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Original Article

The therapeutic effects of X-ray devitalization and replantation and alcoholic devitalization and replantation in adolescent patients with lower limb osteosarcoma

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Abstract: Objective: To compare and analyze the therapeutic effects of X-ray devitalization and replantation and alcoholic devitalization and replantation in adolescent patients with lower limb osteosarcoma. Methods: We collected clinical data for 43 osteosarcoma patients with limb salvage treatment treated in our hospital from February 2014 to February 2018. The patients were divided into x-ray devitalization and replantation group (n=23) and alcoholic devitalization and replantation group (n=20) based on the treatment methods. The two groups were compared in operation duration, intraoperative blood loss, postoperative fracture healing time, length of tumor bones, MSTS score and ISOLS score, postoperative complications, postoperative follow-ups and postoperative recurrence and metastases. Results: Operation duration and intraoperative blood loss of the alcoholic group were less than that of the X-ray group, while postoperative fracture healing time of the alcoholic group was longer than that of the X-ray group ($P<0.05$). For the X-ray group, MSTS score and ISOLO score of the final follow-up were 26.13±2.65 and 32.53±3.73 respectively. For the alcoholic group, MSTS score and ISOLO score of the final follow-up were 23.69±3.27 and 30.98±3.56 respectively. MSTS score of the X-ray group was higher than that of the alcoholic group ($P<0.05$). There were 2 cases of internal fixation failure and 2 cases of adhesive knee joints stiffness in the X-ray group. As for the alcoholic group, there were 2 cases of internal fixation failure and 2 cases of incision soft tissue infection. There were no statistically significant differences in postoperative complications, recurrence, and metastases between the two groups ($P>0.05$). Conclusion: Both methods are convenient, inexpensive, and effective for adolescent patients with lower limb osteosarcoma. Alcoholic devitalization and replantation results in shorter operation duration and less intraoperative blood loss, while X-ray devitalization and replantation results in better postoperative limb function restoration.

Keywords: X-ray devitalization and replantation, alcoholic devitalization and replantation, lower limb, osteosarcoma (OS)

Introduction

Osteosarcoma (OS) is the most common primary malignant bone tumor among adolescents. It frequently occurs at the metaphysis of the long bone in the lower limbs, especially at distal femur and proximal tibia [1]. With the rapid development of modern medical technology, especially with the combined application of chemotherapeutics and clinical surgery, the postoperative survival rate raised from 20% to 70% [1]. Excision with neoadjuvant chemotherapy is the gold standard for treating osteosarcoma of the extremities. Under the premise of tumor's complete removal, surgical treatments of osteosarcoma are required to be beneficial to anatomical reconstruction and functional rehabilitation after tumor resection and lower the risks of postoperative recurrences [2]. Biological reconstruction applies autografts or allografts to bone reconstruction. The most common methods are prosthetic replacement and autogenous bone grafts. The former one has good early function but higher complication rates in the long run. The latter one has become an important bone reconstruction method for its high suitability and satisfactory healing rate [3]. The inactivated replantation of

tumor bone segment includes high temperature boiling, X-ray devitalization and replantation and alcoholic devitalization and replantation, etc. X-ray devitalization and replantation treatment on tumor bone segment is a primary choice after excision of osteosarcoma of the extremities. It provides good clinical effects, low recurrence risks and high security [4]. For treating malignant bone tumors and bone defects, alcoholic devitalization and replantation treatment on tumor bone segment controls oncological factors, offers limb salvage and raises patients' survival rate [5]. At present, there are many methods of autologous inactivated bone transplantation. It has been widely reported on radiation inactivation and alcohol-inactivated replantation, but few experiments were conducted on the comparison of the clinical effects of the two procedures. Our research adopted X-ray devitalization and replantation method and alcoholic devitalization and replantation method to treat adolescent patients with lower limb osteosarcoma. We compared the clinical effects, postoperative complications, recurrences, and metastases in the following study.

