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Current Status and Prospects of Clinical Treatment of Osteosarcoma

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Abstract

Osteosarcoma, one of the common malignant tumors in the skeletal system, originates in mesenchymal tissue, and the most susceptible area of occurrence is the metaphysis with its abundant blood supply. Tumors are characterized by highly malignant spindle stromal cells that can produce bone-like tissue. Most of the osteosarcoma are primary, and a few are secondary. Osteosarcoma occurs primarily in children and adolescents undergoing vigorous bone growth and development. Most cases involve rapid tumor development and early blood metastasis. In recent years, research has grown in the areas of molecular biology, imaging medicine, biological materials, applied anatomy, surgical techniques, biomechanics, and comprehensive treatment of tumors. With developments in molecular biology and tissue bioengineering, treatment methods have also made great progress, especially in comprehensive limb salvage treatment, which significantly enhances the quality of life after surgery and improves the 5-year survival rate of patients with malignant tumors. This article provides a review of limb salvage, immunotherapy, gene therapy, and targeted therapy from traditional amputation to neoadjuvant chemotherapy, providing a reference for current clinical treatments for osteosarcoma.

Keywords

osteosarcoma, treatment, chemotherapy, immunotherapy, prognosis

Abbreviations

ADH, alkaline phosphatase; ADM, adriamycin; CAR-T, chimeric antigen receptor T; CDK, cyclin-dependent kinase; DC, dendritic cell; DDP, cisplatin; HIFU, high-intensity focused ultrasound; HLA, human leukocyte antigen; IDH, isocitrate dehydrogenase; IL-2, interleukin-2; PARP, poly ADP ribose polymerase; RFA, radiofrequency ablation; RTX, receptor tyrosine kinase; MTX, methotrexate; NK, natural killer; TSCs, tumor stem cells; TACE, transcatheter arterial chemoembolization; TKI, tyrosine kinase inhibitor

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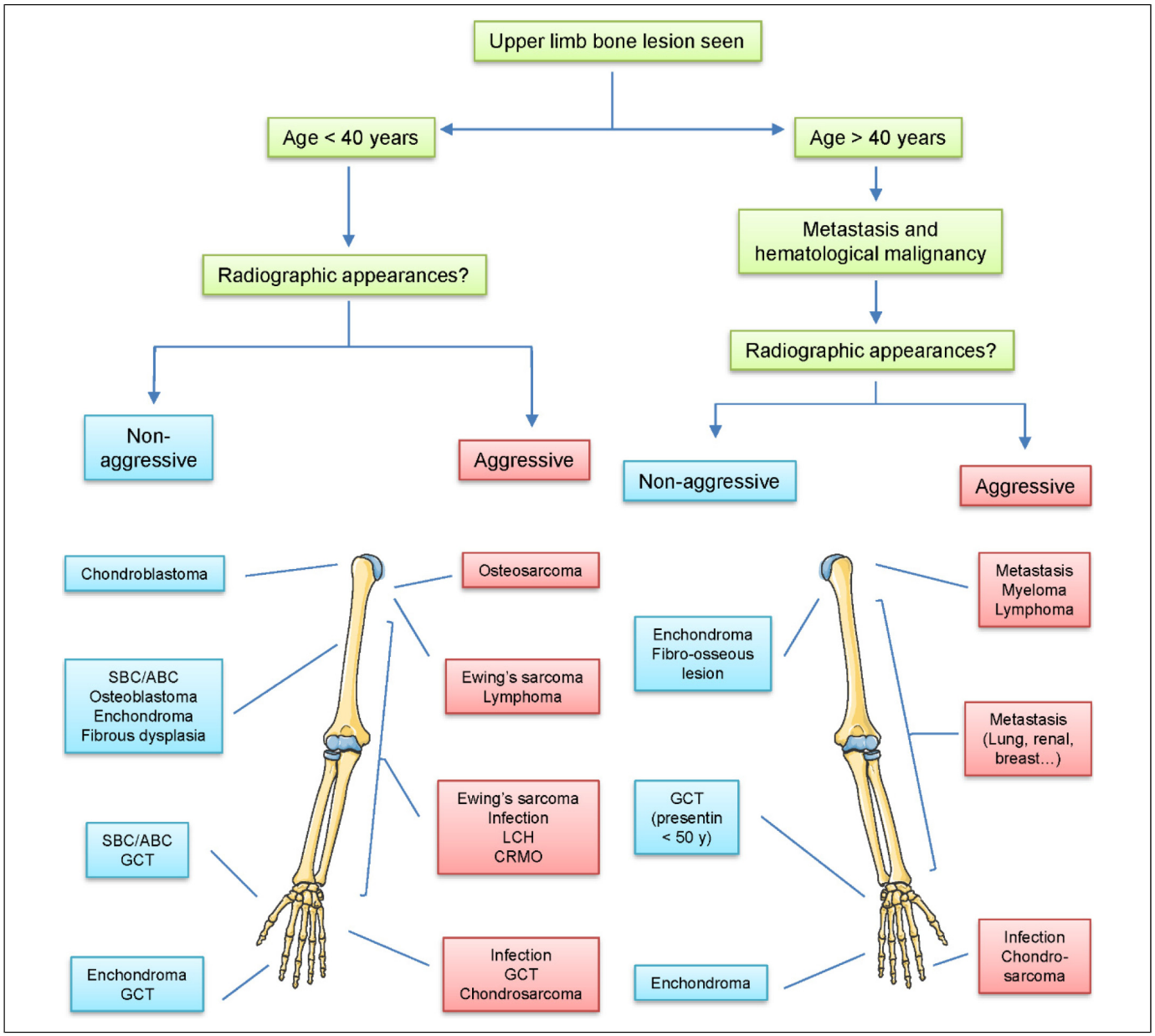

