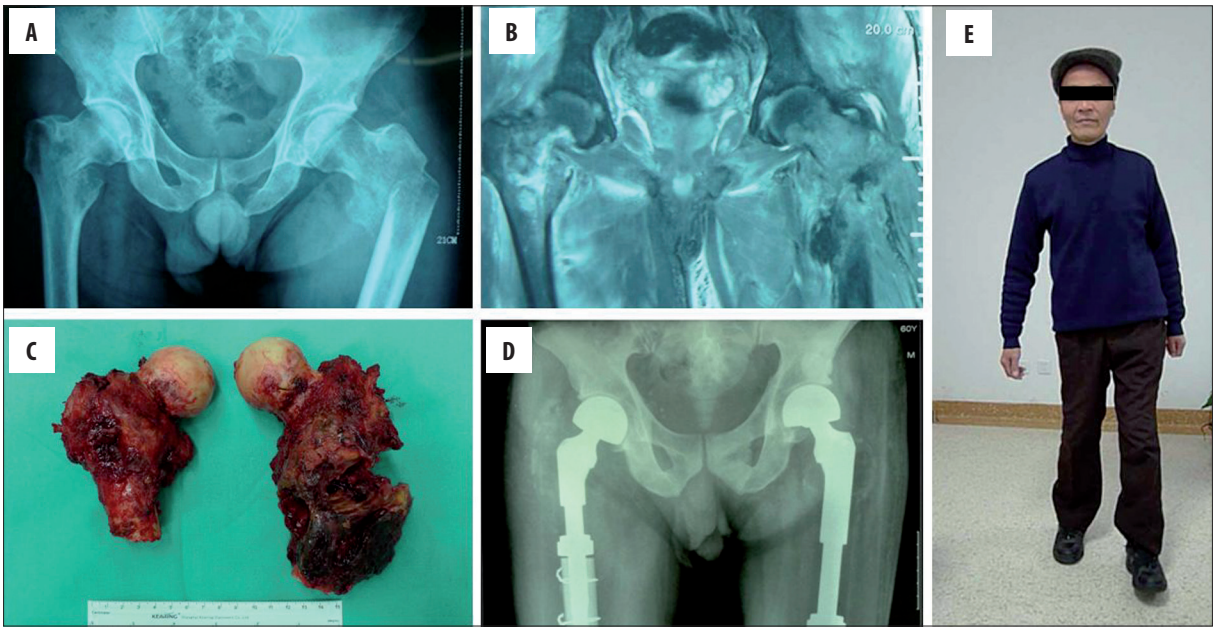

Figure 3. Pathological fracture of the proximal end of bilateral femurs due to the metastasis of prostate cancer. (**A**) Pre-operative X ray; (**B**) hyperintese in T2 weighted images of MRI; (**C**) post-operative gross observation; (**D**) post-operative X ray; (**E**) gait at 3 months after surgery.

Representative cases

Case 1: Male, 43 years old, lung cancer. He was admitted due to pain and presence of pain and bump at the right hip for 2 months. On examination, a mass was found in the right lung and subsequent pathological examination revealed lung cancer. Radical resection for lung cancer and marginal resection of the bone cancer were performed (Figure 2).

Case 2: Male, 56 years old, prostate cancer concomitant with pathological fracture at proximal end of bilateral femurs. En bloc resection of the bone cancer and bilateral prosthetic replacement were performed (Figure 3).

Case 4: Male, 45 years old, renal carcinoma. Pathological fracture at the left humerus was found and subsequent pathological examination confirmed renal carcinoma. Left radical nephrectomy and en bloc resection of cancer at the left humerus were performed, followed by artificial prosthetic replacement (Figure 4).

Case 17: Male, 62 year old, swelling and pain at left forearm 2 years after resection of rectal cancer. Implantation of inactivated bone and internal fixation with plates were performed after marginal resection of the bone cancer (Figure 5).

Discussion

The bone is the third most common site of cancer metastasis, following lung and liver. In addition to the limbs, the