Materials and methods

Clinical data and information collection

From February 2014 to February 2018, 43 osteosarcoma patients with limb salvage treatment treated in our hospital were selected as the research subjects, including 27 male cases and 16 female ones between 11-17 years old with an average age of 13.89±3.87 years old. 35 cases were at Enneking staging IIb, and 8 cases were at Enneking staging III. In terms of tumor locations, there were 32 femur cases, 7 tibia cases and 4 humerus cases. Inclusion criteria: 1. patients whose preoperative pathology met the diagnostic criteria for primary osteosarcoma of the extremities; 2. patients with uninvolved important blood vessels and nerves; 3. patients without distant metastases and pathological fractures, examined by imagological examination; 4. patients with fare body condition that has tolerance to chemotherapy and other comprehensive therapies; 5. patients with more residual bone mass of tumor segment bones, fair condition of local soft tissue and were suitable for implant fixation; 6. patients that were treated for the first time, with longer life expectancy and could maintain good limb function post-operative. Exclusion criteria: 1. patients with distant metastases or pathological fractures pre-operation; 2. patients with tumor tissues surrounding important blood vessels and nerves, increasing the difficulty of limb salvage; 3. patients with metastatic bone tumor. Patients were divided into the X-ray group (n=23) and the alcoholic group (n=20) based on the treatment methods they adopted. The research was conducted according to the principles of the World Medical Association Declaration of Helsinki. This study was approved by the Ethical Committee of the Zhejiang Wenling First People's Hospital. All subjects gave written informed consent.

Methods

Preoperative preparation: We conducted relative tests, excluded operational contraindications, assessed tumor locations, range of involvement and the adjacent structures of surrounding tissues, blood vessels and nerves. We also provided 2 periods of neoadjuvant chemotherapy with adriamycin, cisplatin, ifosfamide and high-dose methotrexate. After chemotherapy, we used imagological examination to assess the sensibility of neoadjuvant chemotherapy. Conventional antibiotics were applied pre-operation for infection prevention.

Operative methods: X-ray devitalization and replantation. 1. Extensive removal of the tumor bone segment: after anesthesia, based on the MRI results and the excision principle of malignant bone tumors, complete tumor bone segment resection reached the safety limits according to the excision extension decided pre-operation, and cicatrices and tumors were resected at the preoperative biopsy. The margin of osteotomy was inside normal tissues, and was at least 1 cm away from the upper and lower margin of the tumor. The principle of tumor-free technique was followed during operation, and epiphysis and articular surfaces were protected. Margins removed were sent for intraoperative frozen pathological examination and tested negative. Tumor tissues removed were sent for routine pathological examination. 2. Inactivation of tumor bone segment: wrapped with sterile saline gauze and sterile wet cotton pad, 6MV-X electron linear accelerator was used to provide 60 Gy isocenter radiation inactivation. The average radiation time was 30

Table 1. Comparison of clinical data and information between the two groups

Groups	Age (years old)	Gender (Male/Female)	Enneking staging (IIb staging/III staging)	Tumor location (femur/tibia/humerus)
The X-ray group (n=23)	13.57±3.27	15/8	19/4	18/3/2
The alcoholic group (n=20)	14.25±3.61	12/8	16/4	14/4/2
t/χ^2	0.648	0.125	0.048	0.415
P	0.521	0.724	0.826	0.520

mins and the dose rate was 1.8-2.0 Gy/min. 3. Replantation of tumor bone segment: the inactivated tumor bone was rinsed repeatedly with iodine solutions and massive sterile saline solutions, and replantation was imposed in situ; appropriate locking reconstruction plate and screw was selected for internal fixation, and adequate hemostasis was provided, rinsed; wounds were then closed and drainage tube was placed.

Alcoholic devitalization and replantation. The procedures of extensive removal and replantation of the tumor bone segment were the same as the ones for the X-ray treatment. Inactivation of tumor bone segment: the tumor tissue in the tumor bone segment was removed, nail track was preset, prefixed with titanium plate screw or/and intramedullary nail, and placed in 99% alcoholic solution, immersed for 50 mins and inactivated.