Figure 1. Common bone lesions according to age and location in the upper limb. The incidence of different bone lesions varies at different sites within the upper limb and age.
Abbreviations: CRMO, chronic recurrent multifocal osteomyelitis; GCT, giant cell tumor; LCH, Langerhans cell histiocytosis; SBC/ABC, simple bone cysts/aneurysmal bone cysts.

Introduction

The diagnosis and treatment of tumors in bone is a difficult problem in orthopedics. The incidence of different bone lesions significantly varies at various sites within the limb, and age is one of the important factors in tumorigenesis (Figure 1). The 5-year survival rate of patients with osteosarcoma has been about 20% due to limitations in treatment. Despite recent advances in molecular biology, biomaterials, imaging medicine, applied anatomy, biomechanics, surgical techniques, and comprehensive treatment of tumors, progress has been slow.[1–3] Neoadjuvant chemotherapy has been recognized as an especially effective treatment for osteosarcoma since the initiation of its use in the 1980s.[4] The survival rate of osteosarcoma has improved considerably, and the rate of limb salvage has reached more than 65%.[5, 6] However, since 80% of patients with osteosarcoma have distant metastasis at the time of initial diagnosis, the prognosis is extremely poor regardless of the treatment taken by 20% to 30% of patients.[7] Therefore, improving the treatment efficacy and survival rate of patients with osteosarcoma remains an urgent issue to be solved in clinical practice. In this review, we provide limb salvage, immunotherapy, gene therapy, and targeted therapy from traditional amputation to neoadjuvant chemotherapy for current clinical treatments for osteosarcoma.

