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Article

# Clinical effects of surgical resection of osteosarcoma in proximal fibula and long-term follow-up of health status

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**Abstract: Purpose:** This study aimed to evaluate the health status and quality of life in patients with osteosarcoma of the proximal fibula following surgical treatment. The procedure necessarily involved resection of the peroneal nerve, resulting in iatrogenic footdrop. **Methods:** From January 2005 to 26 August 2020 patients with osteosarcoma in the proximal fibula were treated at the oncology department of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Clinical-pathological features as well as outcomes of these patients were investigated. Meanwhile, to clarify their health status, the SF-36 health survey questionnaire was administered at 12, 24, and 36 months post-diagnosis. **Results:** The outcomes for patients with osteosarcoma in the proximal fibula were encouraging. Both the three-year disease-free survival rate and the overall survival rate were recorded at 88.5% (23/26). Data from the SF-36 health survey questionnaire, completed by 20 patients who underwent limb-sparing surgery, revealed that at 24 months, patients perceived themselves as less healthy, both physically and emotionally, compared to their status at 12 months. Despite observing significant recovery at 36 months, the health status did not return to the levels reported at 12 months. The majority of patients (n = 17) identified "footdrop after surgery" as the primary factor affecting their quality of life. **Conclusions:** Osteosarcomas affecting the proximal fibula typically demonstrate a favorable prognosis following multi-modal treatment. However, patients' health status, including psychological well-being, requires improvement. Oncologists should strive to achieve an "equilibrium point" that minimizes the risk of recurrence while preserving peroneal nerve function.

**Keywords:** osteosarcoma; proximal fibula; SF-36; psychology

## 1. Background

Osteosarcoma represents the most prevalent malignant primary bone tumor in juvenile populations [1]. This condition predominantly affects the metaphyseal region of long bones, with the distal femur, proximal tibia, and proximal humerus being the most frequently affected sites. More than 70% of osteosarcomas originate around the knee joint. However, osteosarcoma in the proximal fibula, a bony structure near the knee joint, is an exceedingly rare occurrence. It is reported that the fibula is the site of 2.4% of primary bone tumors [2]. The proximal fibula presents a challenging surgical area due to the intricate interplay of adjacent neurovascular pathways. These structures are either preserved or resected based on their proximity to the tumorous growth. In slender tubular bones, such as the fibula, surgical margins

may extend more proximally or distally than indicated by MRI findings. Consequently, a comprehensive resection with wide margins is often necessary to ensure tumor-free surgical boundaries. This approach may occasionally necessitate the excision of the peroneal nerve to maintain adequate surgical margins, resulting in iatrogenic footdrop. As a result, a functional ankle-foot orthosis must be applied postoperatively to address this functional limitation.

Although osteosarcoma is the most common primary malignant bone tumor in children and young adults, several studies have reported encouraging outcomes for osteosarcoma in the proximal fibula [3–7]. The majority of patients affected are in their second decade of life [5–9]. As these adolescents recover from treatment, they reintegrate into society to varying degrees, participating in work or study. However, even if they survive, the footdrop caused by the removal of the common peroneal nerve can significantly impact their mental health, with physical disability or loss of function potentially leading to feelings of inferiority. In contrast to some other countries, China does not place as much emphasis on the mental health of adolescents, particularly among adolescent cancer patients. Therefore, the psychological effects of common peroneal nerve resection-induced footdrop on adolescents with peroneal osteosarcoma remain unclear. Post-treatment quality of life (QOL), also referred to as health status, has become a primary concern for patients. This has led many clinicians to investigate deliberate marginal resection of osteosarcoma located in the proximal fibula to preserve limb functionality [8,10,11]. However, despite the resulting footdrop, many researchers maintain that establishing tumor-free resection margins, which subsequently reduce the risk of recurrence and improve survival rates, is of greater importance [3,4].