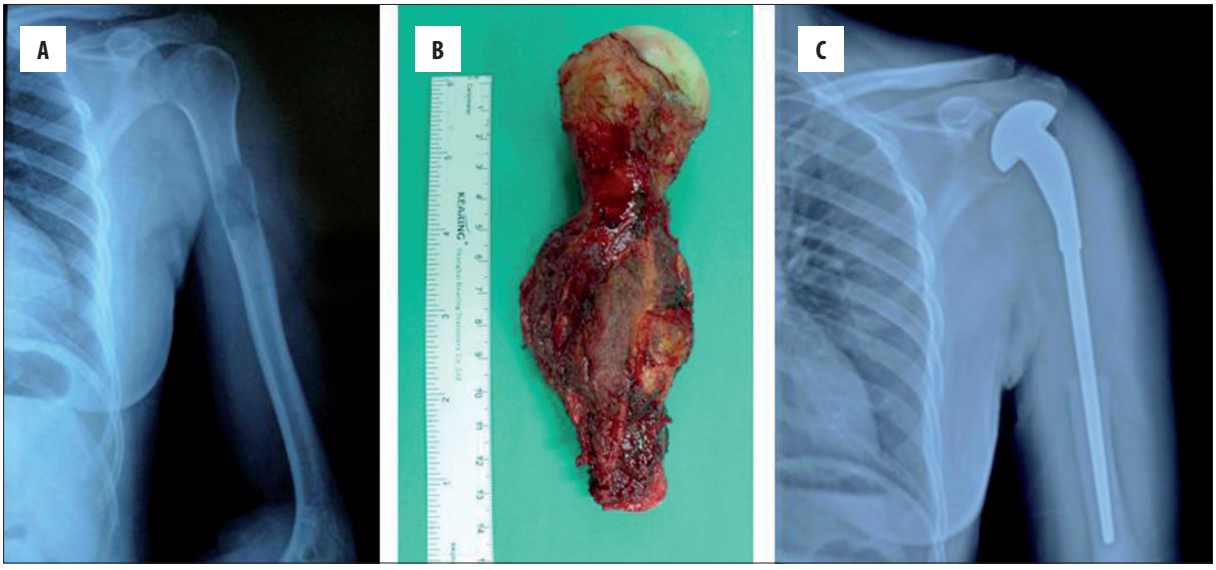

Figure 4. Pathological fracture at the left humerus due to the metastasis of renal carcinoma. (**A**) X-ray revealed osteolytic lesion and fracture at the left humerus; (**B**) post-operative gross observation; (**C**) post-operative X-ray.

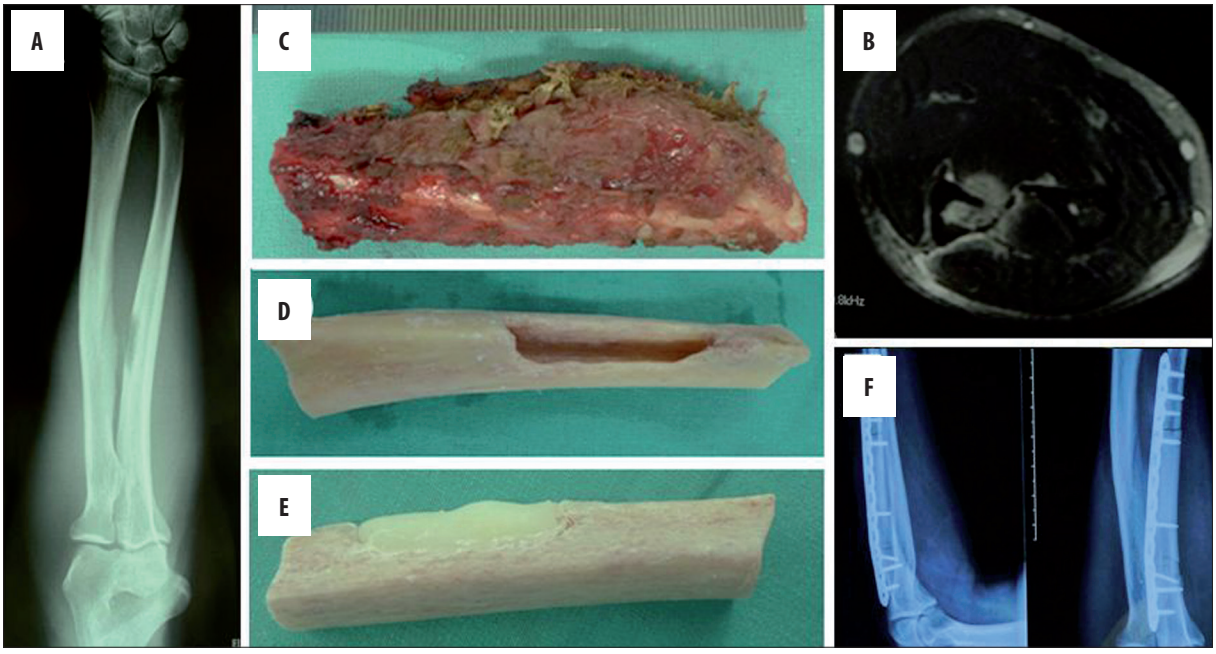

Figure 5. Metastatic bone cancer in the left forearm. (**A**) pre-operative X ray revealed local bone destruction at the middle of ulna; (**B**) hypertense in T2 weighted image of MRI and soft tissue mass; (**C**) post-operative gross observation; (**D**) lesioned bone after removal of cancer; (**E**) inactivated cancer-bearing none and filling of bone cerement; (**F**) post-operative X ray showed replantation of inactivated bone and fixation with plates.

spine is also a common site of cancer metastasis [3,16]. In the present study, we primarily focus on the surgical treatment of metastatic bone cancer of the limbs. Comprehensive therapy is preferred for the metastatic bone cancer, including surgical intervention, chemotherapy, radiotherapy and other conservative therapies [7,8,17]. Metastatic bone cancer is a systemic disease, thus surgical therapy is usually performed on the basis of other adjunctive therapies.