Chemotherapy

Clinical treatment of osteosarcoma has made great progress in recent years largely due to improvements in chemotherapy. With the development of limb salvage surgery, neoadjuvant chemotherapy, and immunotherapy, the 5-year survival rate has significantly improved.[8–11] However, malignant bone tumors still result in extremely high mortality and disability so a treatment multidisciplinary treatment strategy is important. Surgery and neoadjuvant chemotherapy have become widely recognized as the standard mode for the treatment of osteosarcoma.[12]

Traditional chemotherapy treatments used in clinical practice are based on several regimens proposed by Rosen et al in the 1980s, and there is currently no breakthrough in curative effect.[13] Because osteosarcoma tumors are relatively resistant, the efficacy of single-agent chemotherapy has been less than ideal and only a few drugs can produce more than 15% efficiency.[14] The main drugs currently used for osteosarcoma chemotherapy include methotrexate (MTX), adriamycin (ADM), cisplatin (DDP), ifosfamide, vincristine, epirubicin, cyclophosphamide, and etoposide.[15–17] MTX, ADM, DDP, and ifosfamide are the most commonly used and are combined in different ways. At present, the map scheme composed of high-dose MTX, ADM, and DDP is the standard scheme for most treatment centers in Europe and America.

Importantly, the sensitivity of chemotherapy for osteosarcoma cells directly affects the survival rate of patients. Chemotherapy must be systematic and regularized to reduce drug resistance.[18–20] To eliminate the characteristics of drug resistance caused by single-agent chemotherapy, combined chemotherapy has been developed. The main objective is to synergize the effects of combined antineoplastic drugs, reduce the toxicity of a single drug, and reduce drug resistance. Besides, the use of natural compounds in the treatment of cancers has received much attention in occurring years.[21]

The emergence of neoadjuvant chemotherapy in recent years has improved survival and reduced recurrence and metastasis; in addition, it has increased limb salvage rate. Surgery supplemented with chemotherapy is not simply a matter of "preoperative chemotherapy + surgery + postoperative chemotherapy." The new approach, based on the pathological grade of postoperative histopathology, is to adjust the postoperative chemotherapy regimen according to the tumor necrosis rate after preoperative chemotherapy.[21] Neoadjuvant chemotherapy has become the standard protocol for osteosarcoma, and treating early micrometastases and primary lesions improves the postoperative success rate of limb salvage surgery.

Attention should be paid to the basic principle of neoadjuvant chemotherapy—that is, the evaluation of preoperative chemotherapy efficacy and assessment of whether to adjust the postoperative chemotherapy regimen.[9, 22] Because the evaluation of tumor necrosis rate needs to happen after surgical removal of pathological specimens, a judgment is not possible before surgery. A noninvasive means to evaluate the degree of preoperative tumor necrosis before surgery would have even greater value in judging prognosis and guiding treatment.[23] Some valuable factors for judging the effect of chemotherapy include clinical observations, such as the alleviation of pain or symptoms, whether the tumor mass is reduced, and whether isocitrate dehydrogenase (IDH) and alkaline phosphatase (AKP) are decreased on testing.[24] Also important are the presence and extent of metastasis and characteristics such as tumor size, soft tissue mass, reaction area, degree of ossification, and appearance of blood vessels on computed tomography, x-ray, and magnetic resonance imaging.[25]

Molecular Targeted Therapy

After decades of development, the conventional treatment for osteosarcoma has been standardized. In various bone tumor centers in China, the comprehensive treatment of surgery, neoadjuvant chemotherapy, and postoperative adjuvant chemotherapy have obtained a 5-year survival rate of 60% to 70%.[26] However, for patients with poor chemotherapy efficacy and difficulty tolerating chemotherapy, the current second-line treatment is still challenging. Besides, due to the high heterogeneity and low incidence of osteosarcoma, it is difficult to target specific driving genes.

Receptor tyrosine kinase (RTK) is a key upstream molecule, which participated in a variety of signal pathways related to cell growth, apoptosis, and survival.[27–29] Abnormal amplification or activating mutation of RTK leads to continuous activation of downstream signals, resulting in uncontrolled growth of tumor cells.[30] The multi-target tyrosine kinase inhibitor (TKI) designed for RTK is the drug category that has made the fastest progress in the targeted therapy of osteosarcoma. The drugs regorafenib and pazopanib have clearly established their value in many clinical practices for the treatment of osteosarcoma.[31] It is worth mentioning that the use of a TKI in combination with chemotherapy in the preoperative neoadjuvant treatment stage has been explored to reduce the toxicity of chemotherapy and shorten the treatment course. As such, relevant clinical trials are in progress.