Due to the rarity of cases, studies on the clinical characteristics and prognosis of osteosarcoma in the proximal fibula are limited. Moreover, there is a lack of research on the health status and long-term psychological effects on cancer survivors with unavoidable iatrogenic footdrop. This study aims to describe the clinical-pathological features and outcomes of osteosarcomas originating in the proximal fibula. To thoroughly examine the health state of these patients, we employed the SF-36 health survey questionnaire, a standardized instrument for assessing health status among cancer survivors [12–17]. Additionally, we sought to evaluate the long-term psychological effects on these patients during follow-up after treatment completion.

## 2. Methods

### 2.1. Patients

In this retrospective study, 26 patients with osteosarcoma of the proximal fibula were treated by the Department of Oncology at Shanghai Jiao Tong University Affiliated Sixth People’s Hospital from January 2005 to August 2020 (see **Figure 1** for details on patient recruitment).

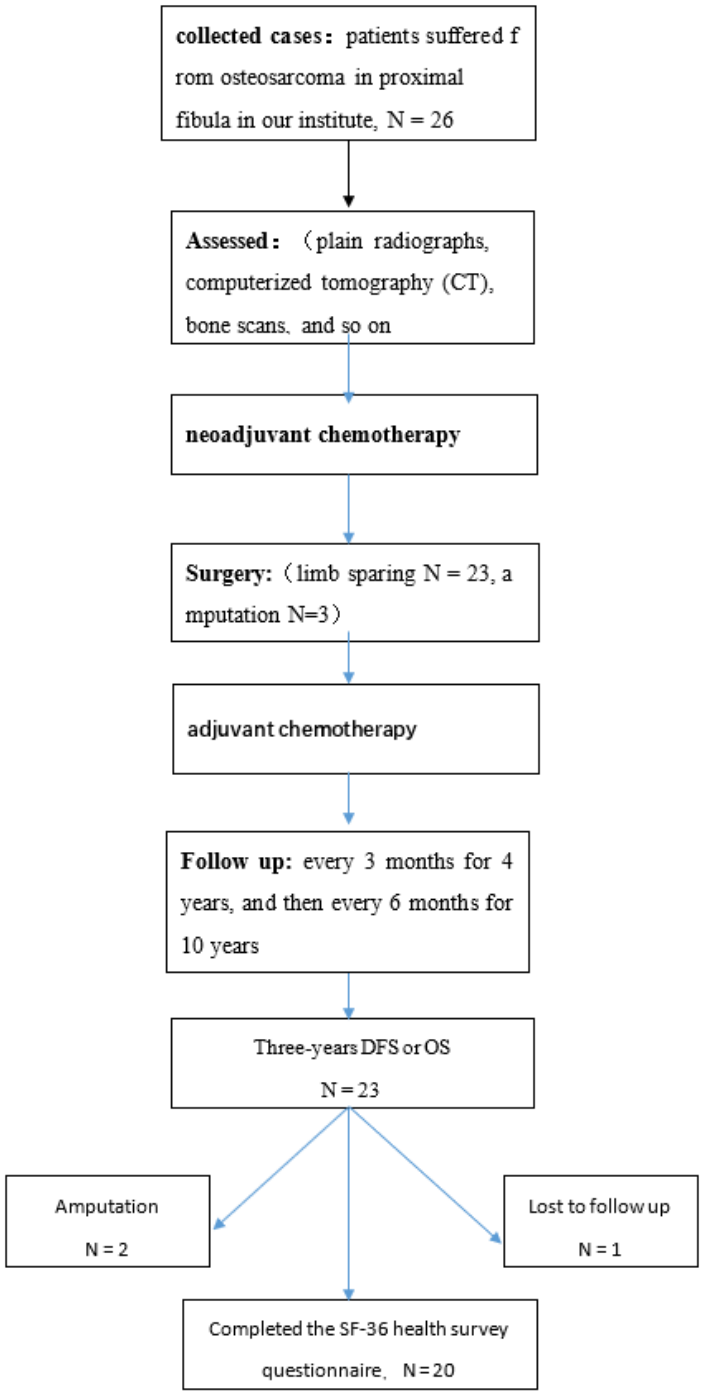


**Figure 1.** Flowchart of recruitment.

The inclusion criteria were as follows: (1) Histologically confirmed high-grade osteosarcoma according to the Enneking staging criteria at Shanghai Jiao Tong University Affiliated Sixth People's Hospital; (2) tumors located in the proximal fibula; (3) no antitumor therapy received before admission to the center; (4) magnetic resonance imaging (MRI) performed at initial presentation; (5) complete clinical and follow-up data available; and (6) limb-preserving surgery with Malawer Type II resection and two rounds of neoadjuvant chemotherapy carried out before surgery.

The exclusion criteria were as follows: (1) Evidence of distal metastasis at initial diagnosis; (2) failure to receive the standard treatment protocol at the center, including neoadjuvant therapy, surgery, and adjuvant chemotherapy; and (3) patients who underwent amputation.

Following the inclusion criteria, 26 patients with proximal fibular osteosarcoma were initially identified. Three cases were excluded due to amputation, resulting in the inclusion of 23 patients with proximal fibular osteosarcoma.