Postoperative management: Conventional prophylactic antibiotics were applied for 48 hours. Fixation braces were used, and patients were required to rest in bed for 2 to 3 months. Body recovery exercises were arranged based on imagological results. Routine chemotherapy was given post-operative.

Observation indexes

1. MSTS score [6] was adopted to assess patients' limb function: there are numerical values (from 0 to 5) for each of the six categories, including pain, acceptance, supports, walking, gait, and function. 2. ISOLS score [7] was adopted to assess the healing process of autogenous bone grafts: there are numerical values (from 0 to 4) for each of the nine categories, including bone reconstruction, interface, anchoring, replantation, fusion, resorption, fractures, shortening, and internal fixation. 3. The intraoperative blood loss, operation duration, fracture healing time, length of tumor bone segment and postoperative complications of the two groups were recorded. 4. The incidence of postoperative plate rupture between the two groups were recorded.

Postoperative follow-ups

Reexaminations, either inpatient ones or outpatient ones, were carried every 3 months within 2 years of the operation. Re-examination included physical examination, fracture healing condition observed by X-ray, lune metastases condition examined by chest CT, and recovery condition of the injured limb assessed by MSTS score.

Statistical analysis

Statistical analysis was performed using the SPSS statistical software 20.0. The measurement data were represented by mean ± standard deviation ($\overline{x} \pm sd$) and examined by t test or Wilcoxon signed rank test. The enumeration data were examined by χ^2. And $P<0.05$ was considered as statistically significant.

Results

Comparison of general information of the two groups of patients

The general clinical data of the two groups of patients were compared in terms of age, gender, Enneking staging and tumor location The difference was not statistically significant. See **Table 1**.

Comparison of treatment-related indexes between the two groups

Operation duration and intraoperative blood loss of the alcoholic group were less than that of the X-ray group (t=6.360, 6.653, P=0.000); while postoperative fracture healing time of the alcoholic group was longer than that of the X-ray group (t=10.044, P<0.05). See **Table 2**.

Table 2. Comparison of treatment-related indexes between the two groups ($\bar{x} \pm sd$)

	Operation duration (min)	Intraoperative blood loss (ml)	Length of tumor bones (cm)	Fracture healing time (week)
The X-ray group (n=23)	397.84±20.28	481.26±58.93	19.02±4.12	37.83±5.21
The alcoholic group (n=20)	361.37±16.82	369.28±50.19	18.25±3.63	58.75±8.29
t	6.360	6.653	0.646	10.044
P	0.000	0.000	0.522	0.000

Table 3. Comparison of MSTS score and ISOLS score between the two groups ($\bar{x} \pm sd$, score)

	MSTS	ISOLO
The X-ray group (n=23)	26.13±2.65	32.53±3.73
The alcoholic group (n=20)	25.69±3.27	30.98±3.56
t	2.702	1.388
P	0.400	0.173

Comparison of MSTS score and ISOLS score between the two groups

There were no statistically significant differences in MSTS score and ISOLO score between the two groups (t=2.702, 1.388, P>0.05). See **Table 3**.

Comparison of postoperative complications between the two groups

There were 2 cases of internal fixation failure and 2 cases of adhesive knee joints stiffness in the X-ray group. As for the alcoholic group, there were 2 cases of internal fixation failure and 2 cases of incision soft tissue infection. There was no statistically significant difference in postoperative complications between the two groups (P>0.05). See **Table 4**.

Comparison of postoperative recurrence and metastases between the two groups

One patient of the X-ray group recurred 20 weeks after operation, who underwent amputation and was still alive by the latest follow-up date. One patient of the alcoholic group recurred 16 weeks after operation, who underwent amputation and died of lung metastasis 6 months later. Another patient of the alcoholic group recurred 17 weeks after operation, who underwent amputation, treated with Apatinib and was still alive by the latest follow-up date. There were no statistically significant differences in local recurrences and lung metastases between the two groups (P>0.05). See **Table 5**.

Comparison of the incidence of postoperative plate rupture between the two groups

There was no statistically significant difference in the incidence of postoperative plate rupture between the two groups of patients, with 1 case in the X-ray group and 2 cases in the alcoholic group (P>0.05).