Mutations of cell cycle-related molecules such as CCNE1 amplification, retinoblastoma gene 1 inactivation, and cyclin-dependent kinase (CDK)4/6 amplification can often be detected in osteosarcoma.[32] CCNE1 amplification is thought to be related to chemotherapy resistance in many tumor species.[33–36] The frequency of CCNE1 amplification in osteosarcoma can be as high as 30%. Although there is no drug directly targeting CCNE1 at present, it is theoretically feasible to treat it by acting on its downstream cyclin CDK1/2/5/9 and using multi-target CDK inhibitors such as dinaciclib.[37–39] Some teams have also used patient-derived xenograft animal models to obtain clear therapeutic effects in osteosarcoma.[40–42]

CDK4/6 inhibitors such as piperacillin and abemaciclib are among the most mature drugs in the arena of cyclins, and have occupied a high position in the treatment of breast cancer and liposarcoma.[43–45] However, because CDK4/6 amplification alone is rare in high-grade osteosarcoma, it would be difficult to design clinical trials for this mutation.

For osteosarcoma with multiple suspected carcinogenic mutations, it is also difficult to determine the indication by defining the cutoff of CDK4/6 amplified copy number.[46] In addition, the treatment cost of CDK4/6 inhibitors, and the risk of blood toxicity and other risks associated with off-label use are great obstacles to their individualized use.[47]

PTEN-PI3K-AKT-TSC1/2-MTOR is an important signaling pathway related to protein synthesis and cell growth.[48–50] Many molecules associated with this pathway have been detected in osteosarcoma.[51–53] Mutations of the genes *PTEN* and *TSC1/2* occur with relatively high frequency, with *PTEN*, a tumor suppressor gene, found in more than 50% of high-grade osteosarcoma cases.[54] The PTEN-P13K pathway involves many molecules, providing opportunities for targeted therapy. For example, everolimus, a second-line drug for osteosarcoma, is a typical mTOR inhibitor and has been listed in the drug guidelines of the National Comprehensive Cancer Network.[55] However, everolimus inhibits only mTORC1 and has very little effect on mTORC2, which may also be an important reason for its limited effect on osteosarcoma.[56]

BRCA is an important tumor suppressor gene, and its mutation frequency in osteosarcoma is also very high, making it a possible initiator of tumorigenesis.[57–60] Some studies have found that more than 80% of osteosarcomas show a BRCA-like phenotype, with characteristics including large single-nucleotide mutations, loss of heterozygosity, and telomere allele imbalance.[61–63] Homologous DNA repair-deficient cancers caused by BRCA mutation provide opportunities for the use of poly ADP ribose polymerase (PARP) inhibitors such as olaparib to produce a "synthetic lethal" effect, resulting in the death of large numbers of tumor cells. With impressive clinical results, it has become a first-line drug in the treatment of some ovarian and breast cancers.[64] Considering the widespread presence of BRCA mutations in osteosarcoma, it is desirable to try PARP inhibitors in osteosarcoma cases with mutation-positive/homologous DNA repair-deficient cancer.[65]

Radiotherapy

Ionizing radiation in radiotherapy acts on the target molecule DNA, and tumor cells produce a huge number of reactive oxygen molecules, causing DNA oxidative damage, which ultimately leads to tumor cell death.[66] Radiotherapy is a critical method for the treatment of many malignant bone tumors. In the treatment of spinal vertebral tumors, radiotherapy can directly kill tumor cells while reducing the tumor size for surgical resection.[67] The significance of radiotherapy is greater for spinal tumors that are resected in the lesion and for palliative resection.[68] Moreover, post-loading radiotherapy is radiation therapy at close range and high dose rate.[69] This technique is suitable for locally recurrent tumors or tumors that have been inoperable.[70]