The cohort consisted of 26 individuals (17 men and 9 women) with a median age of 18 years (range: 11–43 years), all diagnosed with high-grade osteosarcoma according to the Enneking staging criteria. Comprehensive clinical data and treatment records were obtained through thorough medical chart reviews. Diagnostic methods included plain radiographs, computed tomography, bone scans, and magnetic resonance imaging. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients or their legal representatives provided informed written consent in accordance with committee rules.

## 2.2. Treatment

During initial surgery, limb-sparing surgery was performed on 23 patients, while three underwent amputation. All operations were conducted by Dr. Yang Qingcheng from the Department of Bone Oncology at Shanghai Sixth People's Hospital. Patients who underwent limb-preserving surgery received a Malawer Type II resection [6], which included extraarticular removal of the proximal fibula, approximately 5 cm of the unaffected diaphysis as determined by MRI, the anterior and lateral muscular compartments, the anterior tibial artery, and the common peroneal nerve. With the knee flexed at 20 degrees, non-absorbable sutures were used to reattach the lateral head of the biceps femoris and the lateral collateral ligament to the lateral tibial wall and surrounding knee capsule.

Four commonly used chemotherapeutic agents were administered according to the scheme presented in **Figure 2**, with a 2–3 week interval between chemotherapy rounds. Two rounds of neoadjuvant chemotherapy utilizing a combination of cisplatin (DDP), ifosfamide (IFO), methotrexate (MTX), and doxorubicin (ADM) were initiated preoperatively [18]. After surgery, patients received three to five cycles of postoperative adjuvant chemotherapy if no complications were noted.

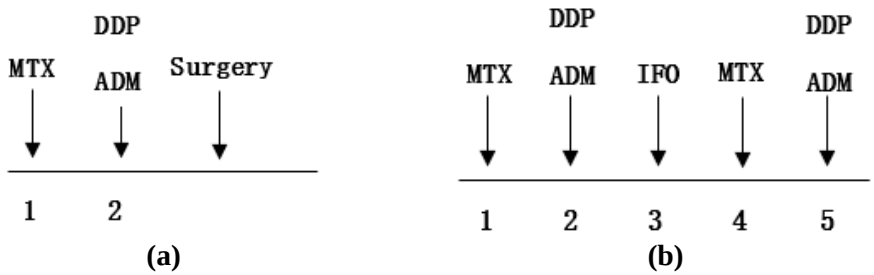


**Figure 2.** An example of chemotherapy protocol, **(a)** neo-adjuvant chemotherapy; **(b)** adjuvant chemotherapy.

### 2.3. Follow-up and SF-36 psychological investigation

During the chemotherapy procedure, patients were monitored every two months using chest CT scans and radiographs of the surgically treated leg. After treatment completion, patients were typically followed up every three months for the first four years and then every six months for the next ten years. Bone scans were performed biannually. Throughout each follow-up, orthopedic doctors evaluated the functional status of patients with limb preservation using Enneking's approach for musculoskeletal surgery for tumors [19].