The majority of metastatic bone cancers are predominantly derived from lung cancer and breast cancer, followed by renal carcinoma, thyroid cancer and prostate cancer [18–20]. Metastatic bone cancer from lung cancer/renal carcinoma is usually characterized by osteolytic lesions [19], thus patients with this disease are susceptible to pathological fracture, and surgical intervention is required. Metastatic bone cancer from breast cancer/prostate cancer is usually osteogenic, especially in patients with prostate cancer [20]. When compared to patients with osteolytic lesions, those with osteogenic lesions seldom develop pathological fracture; conservative therapy is often performed and surgical intervention less often required [20,21].

In the present study, 1 patient with prostate cancer developed metastatic bone cancer and subsequent pathological fracture at the proximal end of bilateral femurs. Thus, for metastatic bone cancer patients with osteogenic lesions, the risk for pathological fracture should also be paid attention to, especially in those with intertrochanteric lesions. Mirels score is an important tool for the evaluation of risk for pathological fracture [22]. Patients with a Mirels score of ≥9 are regarded to have high risk for fracture, and active prophylactic surgery is required. For patients developing pathological fracture, determination of surgical intervention is done based on the general conditions: tolerance to surgery, time from identification of primary disease to metastatic bone cancer, disease progression, expected survival time, extent of post-operative QOL improvement, and post-operative limb function [5,16,21]. Generally, surgical intervention should be considered for patients with favorable general condition, able to tolerate surgery, having no progression of primary disease, with expected survival time of longer than 6 months, and having poor QOL due to pathological fracture [23,24]. Once surgical intervention is determined for the treatment of pathological fracture, the requirements are similar to those in the treatment of primary bone cancer. Wide or marginal resection is needed to reconstruct limb function [25]. The reconstruction should be beneficial for the rapid recovery of limb function or partial load-bearing. Usually, artificial prosthetic replacement is performed in patients with lesions near the joint; implantation of allogeneic bone or inactivated cancer-bearing bone, followed by internal fixation with plates, is recommended for patients with lesions at the bone shaft or non-weight-bearing site. In the present study, lesions were mainly found at the site near the joint, and thus artificial prosthetic replacement was the major strategy for the treatment; the post-operative limb function was markedly improved.

For pathological fracture, surgical treatment aims to relieve the pain and improve the QOL and limb function [4,5,12]. In the present study, surgical intervention was performed in patients with solitary metastatic bone cancer. Results demonstrate that post-operative pain, QOL, and limb function were dramatically improved. However, for patients with multiple bone metastases, surgical intervention is unable to achieve wide resection or resection of foci, and is usually highly invasive. Under this condition, patients usually have high surgical risk. Moreover, these patients have poor prognosis. Thus, selection of surgical intervention should be cautious [26,27].

In the present study, wide resection was performed in the majority of patients and a minority of patients received marginal resection. Post-operative local radiotherapy was also carried out as an adjunctive therapy, achieving favorable control of local tumors. No patients developed local recurrence during the follow-up period. In addition, statistical analysis showed there was no significant difference in the tumor-free survival time between patients receiving wide *vs.* marginal resection. This demonstrates that only systemic treatment is an effective strategy to improve the survival of cancer patients. Nevertheless, the wide or marginal resection of the cancer plays an important role in the control of local cancer and pain, and improvement of QOL and limb function.

In our study, metastatic bone cancer was the first sign in 7 patients and further examinations identified primary diseases. Of these patients, 6 received 1-stage resection of primary cancer and metastatic bone cancer simultaneously. The remaining patient had prostate cancer and pathological fracture at the proximal end of the bilateral femurs. Bilateral lesions were resectable and treatment was similar to that in patients with solitary metastatic bone cancer. One-stage resection of lesions at bilateral femurs was performed, followed by joint replacement, and endocrine therapy was done as a treatment for primary prostate cancer. For patients with resectable primary and metastatic lesions, post-operative chemotherapy and/or radiotherapy is recommended, which may significantly delay disease progression in the tumor-free survival time, elevate survival rate and improve QOL. This should be done in the presence of completely resectable primary and metastatic lesions. For these patients, resection of a single lesion may pronouncedly affect the effectiveness of adjunctive therapy and survival of cancer-bearing patients.

Conclusions

For patients with solitary metastatic bone cancer of the limbs, limb salvage surgery with wide or marginal resection is beneficial for the improvement of post-operative pain, QOL and limb function. In addition, the control of local cancer is also favorable and the local recurrence rate not influenced. For patients with metastatic bone cancer with concomitant primary cancer, 1-stage resection of both lesions is recommended, which may delay disease progression and improve the survival rate. In our study, the time of follow-up was relatively short, and the effect of limb salvage surgery on the overall survival needs to be further investigated in studies with long-term follow-up.

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