Recent research has aimed at the use of radiotherapy sensitizers in cancer treatment. Their application avoids damage to normal tissues while improving the sensitivity of tumor cells to radiotherapy.[71] Although osteosarcoma has poor sensitivity to radiotherapy, radiosensitizers assist in treatment by increasing the sensitivity of tumor cells to radiotherapy and improving the lethality of radiation on tumor cells.[72–76]

Limb Salvage Treatment

Improvements in chemotherapy, imaging technology, and limb reconstruction technology have promoted the development of limb salvage surgery. There is no statistically significant difference in postoperative survival rates between patients undergoing limb salvage surgery and radical surgery.[77] During the surgical treatment of malignant bone tumors, patients and their families are more likely to request limb salvage surgery; thus, the use of the technique in that setting has developed rapidly.[78] At the same time, advances in related technical fields of surgery including materials science, prosthetic manufacturing processes, radiographic diagnostics, physical therapy, interventional techniques, and surgical techniques, have contributed to the wider use of limb salvage surgery when treat malignant bone tumors.[79–82]

After resection, the bone must be reconstructed to restore limb function. In the past, orthopedic tumor surgeons analyzed two-dimensional imaging information and mentally integrated the data to make three-dimensional operation plans.[83] In complex cases, it is difficult to convert the operation plan into physical practice in an operating room. In the past decade, the development of computer-aided tumor surgery has enabled surgeons to plan three-dimensional operations and perform an image-guided osteotomy.[84] This technique results in safer tumor resection and can improve the accuracy of the surgery by copying the preoperative plan, resulting in clinical benefits (Figure 2).

Before deciding whether to perform limb-salvage surgery, it should be fully evaluated whether the function of the limb after salvage surgery would be better than prosthetic function after amputation. The scope of resection of the tumor should be fully estimated before surgery. The resection range should include the tumor body, capsule, reaction zone, and surrounding normal tissues.[85] In fact, such resection is difficult to achieve in most malignant bone tumors, and in clinical practice, most resections are performed closer to 1 cm outside the reaction zone.

If the vascular and nerve is involved, surgery is more difficult. Generally, for patients with sacral nerve invasion or anterior tibial artery damage, limb salvage surgery can still be attempted. If other vascular or nerves are involved, limb salvage surgery should not be performed. However, for tumors around the elbow joint and the knee joint, the affected vascular or nerve can be resected and reconstructed as long as the general condition is good and there is no metastasis.[86] If metastasis has already occurred, surgical resection can be performed under adjuvant chemotherapy and before limb salvage surgery, with an approximate success rate of 30% according to one study.[87] If a pathological fracture has occurred, limb salvage surgery may also be attempted as appropriate.

Artificial prosthesis replacement is currently the most widely used and best-performing method of limb salvage reconstruction. In recent years, the variety and suitability of adjustable