The SF-36, a comprehensive health questionnaire, covers eight health aspects: Physical functioning (PF), role physical (RP), role emotional (RE), social functioning (SF), mental health (MH), vitality (V), bodily pain (BP), and general health perception (GH). The questionnaire consists of 36 items divided into these eight categories, with scores on each scale ranging from 0 to 100, where 100 represents optimal health. SF-36 health assessments were administered at 12, 24, and 36 months after the diagnosis of osteosarcoma.

**Statistical analysis**

Descriptive statistics and comparative analyses were performed using SPSS version 17.0. Descriptive data were reported as means ± SD. The overall survival (OS) time and disease-free survival (DFS) time were calculated using the Kaplan–Meier method. After testing for homogeneity of variance, quantitative variables were analyzed using one-way ANOVA. The level of significance for all two-tailed analyses was set at 0.05.

## 3. Results

### 3.1. Clinical-pathological features and outcomes of 26 patients with osteosarcoma in the proximal fibula

As of August 2020, the average follow-up time for the 26 patients was 43 months (range: 22–115 months). Information on each patient's symptoms was provided, revealing that 25 out of 26 patients experienced discomfort, and 19 had localized edema. The pre-diagnosis symptom duration ranged from 0.7 to 5 months, with a median of two months. Initial assessments found no evidence of distant metastases, and all 26 patients were categorized as being in surgical stage IIB according to the Enneking stage system. Biopsy specimens revealed osteoblastic osteosarcoma in 10 patients, chondroblastic osteosarcoma in 9, and fibroblastic osteosarcoma in 7. Twenty-four patients underwent two cycles of neoadjuvant chemotherapy with cisplatin, ifosfamide, methotrexate, and doxorubicin; 15 of these patients experienced satisfactory (> 90%) tumor necrosis from the chemotherapy, while 9 had unsatisfactory results (**Table 1**).

**Table 1.** clinical features of the recruitments.

| **n** | | |
|---|---|---|
| sex | male | 17 |
| | female | 9 |
| Histological type | fibroblastic | 10 |
| | osteoblastic | 9 |
| | chondroblastic | 7 |
| necrosis | ≥ 90% | 15 |
| | < 90% | 9 |
| Local symptoms | pain | 25 |
| | no pain | 1 |
| | swelling | 19 |
| | no swelling | 7 |
| First surgery | limb-sparing | 23 |
| | amputation | 3 |
| Last follow up | recurence | 2 |
| | metastasis | 4 |
| | none of them | 20 |

Treatment outcomes for proximal fibula osteosarcoma are generally favorable, with both the 3-year overall survival rate and the 3-year disease-free survival rate being 88.5% (23/26). Two patients experienced local recurrences, necessitating further above-knee amputations, and four cases had distant metastases. Among the 23 patients who survived beyond three years without local recurrence or distant metastases, the mean disease-free survival time was 67 months (range: 38–74 months), and the overall mean survival time was 109 months (range: 45–115 months). As of the last follow-up in August 2020, twenty patients had not experienced local recurrence or distant metastases.

For the 20 patients without local recurrence at the final follow-up, the Enneking functional evaluation system revealed scores between 92 and 99 for limb retention patients, with a median score of 96. No complaints of knee instability or signs of valgus instability were detected upon physical examination.

## 3.2. Comparison of SF-36 survey data at three time points

From the cohort of 23 patients who successfully avoided local recurrence or distant metastasis beyond three years (21 with limb-sparing surgery and 2 with amputation), 22 (95.6%, 20 with limb-sparing surgery and 2 with amputation) completed all items on the questionnaire and were available for assessment at three time points. Due to the limited number of amputation patients ($n$ = 2) and the established consensus that limb-salvage surgery offers functional and cosmetic advantages over amputation [20], the data from these 2 patients were excluded from the analysis.

