

## Limb Salvage Strategy by Intra-Arterial Chemotherapy for Local Recurrent Osteosarcoma in Extremities

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### Abstract

**Objective:** The feasibility of intra-arterial chemotherapy for local recurrent extremity osteosarcoma with prosthesis replacement.

**Methods:** 9 local recurrent limb osteosarcoma patients with prosthesis replacement who received treatment during the period from April 2010 to June 2013 at our hospital were recruited, including 3 patients with lung metastasis. All patients were treated with intra-arterial chemotherapy via implanted pump at affected limb.

**Results:** The local recurrent neoplasms calcified and formed clear boundary with normal tissues after 3 to 5 cycles intra-arterial intervention chemotherapy, which indicates the osteosarcoma was controlled effectively to facilitate the osteosarcoma excision. No local recurrence happened during the follow-up visit varied from 12 to 38 months. The late result was better in 6 patients without lung metastasis than 3 patients with lung metastasis, 2 of who died and 1 currently survive without tumor.

**Conclusion:** Intra-arterial intervention chemotherapy could effectively curb the progress of local recurrent osteosarcoma to facilitate the subsequent limb salvage treatment, and prolong the lifetime of patients with lung metastasis.

**Keywords:** Osteosarcoma; Local recurrence; Intra-arterial chemotherapy; Limb salvage

### Introduction

Osteosarcoma is a most common bone primary malignant tumor with high fatality rate. Since 1970's, the survival rate of osteosarcoma increased significantly with the application of chemotherapy, and neo-adjuvant chemotherapy could minimize the tumor and clarify its boundary to facilitate limb salvage, in which prosthesis replacement is one of the most commonly applied strategies. Nonetheless, local recurrence or metastasis would happen in 10% to 20% patients with any limb salvage strategies. Controversy still exists on the treatment of local recurrence, but surgical removal is considered as principle strategy, even amputation is not always necessary. The clear boundary between normal tissues and neoplasm is the prerequisite for surgery, for which we apply intra-arterial intervention chemotherapy to enable the limb salvage.

### Materials and Methods

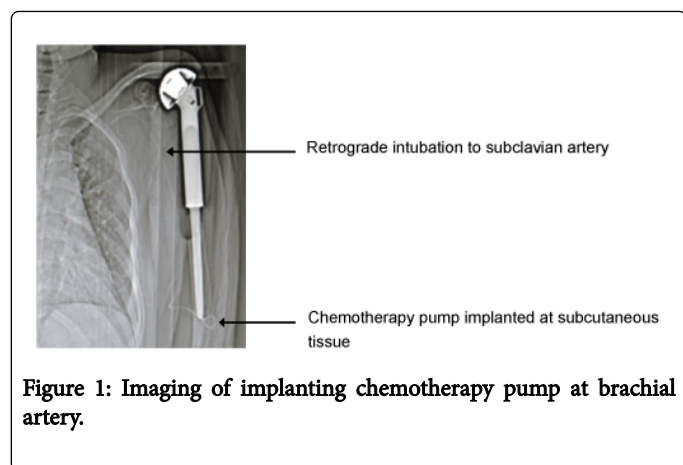
#### Study Object

9 patients with local recurrent limb osteosarcoma with prosthesis replacement from April 2010 to June 2013 were recruited, including 4 males and 5 females, aging between 14 to 35 (with average age of 21 years old), among whom 2 cases had osteosarcoma in proximal humerus, 1 case in distal femur, 4 cases in proximal femur, and 2 cases

in proximal tibia. Local recurrence happened 6 to 22 months (12 months on average) after the first surgery, and the minimal recurrent neoplasm is  $3 \times 4 \times 5 \text{cm}^3$ , the maximal is  $10 \times 12 \times 18 \text{cm}^3$ . 3 cases had lung metastasis, and the pathology of all patients is osteosarcoma.