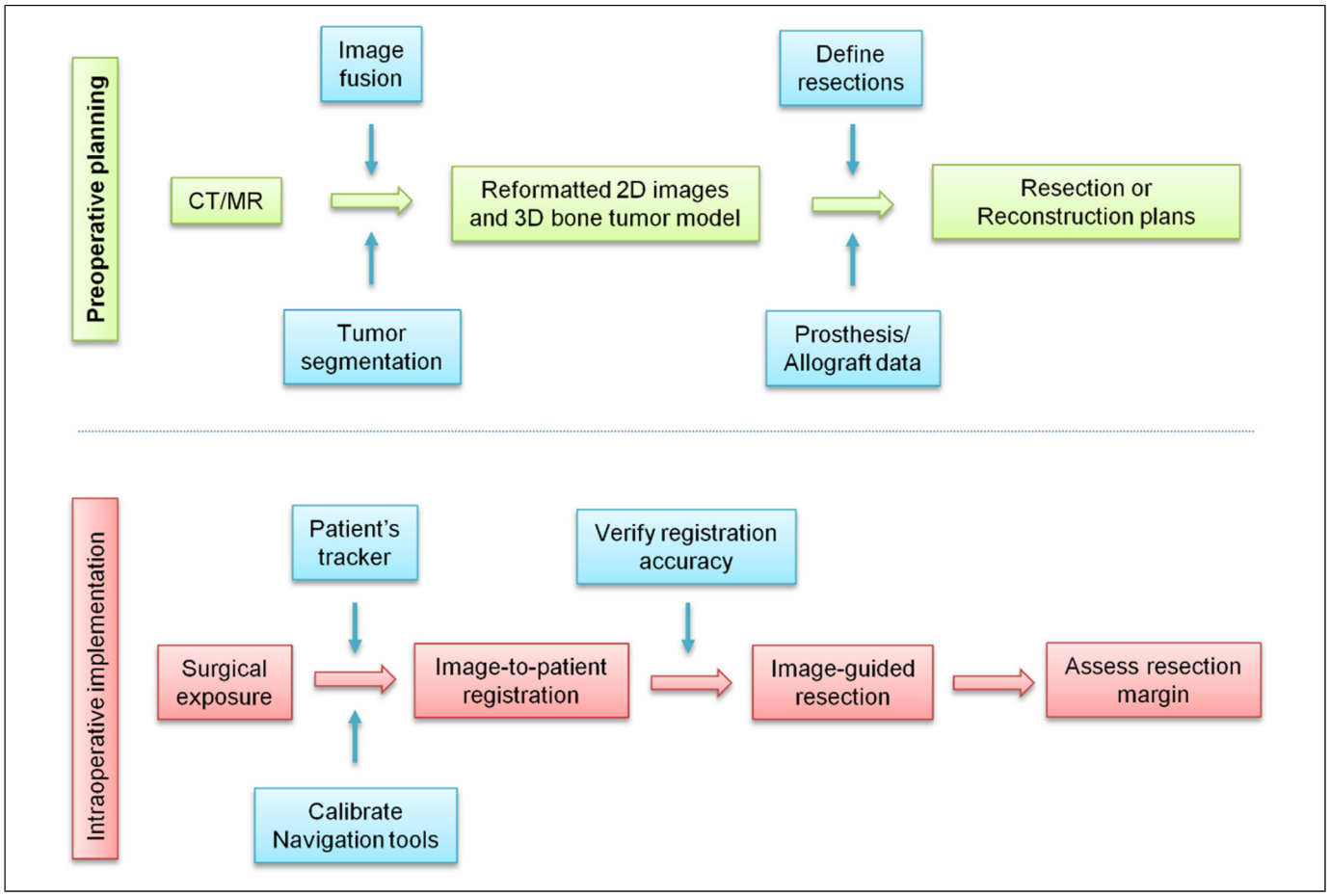

Figure 2. Clinical workflow of computer-assisted tumor surgery. In the surgical treatment of osteosarcoma, multimode image data are obtained using advanced imaging equipment. The computer processes the medical image data and aids in displaying and positioning the anatomical structure of the bones, planning the surgical path, formulating a reasonable and quantitative surgical scheme, conducting the preoperative surgical simulation, and using robot-assisted accurate guidance during surgery. With monitoring and improved accuracy of positioning, this technique can reduce surgical injury and improve the success rate of complex surgical operations.

and individualized prostheses have improved greatly. Recent surveys have shown that the clinical 10-year satisfaction rate of a good quality prosthesis can reach 90%.[88–91] Allogeneic bone transplantation has relatively narrow indications of infection, fracture, absorption, rejection, and infectious diseases. However, its advantages in biological reconstruction have led many institutions to study it.[92]

It is worth noting that tumor prosthesis replacement is different from ordinary joint replacement. Most cancer patients are young and desire a very active life. Meantime, a large defect of the bone tissue requires extensive soft tissue resection, resulting in the need for a stable prosthesis to compensate for poor balance. Patients need early recovery activities after surgery to upgrade their quality of life and minimize movement limitations after surgery.[93]

