Arterial perfusion chemoembolization combined with iodine-125 seeds for stage IIB osteosarcoma: A case report

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Abstract. Osteosarcoma is a highly malignant bone tumor that predominantly affects adolescents. Its aggressive nature, complex treatment options and poor prognosis render it a notable concern in oncology. With advancements in therapy for osteosarcoma, neoadjuvant chemotherapy in conjunction with limb-salvage surgery has emerged as the preferred surgical strategy. However, the physical and emotional trauma associated with surgery, along with the adverse side effects of chemotherapy, can be unacceptable to some patients. In recent years, alternative local treatment modalities such as transarterial chemoembolization (TACE) and iodine-125 seed implantation have garnered considerable attention. These techniques show potential in enhancing local tumor control while minimizing systemic toxicity. TACE involves obstructing the blood supply to the tumor while administering localized chemotherapy, resulting in tumor ischemia and necrosis, which is particularly effective for hypervascular tumors. Meanwhile, iodine-125 seeds act as low-energy radiation sources that can effectively target tumor cells while sparing the surrounding healthy tissue. The present study describes a case of osteosarcoma treated with a combination of TACE and iodine-125 seed implantation. The patient, diagnosed with osteosarcoma of the left knee joint, declined surgical intervention. Consequently, a treatment plan involving TACE paired with iodine-125 seed implantation was established. Post-treatment follow-up demonstrated marked pain relief, improved limb function and a notable reduction in tumor volume with decreased bone destruction visible on imaging. Over a follow-up period of 6 years, there were no signs of disease recurrence or distant metastasis, and no notable chemotherapy-related side effects were reported. The quality of life of the patient was markedly improved. The current case illustrates the antitumor efficacy and reduced toxicity of combining TACE with iodine-125 seed implantation in the management of osteosarcoma.

Introduction

Osteosarcoma is recognized as the most prevalent type of malignant bone tumor, with a notably higher incidence in adolescents aged 15-19 years, presenting with a male-to-female ratio of 1.4:1 (1). In young patients aged 15-19 years, osteosarcoma predominantly arises in the extremities, particularly around the knee, and the lungs serve as the most common site for metastasis, followed by distant bones (2). The diagnosis of osteosarcoma mainly relies on pathological examination and treatment protocols are tailored according to the stage of the tumor. In recent years, neoadjuvant chemotherapy, combined with limb-salvage surgery, has emerged as the primary treatment approach for early-stage osteosarcoma (3). However, the deep-seated location of the tumor and the intricacies of surrounding anatomical structures often render complete surgical removal challenging, which may result in both physical and psychological trauma to the patient (4). Additionally, systemic chemotherapy can lead to complications, such as renal, cardiac and auditory dysfunction (5). Despite notable advancements in surgical techniques and chemotherapy agents in recent decades, the overall prognosis for osteosarcoma remains less than ideal. Consequently, there exists some debate regarding the most appropriate treatment strategy.

The rapid advancement of local treatment technologies has highlighted the benefits of transarterial chemoembolization (TACE) and iodine-125 seed implantation in enhancing local tumor control rates and minimizing treatment toxicity (6,7). These approaches have demonstrated considerable clinical value, particularly in the management of hypervascular tumors.

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Abbreviations: ALP, alkaline phosphatase; DSA, digital subtraction angiography; LDH, lactate dehydrogenase; MAP, methotrexate, doxorubicin and cisplatin; NRS, Numeric Rating Scale; TACE, transarterial chemoembolization

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TACE embolization involves administering chemotherapy drugs directly through the tumor-feeding artery in combination with vascular embolization techniques. This method achieves multiple therapeutic effects, such as increasing local drug concentrations, reducing systemic toxicity and obstructing the blood supply of the tumor (6). Iodine-125 seed implantation is a type of brachytherapy that entails implanting radioactive seeds into the tumor under imaging guidance. These iodine-125 seeds continuously emit low-dose γ rays, inducing DNA breakage and damage within the tumor by generating free radicals (7). This mechanism allows for the radiation dose to be concentrated precisely on the tumor. Given that the effective radius of the iodine-125 seed is only 1.7 cm, it can effectively target the tumor while minimizing damage to surrounding healthy tissues (8).

To the best of our knowledge, there have been no documented cases of osteosarcoma treated with a combination of TACE and iodine-125 seed therapy. The present study describes a detailed case of a patient with osteosarcoma who received this combined treatment. In addition, the clinical application and advantages of this method in improving local tumor control rates and reducing side effects are discussed in the current study. The successful outcome of the present case offers valuable insights and serves as a reference for future clinical research.