#### Treatment

With complete clinical and imaging diagnosis, the patients were applied with arterial infusion chemotherapy pump implanted at subcutaneous tissue connected with catheter, the patients with osteosarcoma in upper limb were implanted with pump at subclavian artery by selective retrograde intubation via brachial artery of affected limb, and the patients with osteosarcoma in lower limb were implanted with pump at external iliac artery by retrograde intubation via femoral artery of affected limb (Figure 1). With the implanted pump, all patients were administered with epirubicin (EADM)  $50 \text{mg/m}^2$ , cisplatin (CDDP)  $120 \text{mg/m}^2$ , and ifosfamide was additionally applied through vein. At an interval of 2 -3 weeks, chemotherapy enters the next cycle, and B-ultrasound scan and CT were performed after 3-4 cycles chemotherapy. Surgery would be performed when the boundary between tumor and normal tissues and prosthesis was clear enough (Figure 1).



tumor area, X-ray or CT scan on lung were included in each follow-up visit. Among 3 patients with lung metastasis, 2 cases came out with unsatisfactory effects and no obvious improvement on lung metastasis, who died after 7 and 9 months treatment respectively. The rest 1 patient with lung metastasis reacted sensitively to chemotherapy, who later underwent surgical removal of local recurrent tumor and gamma knife treatment on the metastatic lung tumors, and this patient still survive with tumor in stable condition after 16 months' follow-up visit. The other 6 patients were all sensitive to chemotherapy, and the examination during the follow-up visit showed that: B-ultrasound indicated that the signal of blood flow reduced within tumor and artery peak flow velocity in tumor decreased significantly; imaging examination indicated that soft-tissue mass shrunk, the calcification and restoration increased, the boundary between tumor and surrounding tissues was relatively clear, liquefaction and calcification happened in some area, pseudocapsule formed, and tumor tended to repair (Figure 2 and 3). Surgery was performed in these 6 cases after chemotherapy to enable limb salvage, and no local recurrence was found during the follow-up visit (Table 1).

## Results

Follow-up visit varied from 12 to 38 months, averaged at 29 months. Inquiry on progress of disease, B-ultrasound and X-ray or CT scan on

Parameters	Case1	Case2	Case3	Case4	Case5	Case6	Case7	Case8	Case9
Age	35	21	16	23	14	22	18	20	19
Gender	female	male	male	male	female	female	male	male	female
Site	Proximal humerus	Distal femur	Proximal femur	Distal femur	Proximal humerus	Proximal tibia	Distal femur	Distal femur	Proximal tibia
Time to relapse	22 months	16 months	8 months	15 months	6 months	11 months	10 months	9 months	10 months
Lung metastases	none	none	yes	none	yes	none	none	none	yes
Tumor size (cm3)	5×7×8	9×10×11	6×8×9	10×12×18	5×7×10	3×4×5	5×6×7	6×7×9	9×10×12
Resection of recurrence	yes	yes	yes	yes	none	yes	yes	yes	none
The result	alive	alive	Survival with tumor	alive	die	alive	alive	alive	die