The scores of overall health, physical functioning, role physical, role emotional, social functioning, mental health, vitality, bodily pain, and general health perception

from 20 patients were presented in **Table 2**. At the 24-month time point, the scores of overall health, role physical, role emotional, social functioning, general health, mental health, and vitality were significantly lower ($P < 0.05$) compared to those at the 12-month time point. However, the scores of physical functioning and bodily pain remained constant between these two time points ($P > 0.05$).

**Table 2.** Comparison of data from SF-36 health survey questionnaire at three time points.

| Items | 12 months | 24 months | 36 months | *P*-value |
|---|---|---|---|---|
| Overall health | 137.26 ± 4.24 | 114.95 ± 12.48 | 123.43 ± 8.31 | ＜ 0.05* |
| Physical functioning | 82.04 ± 7.96 | 83.63 ± 4.92 | 80.45 ± 7.38 | ＞ 0.05 |
| Role-physical | 92.04 ± 14.19 | 80.68 ± 18.79 | 76.13 ± 21.09 | ＜ 0.05* |
| Bodily pain | 94.95 ± 11.20 | 96.36 ± 7.28 | 96.63 ± 7.30 | ＞ 0.05 |
| General health | 64.31 ± 4.70 | 43.41 ± 9.31 | 51.33 ± 1.97 | ＜ 0.05* |
| Vitality | 89.09 ± 5.70 | 65.00 ± 19.94 | 76.14 ± 12.53 | ＜ 0.05* |
| Social functioning | 99.43 ± 2.66 | 70.45 ± 20.24 | 86.36 ± 9.38 | ＜ 0.05* |
| Mental health | 90.54 ± 6.70 | 65.27 ± 16.53 | 77.27 ± 11.60 | ＜ 0.05* |
| Role-Emotional | 89.37 ± 15.92 | 37.85 ± 33.00 | 60.56 ± 24.43 | ＜ 0.05* |

* One way ANOVA was conducted after homogeneity of variance test.

At the 36-month time point, the scores of overall health, role emotional, social functioning, general health, mental health, and vitality were significantly higher ($P < 0.05$) compared to those at the 24-month time point. The scores of role physical at the 36-month time point increased without a significant difference compared to those at 24 months. Nonetheless, the scores of overall health, role physical, role emotional, social functioning, general health, mental health, and vitality at the 36-month time point remained significantly lower ($P < 0.05$) than those at 12 months.

The scores of physical functioning and bodily pain remained constant at all three time points ($P > 0.05$). During the three-year follow-up, only 2 out of 20 patients sought psychological intervention from a professional clinician. When asked about the major factor affecting their quality of life during follow-up, 17 patients chose “footdrop after surgery”, 3 chose “scar on the skin”, and 2 chose “obesity induced by insufficient exercise”.

## 4. Discussion

Recent advancements in oncology have led to an increase in the number of long-term cancer survivors, including those with osteosarcoma, which is the most common malignant primary bone tumor in childhood. Consequently, there has been a growing focus on the long-term side effects of treatment that may impact the quality of life, including psychological side effects.

The proximal fibula is a relatively uncommon site for osteosarcoma occurrence. However, data from 26 cases of osteosarcoma in the proximal fibula suggest that this rare location may be associated with a favorable prognosis, with an 88.5% 3-year disease-free survival and overall survival rate. Simultaneously, previous reports and

data from our institute indicate that the majority of proximal fibula osteosarcoma patients are in their second decade of life. All of the above findings underscore the importance of addressing health status concerns, including psychological well-being, after successful treatment.

Surgical treatment remains the primary approach for managing osteosarcoma in the proximal fibula. However, to ensure a safe surgical margin, sacrificing the peroneal nerve is unavoidable, resulting in an iatrogenic footdrop. Although some surgeons have attempted to preserve the peroneal nerve through marginal or intralesional procedures, most researchers maintain that achieving tumor-free resection limits takes precedence, even at the cost of a resultant drop foot.