Case report

In September 2018, a 13-year-old female patient presented to Banan District Third People's Hospital (Chongqing, China) with a 3-month history of swelling in the left knee joint (Fig. 1A and D). The swelling progressively worsened, accompanied by severe pain rated 8 on the Numeric Rating Scale (NRS) (9), which gradually impacted their gait. An MRI conducted at the local hospital revealed osteolysis of the lower left femur with surrounding soft tissue masses, the largest measuring 12.6 cm, suggesting a malignant tumor. Following the initial assessment, a CT-guided puncture biopsy was carried out on the left femoral mass, and the pathological results established the diagnosis of a high-grade osteosarcoma. The local hospital recommended amputation; however, the patient declined the procedure. In search of further treatment options, the patient presented to Banan Hospital of Chongqing Medical University (Chongqing, China) in October 2018. Laboratory tests revealed elevated levels of alkaline phosphatase (ALP) at 1,752 U/l (reference range: 30-130 U/l) and lactate dehydrogenase (LDH) at 735 U/l (reference range: 120-250 U/l), while all other tests (e.g., bilirubin, ALT, AST and reticulocyte counts) returned normal results. Based on the American Joint Committee on Cancer staging system for malignant tumors (10,11) and the Enneking grading system (12), the patient was classified as having stage IIB osteosarcoma. After a multidisciplinary team discussion, it was recommended that the patient undergo neoadjuvant chemotherapy followed by limb-sparing surgery, in accordance with current treatment guidelines, especially considering the invasion of the tumor into surrounding blood vessels. However, the patient refused surgical intervention due to psychological and other personal reasons. Consequently, an alternative treatment plan was formulated, consisting of TACE and iodine-125 seed implantation, complemented by systemic intravenous chemotherapy; the treatment process is shown in Fig. S1. The team clearly communicated to the patient and their guardians the structural instability of the femur and the possibility of spontaneous fracture occurring under minimal stress. The discussion highlighted that pathological fractures could result in notable pain, functional impairment and complications in future treatment. To mitigate these risks, the patient was advised to completely avoid weight-bearing on the affected limb, and to use crutches for mobility to minimize mechanical stress on the femur. The patient and their family acknowledged the associated risks and agreed to adhere strictly to the recommended precautions.

In October 2018, on day 6 following admission, the patient underwent left femoral TACE, guided by a digital subtraction angiography (DSA) machine (Allura Xper FD20; Philips Medical Systems, Inc.). The right femoral artery was punctured under local anesthesia, and a 5 F femoral artery sheath (Terumo Corporation) was introduced. Subsequently, a 5 F vertebral catheter (Terumo Corporation) was utilized for super-selective catheterization of the left superficial femoral artery. Angiographic imaging revealed multiple branch vessels from the left superficial femoral artery supplying the tumor. The vertebral catheter was positioned within the left superficial femoral artery, allowing for the administration of the first-line chemotherapy regimen for osteosarcoma: Methotrexate, doxorubicin and cisplatin (MAP), via continuous arterial infusion. This regimen included cisplatin at 120 mg/m^2 (administered continuously for 24 h on the day 1), doxorubicin at 37.5 mg/m^2 (maintained for 24 h on day 2) and methotrexate at 12 g/kg (administered over 24 h on day 3). During the chemotherapy infusion, the patient received daily subcutaneous injections of low-molecular-weight heparin sodium at 3,000 U for anticoagulation. After completing the arterial infusion chemotherapy, a 2.7 F microcatheter (Hunan APT Medical Inc.) was used for super-selective catheterization of the tumor-supplying arteries under DSA guidance. Embolization was carried out using 300-500 μm embolization microspheres (Jiangsu Hengrui Pharmaceuticals Co., Ltd.) until the tumor-supplying arteries were no longer visible and the vessels appeared tapered (Fig. 2). In December 2018, a repeat of the aforementioned procedure was performed for the second TACE treatment.

After two TACE treatments, at the time of follow-up in January 2019, the left knee swelling was considerably diminished, and the pain score was decreased to 4, as measured using the NRS. Enhanced CT follow-up (Fig. 3A and B) revealed a notable reduction in tumor blood supply and a decrease in the maximum tumor diameter. Subsequently, a plan for iodine-125 seed implantation was developed for the patient. Prior to the procedure, a treatment planning system (Beijing Tianhang Kelin Technology Development Co., Ltd.) was utilized to establish the initial implantation strategy. During surgery, guidance was provided using a GE Revolution HD CT (GE Healthcare), with a 5-mm slice thickness chosen for spiral scanning. A total of 80 iodine-125 seeds, each with an activity of 0.8 mCi, were implanted to achieve a prescribed dose of 140 Gy (Fig. 3C-F). A total of 3 days post-iodine-125 seed implantation, the MAP regimen for systemic intravenous chemotherapy was initiated. However, on day 1 of chemotherapy, the patient experienced nausea and vomiting. Antiemetic medications, such as ondansetron (8 mg administered intravenously once daily) and