Discussion

OS is a common malignant disease that grows rapidly with strong aggressiveness and invasiveness. It is a serious threat to patients' life because of its extremely high disability rate and death rate. With the development and improvement of surgical technology, chemotherapy, CT and MRI technology and postoperative rehabilitation, "neoadjuvant chemotherapy, surgical limb salvage and adjuvant chemotherapy" have become the primary treatment methods [8]. Limb salvage includes extensive and complete tumor resection, tumor-type artificial metal prosthesis replacement and biological reconstruction. The basic principles of limb salvage are no residual lesions of surgical margin, retain the affected limbs to the maximum, reduce postoperative complications, improve limb function, and promote life quality. Reconstruction on bones and soft tissue defects after resection helps improve patients' postoperative life quality. Biological reconstruction results in long service life, less complications, autologous joints preservation, better postoperative function restoration, etc. The devitalization and replantation treatment has been adopted widely, especially among adolescent patients. The inactivate bone structure and its immunology match the patients well, and the continuity and original shape of backbone can be maintain-

Table 4. Comparison of postoperative complications between the two groups (n, %)

	Internal fixation failure	Soft tissue infection	Adhesive knee joints stiffness
The X-ray group (n=23)	2 (8.70)	0 (0)	2 (8.70)
The alcoholic group (n=20)	2 (10.00)	2 (10.00)	0 (0)
χ^2	0.022	2.412	1.824
P	0.833	0.210	0.177

Table 5. Comparison of postoperative recurrence and metastases between the two groups (n, %)

	Local recurrences	Lung metastases
The X-ray group (n=23)	1 (4.35)	0 (0)
The alcoholic group (n=20)	2 (10.00)	1 (5.00)
χ^2	0.527	1.177
P	0.468	0.278

ed. Also, it is easy to operate and comparatively economical. However, in the process of bone tissues' repair and reconstruction, pathological fractures are prone to occur, and local residuals are common due to incomplete tumor inactivation.

Our research showed that operation duration and intraoperative blood loss of the alcoholic group were less than that of the X-ray group, while postoperative fracture healing time of the alcoholic group was longer than that of the X-ray group. The primary causes are: 1. The X-ray treatment procedures are more complicated and time-consuming; hence it increases operation duration and intraoperative blood loss. 2. The X-ray treatment retains more bone healing substances than the alcoholic one. 3. The alcoholic treatment requires longer time to complete revascularization and achieves osseointegration with the peripheral normal bones. The X-ray treatment results in less autogenous bone healing time, which helps patients to do postoperative rehabilitation exercises sooner and generates better limb function restoration. Xu et al. [9] showed that for osteosarcoma of the distal bone, alcoholic devitalization and replantation has the same results as prosthesis, and it is even safer for avoiding prosthesis-related complications. Also, it improves patients' postoperative functions to some extent, making this method easier to be carried out in primary hospitals. Xiu et al. [10] adopted alcoholic devitalization and replantation to treat patients with osteosarcoma of distal femur. 9 cases were at Enneking staging IIb and 1 case was at staging III. All the patients achieved the first stage of recovery. In the final follow-up, the mean ISOLS score was 31 (87%) and MSTS score was 23 (77%). 1 patient died of local recurrence and multiple metastases 13 months after operation, 3 other patients died of multiple metastases respectively 9 months, 12 months, and 24 months after operation. These cases prove the effectiveness and safety of alcoholic devitalization and replantation. Yu et al. [11] adopted the alcoholic treatment for osteosarcoma of distal femur, and found that it helps maintain important articular structures and attain long-term good limb function. In the final follow-up, patients' ISOLS scores were from 28 to 34, with a mean score of 31 (87%), and their MSTS score were from 19 to 28, with a mean score of 23 (77%). In the study conducted by Zhang et al. [12], patients with malignant limb tumors all received en bloc resection. They received a single dose of 50 Gy external beam radiation and the affected bone segment was replanted. The average MSTS score was 78.8% (50-93.3%) and most patients had strong osseointegration. Oike et al. [13] retrospectively analyzed 10 years' clinical data of 27 patients that were treated with the X-ray method, and the survival rate was 88.9%. In the final follow-up, the average MSTS score was 84.3%. There were 9 cases of postoperative fracture nonunion, 4 cases of subchondral bone collapses and 4 cases of deep infection.