Data from the SF-36 health survey questionnaire, completed by 20 patients who underwent limb-sparing surgery, revealed that at the 24-month time point, patients perceived themselves as less healthy, both physically and emotionally, compared to their status at 12 months. At the 36-month time point, despite significant recovery, the health status still did not parallel that at 12 months. The remarkable deterioration of health status at the 24-month time point could be attributed to two factors: 1) At the 12-month time point, patients had just completed their hospital treatment and had not yet engaged in social or school activities. 2) At the 24-month time point, most patients had participated in social or school activities and perceived the side effects of their previous treatment. The improvement in health status at the 36-month time point might be a result of patients' self-adjustment, as only two patients underwent psychological intervention, and scores of physical functioning remained constant at all three follow-up time points.

It is disappointing that only two patients sought psychological intervention from a professional clinician. In China, psychological health and its related issues are still unfamiliar to the majority of people. In cases of psychological disorder, most individuals choose "self-adjustment" over seeking help from a professional clinician.

The data indicated that the major factor affecting patients' quality of life during follow-up was "drop foot after surgery". This phenomenon presents a challenge to surgeons. While achieving tumor-free resection limits is a priority, the health status of patients after being cured should also be considered. We wonder if an "equilibrium point"—minimizing the risk of recurrence while preserving the function of the peroneal nerve—could be reached through the cooperation of surgery, radiation, and medical oncology.

This study has several limitations that should be acknowledged. First, the potential patient selection bias inherent in the retrospective study design may influence the validity of the data. Second, the small sample size ($n$ = 26) limits the ability to draw definitive conclusions. Additionally, while the SF-36 health survey questionnaire was used to assess overall health, physical functioning, role-physical, role-emotional, social functioning, mental health, vitality, bodily pain, and general health among cancer survivors, suggesting that footdrop due to surgery would impact patients' psychological well-being, there is a need to incorporate other assessment tools, such as the Musculoskeletal Tumor Society Scoring System 93 (MSTS 93), to further confirm this finding. Future studies will aim to refine the scoring system to address this limitation. Despite these limitations, this article is the first to investigate the health status of patients with osteosarcoma in the proximal fibula treated with

limb-sparing surgery while summarizing the clinical-pathological features of this osteosarcoma subgroup. To more accurately explore the health status of these patients, studies with larger sample sizes are necessary.

## 5. Conclusions

In general, osteosarcoma patients with proximal fibula involvement tend to demonstrate favorable prognoses after the introduction of multi-modal treatment. However, their health status, including psychological well-being, requires improvement and may benefit from psychological intervention. Clinicians in oncology should strive to reach an "equilibrium point" by minimizing the risk of recurrence while preserving the function of the peroneal nerve.

**Author contributions:** Conceptualization, ZL (Zimei Liu); methodology, ZL (Zimei Liu); validation, ZL (Zimei Liu) and LJ; formal analysis, ZL (Zimei Liu), DZ and ZL (Zhenzhen Liu); investigation, DZ; data curation, ZL (Zhenzhen Liu) and DZ; writing—original draft preparation, ZL (Zimei Liu), DZ and LJ; writing—review and editing, LJ; supervision, LJ; project administration, LJ. LJ is responsible for the overall content as guarantor. ZL (Zimei Liu) and DZ contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

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**Informed consent:** Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

**Availability of data and materials:** The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

**Conflict of interest:** The authors declare no conflict of interest.

## Abbreviation

| | |
|---|---|
| QOL | quality of life |
| CT | computerized tomography |
| MRI | magnetic resonance imaging |
| DFS | disease-free survival |
| OS | overall-survival |
| PF | physical functioning |
| RP | role physical |
| RE | role emotional |
| SF | social functioning |
| MH | mental health |
| V | vitality |
| BP | bodily pain |
| GH | general health perception |

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