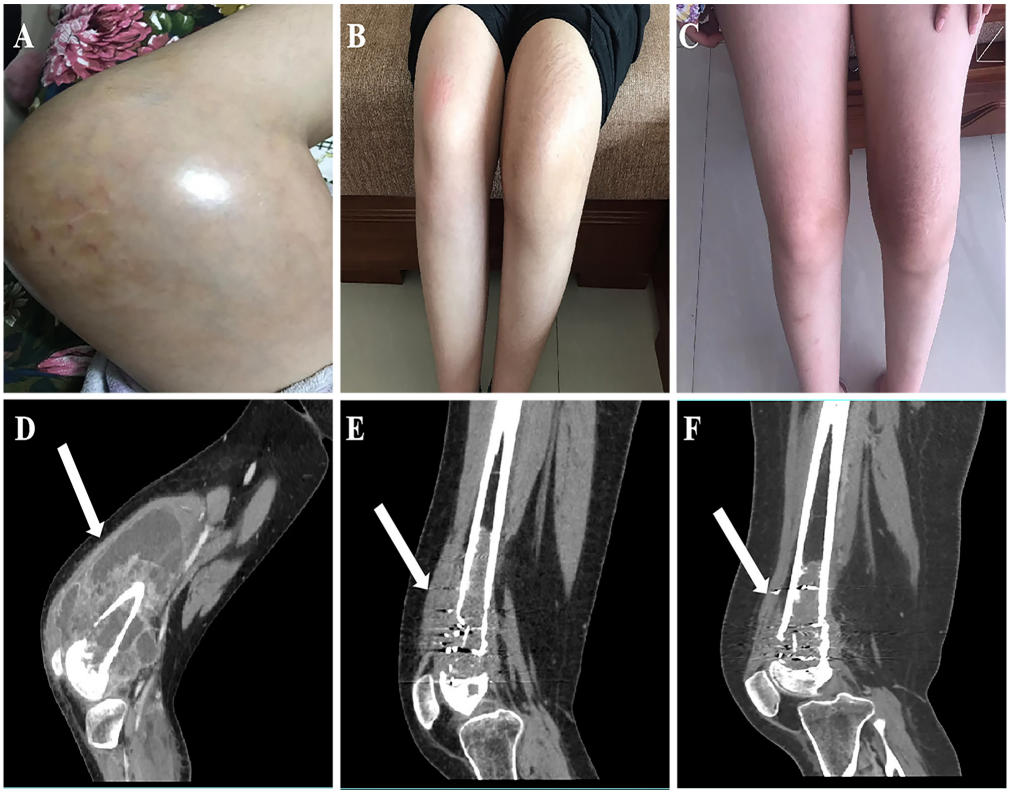

Figure 1. Dynamic changes in the degree of left knee swelling and enhanced CT findings before and after surgery. (A) Preoperatively, the left knee joint exhibited notable swelling and was in a passive flexed position. (B) A total of 6 months post-operation, a partial reduction in swelling of the left knee joint was observed, and (C) a total of 11 months post-operation, further subsidence of swelling in the left knee joint was noted. (D) Preoperative enhanced CT image displayed a large soft tissue mass in the left knee joint, measuring ~12.6 cm in maximum diameter and showing inhomogeneous enhancement. (E) A total of 6 months after the operation, enhanced CT imaging indicated that the mass had decreased, with most tumor tissue having been excised, and (F) a total of 11 months post-operation, enhanced CT imaging revealed a further reduction in mass size.