**Table 1:** The conditions and treatments to patients.

## Discussion

### The current treatment strategies of osteosarcoma

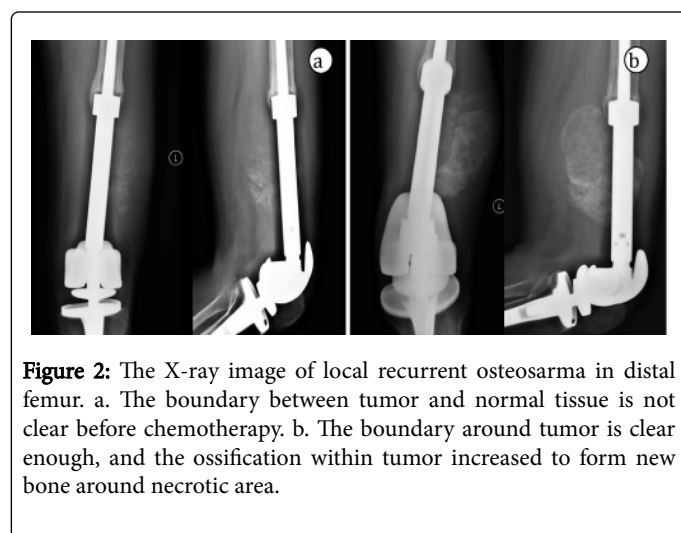
Osteosarcoma is the most common bone primary malignant tumor with high fatality rate. Since 1970's, the survival rate of osteosarcoma increased significantly after the application of chemotherapy, and neo-adjuvant chemotherapy is not only effective in tiny metastases but also minimize the primary foci and clarify its boundary. To a large extent, the recent progress on the treatment of osteosarcoma results from the application of neo-adjuvant chemotherapy, and the limb salvage treatment of osteosarcoma has become the mainstream with the progress of neo-adjuvant chemotherapy, surgical techniques, and bone reconstruction, in which prosthesis replacement is one of the most commonly applied strategies. It is considered that limb salvage surgery should meet the following 3 prerequisites: (1) The primary osteosarcoma should be sensitive to chemotherapy on clinical and

imaging indexes. (2) Enough tumor removal boundaries. (3) Limb is reconstructed with enough function through simple, effective, and low risk mode to facilitate the recovery of postoperative chemotherapy as soon as possible. The main taboo of limb salvage surgery includes patients at too young age, and patients with huge tumor, soft tissue in terrible conditions, progressively enlarged tumor after chemotherapy, and local infection and failure in limb salvage therapy.

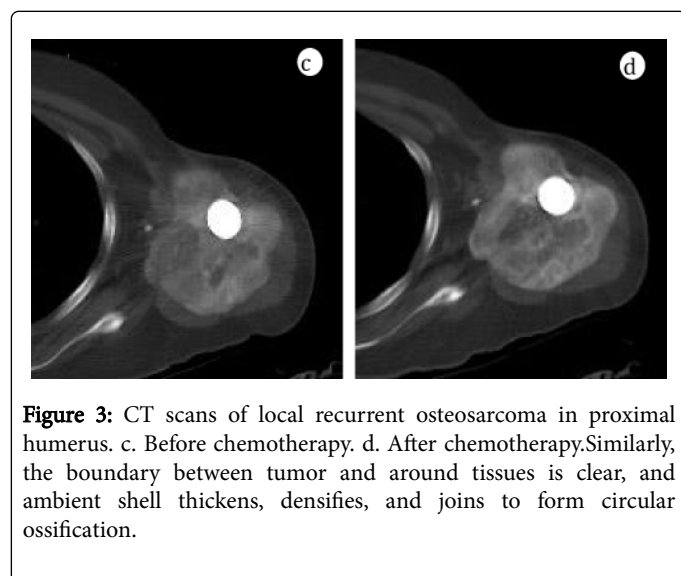
### The factors of local recurrence

No matter limb salvage surgery or amputation is applied, there is certain rate of metastasis and local recurrence, and it is commonly accepted that local recurrence would happen on 10% to 20% cases after limb salvage surgery. It is demonstrated that three factors are related to local recurrence, including the surgical margin, tumor necrotic degree after chemotherapy, and the anatomical relationship between tumor and neurovascular bundle [1]. It is generally accepted that wide range

excision is the primary principle of limb salvage surgery, which means soft tissue should be beyond tumor boundary for 2 to 3 cm under naked eyes, and bone is beyond tumor boundary for 3 to 5 cm, or operation should be ensured in normal tissues according to tumor free principle based on Enneking staging. It is controversial in clinic between limb salvage surgery and wide excision, as tumor usually affects nearby vessels and nerves which make it difficult to keep vessels, nerves, and enough soft tissues to enable both limb salvage surgery and wide excision at the same time. It is indicated that local recurrence is related to patients' reactivity to chemotherapy, namely, local recurrence is more common in patients who has enough surgery excision scope but with poor reactivity to chemotherapy than the contrary [2]. According to Grimer [3], no local recurrence happens even with marginal excision when tumor necrosis is more than 90% after chemotherapy, on the contrary, local recurrence happens in more than 36% patients who are insensitive to chemotherapy, and 4% in patients under wide excision margin but insensitive to chemotherapy.