Postoperative fracture nonunion, subchondral bone collapses, deep infection, fractures, and internal fixation failures are the common complications of the devitalization and replantation treatments [5, 6, 14]. In our research, there were 2 cases of internal fixation failure and 2 cases of adhesive knee joints stiffness in the X-ray group. As for the alcoholic group, there were 2 cases of internal fixation failure and 2 cases of incision soft tissue infection. Patients with internal fixation failures were treated with open reduction, replantation, and

internal fixation. Locking compression plate strengthens the fixation of tumor bone segment and reduces breakage.

The primary goal of treating malignant bone tumors is to reduce the local recurrence rate and distant metastasis rate. The overall survival rate for patients with metastases is around 20% to 30%. While for patients with no metastases, the overall survival rate is 70% to 80%. The metastases location also affects patients' condition, those with only lung diseases have higher survival rate than those with bone metastasis diseases [2]. Our research suggests that, local recurrence rate of the X-ray group and the alcoholic group were respectively 1 (4.35%) and 2 (10.00%), and the metastases rate were 0 (0. 00) and 1 (5.00%), which further proves the safety of both treatments. The theory of alcoholic treatment is that alcohol causes the degeneration and necrosis of tumor shells and blocks the blood flow and nutrition of the tumor tissues. The tumor cells would be necrosed when the peripheral vascular growth. The study conducted by Wu et al. [14] demonstrated that patients received external beam radiotherapy and autologous transplantation were healed 20 months after operation, and the rates of patients healed 6 months, 9 months 12 months and 18 months respectively were 10.4%, 49.4%, 64.9% and 87.9%. The complication rate was 29%, the tumor recurrence rate was 15% and the 5-year survival rate was 83%. Karnofsky score, postoperative chemotherapy cycle, metastases, length of inactivated tumor segment, duration of the disease, and neoplasm staging are the individual factors that influence the overall survival rate [5, 15]. Surgical removal of the tumor lesion is still the primary method of treating osteosarcoma. The excision process of tumor bone segment and soft tissue mass must be safe and effective, ensuring there are no residual tumor lesion on surgical margins. The treatment principle of neoadjuvant chemotherapy must be strictly followed. Complete and standardized chemotherapy can eliminate pulmonary micro metastases, delay lung metastases, reduce the distant metastasis rate, and ameliorate the overall survival rate and progression-free survival rate. The 3-year overall survival rate and progression-free survival rate of patients received complete HD-MTX combined chemotherapy with multiple drugs at high dose were respectively 77.3% and 54.0%. Compared with that, the 3-year overall survival rate and progression-free survival rate of patients received incomplete chemotherapy were respectively 44.4% and 27.8% [15]. For adolescent patients with lower limb osteosarcoma, both treatments are convenient, inexpensive, and effective. However, the alcoholic treatment generates less intraoperative blood loss and requires shorter operational duration, while the X-ray treatment generates better postoperative limb function restoration [16-20].

There are a few limitations in our study. Firstly, the number of patients included in this study is small, which is prone to causing deviation at this time. Secondly, the study follow-up time is relatively short, and long-term complications cannot be fully observed. Therefore, the sample size needs to be expanded for further verification and follow-up records.

In conclusion, both methods are convenient, inexpensive, and effective for adolescent patients with lower limb osteosarcoma. Alcoholic devitalization and replantation results in shorter operation duration and less intraoperative blood loss, while X-ray devitalization and replantation results in better postoperative limb function restoration. Standardized osteosarcoma operation, resection and chemotherapy contribute to delaying tumor metastases and improving prognosis. Radiation and alcohol inactivation have high safety and are a good choice for patients undergoing autologous bone inactivation and replantation.

Disclosure of conflict of interest

None.

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