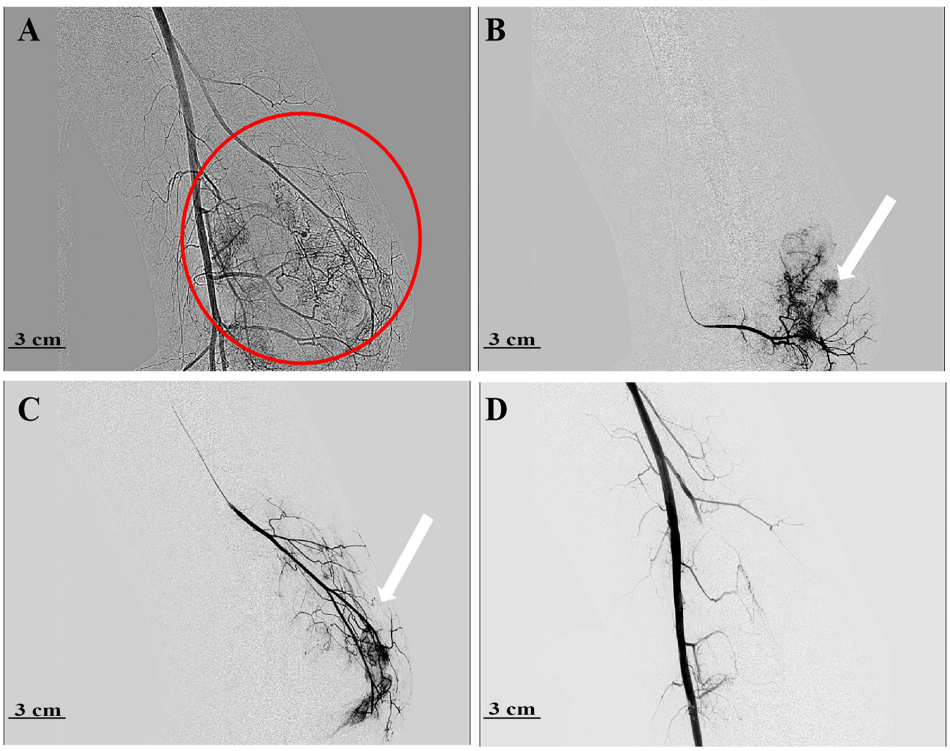

Figure 2. Process of transcatheter arterial embolization of tumor vessels. (A) Digital subtraction angiography imaging revealed that the tumor located in the lower part of the left thigh was vascularized, showing multiple neovascularizations. (B) The abundant blood supply to the tumor was indicated with white arrows. (C) A microcatheter was strategically used to super-selectively cannulate the tumor blood vessels, with the abundant blood supply to the tumor indicated with white arrows. (D) Following the embolization of the tumor blood vessels with microspheres, the blood supply to the tumor was eliminated.