Although limb salvage surgery has become the treatment of choice for malignant bone tumors, tumor residuals are still the primary cause of recurrence. However, removing too much tissue affects the reconstruction of bone and soft tissue. Intraoperative radiotherapy can help locally control the tumor and improve postoperative functional recovery.[94]

Interventional Therapy

Interventional treatment of osteosarcoma is both a palliative treatment for tumors and an adjuvant treatment for limb salvage surgery. The 2 main types of therapy are intravascular and nonvascular intervention.[95, 96] Nonvascular intervention refers to tumor ablation with a percutaneous puncture, while intravascular intervention includes intra-arterial infusion chemotherapy and arterial embolization.[97] Arterial infusion chemotherapy can effectively control tumor growth, reduce the probability of tumor border implantation, and improve the resection rate and limb salvage rate in tumor surgery. Moreover, arterial infusion chemotherapy can improve clinical symptoms, reduce tumor size, and decrease vascular endothelial cell necrosis, vascular occlusion, and blood supply to the tumor.[98]

Arterial embolization refers to inject an embolic agent into the main artery supplying blood to embolize the blood vessels and cause tumor necrosis due to ischemia. In the treatment of malignant bone tumors, simple embolization can decrease intraoperative bleeding and improve the resection rate and limb salvage rate.[99]

Selective arterial embolization and transcatheter arterial chemoembolization (TACE) are the most common methods used in the clinic. Selective arterial embolization uses either spring coils or small gelatin microspheres to cut off the blood supply of the tumor, thus resulting in ischemia and tumor cell necrosis.[100] Mavrogenis et al[101] employed this method to treat 19 patients with advanced osteosarcoma. The pain of all patients was relieved 3 days after embolization, and 5 patients achieved continuous relief after repeated embolization. Because it reduces pain rapidly and can be repeated multiple times, arterial embolization has advantages over radiotherapy and chemotherapy for patients with advanced cancer.

The TACE procedure involves inserting the catheter selectively and injecting chemotherapy drugs into the target artery supplying blood to the tumor. TACE is mainly used in limb salvage surgery or adjuvant therapy before radical surgery, to promote tumor necrosis, reduce complications, and improve the success rate of surgery.[102, 103]

Immunotherapy

Immunotherapy modulates the body's own immune function to kill tumor cells. Techniques include specific and nonspecific immunotherapy, immuno-directed therapy, and adoptive immunotherapy.[104–107] T cell-mediated cellular immunity makes a valuable contribution toward the fight against tumor cells, and natural killer (NK) cell-mediated natural immunity is the first line of defense against tumors.[108] Due to the development of new tumor molecular biology techniques and the establishment of immunoassay indicators, doctors can accurately assess quantitative and qualitative changes in tumor molecules and cellular immune functions.[109–111] Moreover, immunotherapy can play an important role along with traditional surgery, radiotherapy, and chemotherapy.

At present, research achievements in osteosarcoma immunotherapy primarily involve cytokine therapy and dendritic cell (DC) therapy.[8] Chimeric antigen receptor T (CAR-T) cell immunotherapy and immune checkpoint blocking drugs are also becoming hotspots for tumor research.

DCs have a strong antigen-presenting ability. They can be incubated with tumor neoantigen and were injected into patients as a vaccine to produce a specific antitumor immune response. In one experiment using a rat osteosarcoma model, DCs were combined by electrofusion with UMR106 cell line and injected into rats. The results showed that the fusion vaccine could effectively activate cytotoxic T cells and stimulate T lymphocyte proliferation, leading to atrophy and even the disappearance of the tumor.[112]