**Figure 2:** The X-ray image of local recurrent osteosarcoma in distal femur. a. The boundary between tumor and normal tissue is not clear before chemotherapy. b. The boundary around tumor is clear enough, and the ossification within tumor increased to form new bone around necrotic area.



**Figure 3:** CT scans of local recurrent osteosarcoma in proximal humerus. c. Before chemotherapy. d. After chemotherapy. Similarly, the boundary between tumor and around tissues is clear, and ambient shell thickens, densifies, and joins to form circular ossification.

### Current therapy strategies of local recurrence

Local recurrence usually came out with worse prognosis, and it is controversial on its treatment, and surgery is commonly considered as

the mainstream treatment, but amputation is not always necessary. It is generally agreed that first-line chemotherapy could be applied in patients with local recurrence in more than 1 year after surgery, instead, second-line chemotherapy in patients with local recurrence within 1 year after surgery. Both Nathan [4] and MSKCC group [5] agreed on second-line chemotherapy in their therapeutic strategies for local recurrent osteosarcoma, but it is not clear on effects. As the morbidity of osteosarcoma is relatively low and local recurrent pattern is diversified, no direct evidence from large-scale random clinic study can prove the effects of second-line chemotherapy.

### Therapy strategies of local recurrence in our department

It is known that local recurrence is related to tumors' reactivity or sensitivity to chemotherapy, which could be enhanced by increasing chemotherapeutics' dose, and by adjusting drug administration time, or changing drug administrating methods [6]. Compared with intravenous administration, intra-artery infusion could increase the concentration of chemotherapeutics by 1.5 to 4 folds inside primary tumors, and chemotherapeutics concentration is directly related to tumor tissue necrosis, especially concentration dependent chemotherapeutics, such as epirubicin and cisplatin. We implanted arterial infusion pump at subcutaneous tissue connected with catheter intubated in relative artery to administer epirubicin and cisplatin, keeping high chemotherapeutics concentration inside tumor. The advantages of above strategy include low body dose, less adverse reactions, high local dose, good chemotherapeutic effects, little damage and pain, safer, feasible and repeatable. In previous studies, intra-arterial intervention chemotherapy could effectively treat extremity osteosarcoma [7] and control pathologic fracture [8] as well. Instead of relying on second-line chemotherapy, we applied the same strategy to treat local recurrent osteosarcoma and got the same desirable clinical effects to control the tumor effectively to enable the limb salvage surgery, which is same as the study of He A [9]. According to He A, epirubicin is more effective to intractable recurrent osteosarcoma than second-line chemotherapy. After 3 to 5 cycles of intra-arterial intervention chemotherapy on local recurrent extremity osteosarcoma, the progress of tumor was effectively curbed and the boundary between tumor and normal tissue was clear to facilitate surgery. As for lung metastasis, effectively controlling local recurrent tumor could to some extent prevent the growth of lung metastasis, and also help reduce pain and prolong patient's expectancy.

Local recurrence is obviously related to patients' prognosis, and it is also related to remote metastasis, in another word, repeated local recurrence often accompanies remote metastasis, as a result, the prognosis of such patients is worse [10]. As osteosarcoma is rare disease and local recurrent case is even scarce, there is not enough study on the treatment and prognosis of osteosarcoma local recurrence, and only several retrospective study reports have been published until now. This research indicated that intra-arterial intervention chemotherapy could effectively treat local recurrent osteosarcoma, but it only involved 9 cases with relatively short-term follow-up, further study will be needed in future research.

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