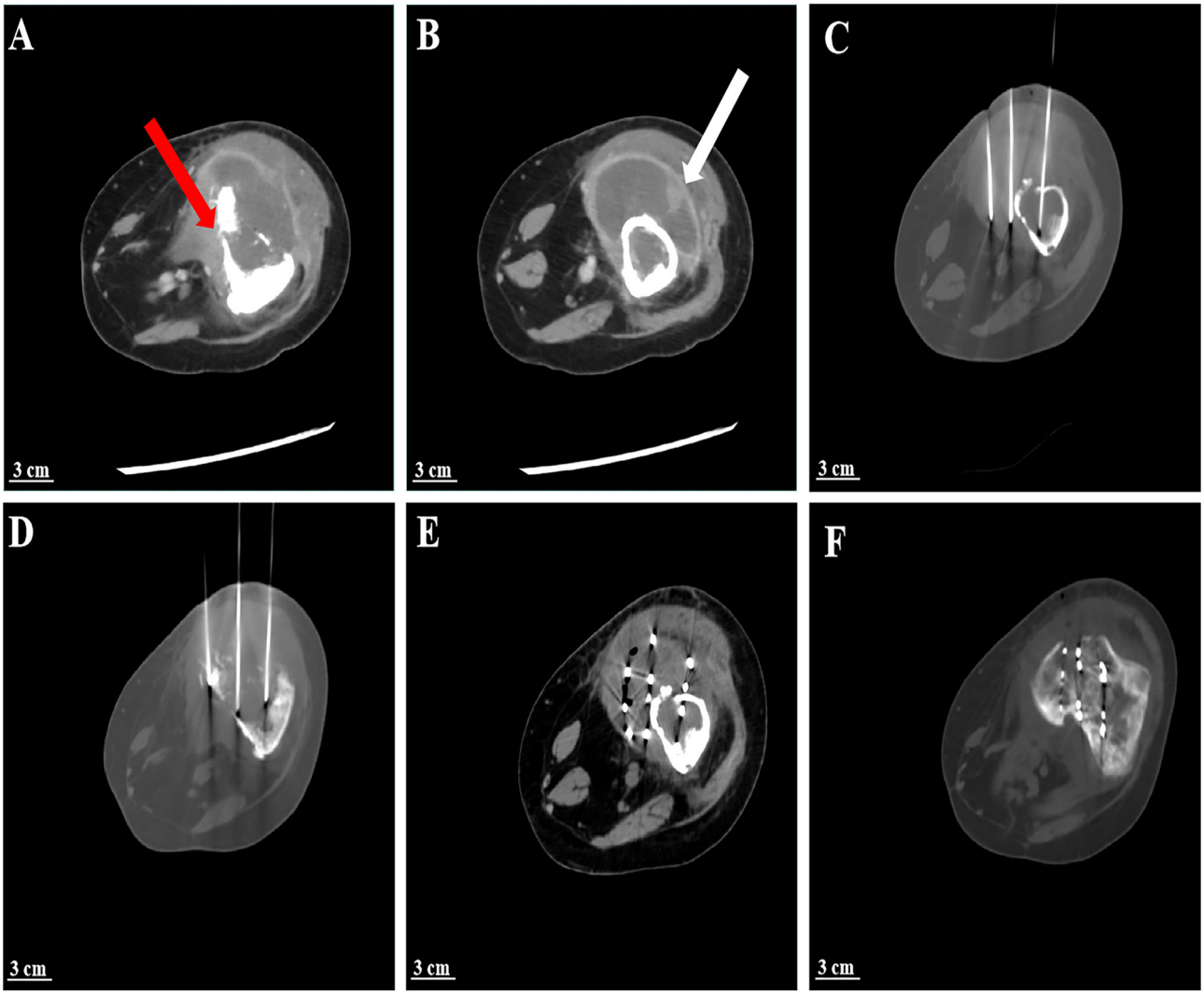

Figure 3. After two TACE treatments, enhanced CT follow-up images and process of iodine-125 seed implantation. (A) A notable reduction in tumor blood supply was detected; the red arrow points to the area of bone destruction in the lower part of the left femur, surrounded by mostly necrotic tumor tissue. (B) The white arrow points to the non-enhanced necrotic tumor tissue around the middle part of the left femur, and a decrease in the maximum tumor diameter was detected. (C) Using an 18 G puncture needle, the tumor was penetrated horizontally through the middle sections of the left femur. (D) Using an 18 G puncture needle, the tumor was penetrated horizontally through the left lower femur at the level of the proximal articular surface. (E) Following the successful insertion of iodine-125 seeds, a real-time CT scan was conducted to confirm their optimal distribution within the tumor located in the middle sections of the left femur. (F) Following the successful insertion of iodine-125 seeds, a real-time CT scan was conducted to confirm their optimal distribution within the tumor located on the proximal articular surface of the left lower femoral segment.

metoclopramide hydrochloride (5 mg administered orally three times/day), were administered as adjunctive therapy, and adjustments were made to the chemotherapy drug dosages. However, despite these interventions, the patient could not endure the side effects of the chemotherapy drugs and was therefore unable to persist with the treatment.

In February, June and September 2019, the patient underwent additional iodine-125 seed implantations due to enhanced CT follow-ups (Fig. 1B and E) indicating areas of sparse particle distribution. A total of 30, 50 and 40 seeds were implanted during these procedures, respectively. Throughout the subsequent treatments, the patient declined systemic intravenous chemotherapy. After 11 months of treatment, follow-up imaging, in accordance with the Response Evaluation Criteria in Solid Tumors version 1.1 (13), revealed a marked reduction in tumor volume. The patient was able to walk using a single crutch, and there was a marked improvement in quality of life (Fig. 1C and F). The pain score had decreased to 2, as measured using the NRS, and both ALP and LDH levels progressively returned to normal ranges (Fig. 4), the rest of the laboratory tests were normal. The patient continued to have follow-up examinations every 6 months. In year 2 following surgery, a repeat biopsy was conducted. Tissue samples were preserved in neutral formalin (4% formaldehyde solution) for 24 h at 20-25˚C. The samples underwent graded alcohol dehydration (70, 80, 90, 95 and 100%), were embedded with paraffin and sliced into 3-4 μm sections. For hematoxylin staining, the sections were submerged in Harris Hematoxylin Stain for 5-10 min, followed by eosin staining (0.5-1% alcohol solution) for 1-3 min at room temperature (20-25˚C). Finally, the samples were sealed with neutral gum and examined under a light microscope. The tissue was predominantly characterized by collagen degeneration and sclerosis, a small amount of

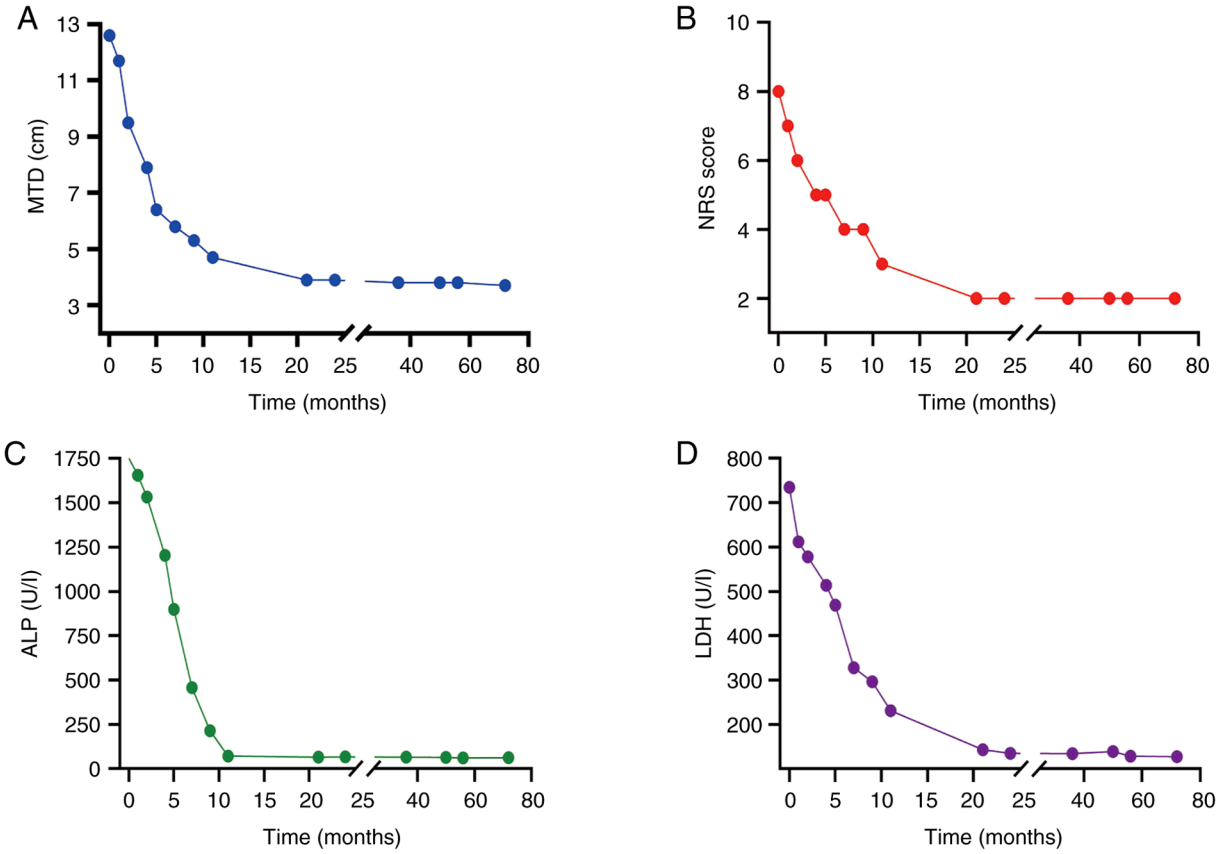

Figure 4. Trends in key indicators during follow-up. (A) MTD was progressively decreased, stabilizing over the course of treatment. (B) NRS pain score was reduced from a preoperative level of 8 to 2. (C) ALP levels were gradually decreased from a preoperative value of 1,752 U/l to the normal range. (D) LDH levels were also diminished from a preoperative level of 735 U/l to within normal limits. MTD, maximum tumor diameter; NRS, Numeric Rating Scale; ALP, alkaline phosphatase; LDH, lactate dehydrogenase.

muscle tissue was noticed at the periphery, and importantly, no residual tumor cells were detected, indicating that the patient had achieved a pathological complete response (Fig. 5). In addition, the patient regained independent ambulation, with their knee range of motion improving from 30-90˚ pre-treatment to 0-110˚ post-treatment. As of the last follow-up in December 2024, the patient has remained stable for >6 years and no secondary tumors were observed.

Discussion

Osteosarcoma is a highly malignant primary bone tumor that primarily affects adolescents. It is characterized by rapid progression, notable local invasiveness and a high likelihood of distant metastasis (1). Currently, the typical treatment approach involves a combination of surgery, radiotherapy and chemotherapy. However, surgical resection often necessitates extensive tissue removal, which can result in asymmetrical limb growth, considerable functional loss and a profound psychological impact on the patient (4). Additionally, multi-cycle systemic chemotherapy is frequently accompanied by severe side effects, which can greatly affect the quality of life of the patient. Although radiotherapy can help control local tumor growth, its effectiveness is limited and it may also cause damage to surrounding healthy tissues (14). Consequently, current research efforts have focused on maximizing the preservation of limb function while minimizing treatment-related toxicities, all while ensuring therapeutic efficacy.

In recent years, the combination of neoadjuvant chemotherapy with limb-saving surgery has enhanced disease-free survival rates for patients with osteosarcoma. A study conducted by Smeland *et al* (15) reported 3- and 5-year event-free survival rates of 59 and 54%, respectively, with this combined therapeutic approach. Limb-saving surgery marks a substantial advancement in the treatment of osteosarcoma, offering a balance between effective cancer management and the preservation of limb function, thus markedly improving the quality of life for young patients. However, this approach also presents challenges related to growth and long-term health. Research using a mouse model of osteosarcoma (16) has indicated that the surgical removal of the primary tumor could accelerate the growth of lung metastases, suggesting that surgery may alter the immune microenvironment, thereby promoting tumor metastasis. Additionally, it has been demonstrated that children who undergo limb-saving surgery are at risk of developing chronic health conditions later in life, such as cardiovascular diseases and secondary malignancies. These risks are likely attributed to the toxic effects of chemotherapy drugs, and multi-cycle chemotherapy can exacerbate these health concerns for patients (17). Gaspar *et al* (18) reported that in the treatment of refractory or recurrent osteosarcoma with lenvatinib combined with etoposide and ifosfamide, 27 out

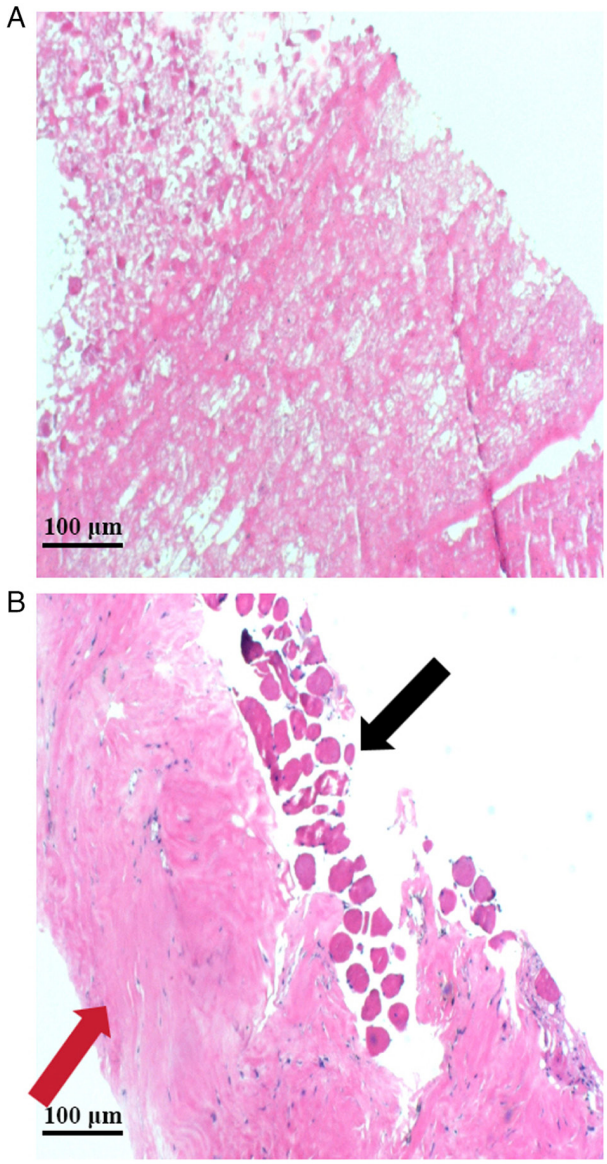

Figure 5. Post-treatment biopsy findings. The biopsy revealed extensive necrosis without any residual tumor cells as evidenced by H&E staining. (A) H&E staining showed a notable amount of coagulated necrotic tissue. (B) Most of the fibrotic tissue was identified as collagen degeneration and sclerosis (indicated by red arrows), with a small quantity of muscle tissue observed at the edge (indicated by black arrows). Magnification, x100. H&E, hematoxylin and eosin.

of 35 patients (77%) experienced neutropenia, 25 patients (71%) suffered from thrombocytopenia, 19 patients (54%) had anemia and 19 patients (54%) saw a decrease in white blood cell count. These findings indicate the toxic side effects associated with chemotherapy agents.

TACE has shown marked efficacy in treating various malignancies, including liver and lung cancer (19,20). Peng *et al* (6) compared preoperative TACE with intravenous chemotherapy in patients with colorectal cancer. The results indicated that adverse events, such as myelosuppression, gastrointestinal reactions, abnormal liver function and neurotoxicity, were considerably lower in the intra-arterial group compared with those in the intravenous group, which also demonstrated a higher disease control rate. Additionally, iodine-125 seeds have been reported to exert promising therapeutic effects in treating malignancies such as prostate cancer and lung cancer (21,22). Sui *et al* (23) explored the combination of iodine-125 seeds and PD-1 therapy for lung cancer, and revealed that all three patients experienced complete or partial remission. Furthermore, Chen *et al* (24) assessed the efficacy of combining iodine-125 seeds with TACE for advanced lung cancer treatment, reporting an objective response rate of 71.42% and a disease control rate of 92.86% at the 6-month time point. Notably, no serious complications were reported during follow-up. The duration of local control ranged from 5 to 12 months, with a median progression-free survival time of 8 months (95% confidence interval: 7.3-8.8 months).

In a case study conducted by Katagiri *et al* (25), a patient diagnosed with pelvic osteosarcoma underwent TACE in conjunction with radiotherapy. Following multiple rounds of intra-arterial chemotherapy and radiation therapy, the patient faced two recurrences at 8 and 14 years after surgery during a 21-year follow-up period. Nevertheless, the patient ultimately achieved complete remission after undergoing aggressive treatment. In the current study, the treatment regimen notably decreased the frequency of chemotherapy compared to the standard regimen. This reduction may be attributed to embolization of the blood supply to the tumor, which obstructs its blood flow, leading to swift tumor necrosis and a decreased need for chemotherapy agents. This method not only diminishes the risk of cardiovascular issues and secondary malignancies, but also enhances the overall quality of life for patients. Arterial embolization may alter the immune microenvironment of the tumor, thereby enhancing the immune response to the tumor. In an animal study (26), hepatic artery embolization was shown to enhance intratumoral and peritumoral PD-L1 expression in a rat model of hepatocellular carcinoma (HCC). In addition, Chao *et al* (27) revealed that TACE is associated with the modulation of serum angiogenic, inflammatory and cell growth cytokines in patients with HCC. Additionally, the present case report used iodine-125 seed implantation, which offers improved local control of the tumor while maximizing the protection of adjacent healthy tissues. Ferrari *et al* (14) previously explored the effects of high-dose ifosfamide in the first-line treatment of patients ≤40 years of age with nonmetastatic osteosarcoma of the extremity. The results showed that the program, while feasible, produces major renal and hematologic toxicity.

In the present case report, a 13-year-old female patient was diagnosed with high-grade osteosarcoma through a pathological biopsy. A treatment plan that combined TACE with iodine-125 seed implantation was subsequently implemented. Postoperative follow-up results revealed notable pain relief, a gradual recovery of limb function and complete tumor remission as observed in imaging studies. Over a follow-up period of >6 years, the patient exhibited effective local tumor control, no distant metastasis, no notable complications and an improvement in quality of life. While the use of arterial chemoembolization has been reported, its combination with iodine-125 seeds for osteosarcoma is novel. The patient had a large tumor volume and rich blood supply at the time of initial treatment, and there was a high risk of bleeding with direct iodine-125 seed implantation. Therefore, arterial embolization was performed followed by seed implantation, and an operation sequence was chosen that not only reduced the

risk of bleeding, but also reduced the dosage of iodine-125 seeds and radiation damage. These findings indicated that the combination of iodine-125 seeds and TACE may demonstrate considerable clinical efficacy in treating osteosarcoma, with fewer adverse effects compared with traditional radiotherapy and chemotherapy. This approach has potential as an essential adjunct therapy for osteosarcoma, yielding improved treatment outcomes and quality of life for patients.

In conclusion, the combination of TACE and iodine-125 seed implantation represents an innovative treatment modality that provides a potential supplementary option for managing osteosarcoma, especially for patients with osteosarcoma with abundant blood supply and no distant metastasis, and those whose tumor is unable to be completely resected or refuse to undergo surgery. The successful treatment of this case strongly supports the clinical application of this method. Although the results are promising, the present study has several limitations. Since the previous biopsy was conducted at another hospital, pre-treatment pathology images cannot be provided. To determine the efficacy and safety of the present treatment plan, further validation through larger clinical studies is necessary to assess its applicability and long-term outcomes for patients with osteosarcoma. Additionally, exploration of optimal dosing and treatment regimens is essential to enhance therapeutic effects while minimizing side effects.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LR and FL contributed to study conceptualization and manuscript writing. LJ and YL conducted the study design and analyzed the data. LY analyzed the re-biopsy pathology slides. LR, LY and YL confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The mother of the patient provided written informed consent for the publication of this research.

Competing interests

The authors declare that they have no competing interests.

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