Cytokines take part in the regulation of multiple cellular physiological and immune response. The interleukin-2 (IL-2) cytokine is an essential element of immunotherapy whose role includes activating effector T cells and enhancing the function of NK cells.[113] Meazza et al[114] used chemotherapy and IL-2 to treat patients with primary pulmonary metastatic osteosarcoma. The results indicated that IL-2 involved in immunotherapy can potentially increase the survival rate of osteosarcoma patients. Interferon has also been used in the cancer treatment and studies have confirmed that it can enhance the sensitivity of chemotherapy drugs during the treatment of osteosarcoma.[12]

CAR-T is a new immunotherapy method that has been successfully applied to treat blood tumors. In the process of identifying tumors, CAR-T after genetic engineering transformation is no longer limited by proteins that evade the major histocompatibility complex.[115–117] CAR-T recognizes tumor antigens in a way independent of human leukocyte antigen (HLA) molecules, recognizes and kills tumor cells across the down-regulation mechanism of HLA expression, and has the advantages of diverse recognition of tumor antigen targets, lasting effects in vivo, and reducing the incidence of rejection reactions.[118–121]

The key to the application of CAR-T cell immunotherapy in osteosarcoma treatment is to find suitable target molecules. At present, HER2, the IL-11 receptor chain, and ganglioside GD2 have been confirmed to be overexpressed in multiple osteosarcoma cells.[122, 123] These receptors may serve as effective targets for CAR-T cell immunotherapy and inhibition of tumor metastasis in osteosarcoma.[124] The antitumor effect and persistence of HER2-CAR-T cells in a certain time range show promise for clinical application.[125]

PD-L1 and PD-1 are immune checkpoint proteins involved in modulating the body's immune response.[126–128] Although checkpoint proteins have a role in preventing autoimmune disease, they can also suppress the immune system's ability to attack tumor cells. Research is deepening on the drug's use to inhibit the action of PD-1/PD-L1 and thereby increase the body's ability to fight tumor cells.[129] Shimizu et al[130] employed a mouse osteosarcoma model to evaluate the efficacy of immune checkpoint inhibitors on lung metastasis. They found that the proliferation and invasion of osteosarcoma cells were inhibited in the PD-1/PD-L1 antibody treatment group. This suggests that PD-1/PD-L1 antibody therapy may be valuable in the treatment of osteosarcoma.[131, 132]

Ablation Treatment

Surgery, radiotherapy, and chemotherapy have traditionally been the main treatments for osteosarcoma. However, functional reconstruction has a high incidence of complications, and radiotherapy and chemotherapy can damage normal tissues and reduce the immune function of the host in addition to killing tumor cells. Because radiofrequency ablation (RFA) is noninvasive or minimally invasive, it has some unique advantages in the treatment of osteosarcoma.[133] Techniques that have been applied in the clinic with good curative effects include RFA, high-intensity focused ultrasound (HIFU) ablation, cryoablation, and microwave ablation.[133–135]

The main mechanisms of HIFU ablation include cavitation effect, thermal effect, and mechanical effect. Among them, thermal effect plays a vital role. Thermal effect refers to the heating of the tissue through the propagation of focused ultrasonic waves.[136] The particles of tissue vibrate at high speed,

and part of the acoustic vibration energy converts into molecular thermal motion energy, resulting in increased temperature. The target area is heated to above 60 °C instantaneously, resulting in protein degeneration, coagulation necrosis, and structural and functional changes of cells in the target tissue.[137]

Cavitation effect involves the formation, expansion, and explosion or implosion of small air bubbles caused by the ultrasound wave vibration.[138] Cavitation can produce locally high temperature, high pressure, free radicals, and strong shock waves, which can denature enzymes and proteins in cells. Cavitation effect can also enhance the thermal effect.[139] Mechanical effect refers to the vibration of tissue caused by ultrasound. Vibration that exceeds the elastic limit of the tissue causes damage. However, some studies have shown that mechanical effects only cause damage to the diseased bone tissue, does not damage the mechanical function of bone.[140]

At present, HIFU treatment is guided by MRI or ultrasound. Ultrasound-guided treatment has the advantages of economy and convenience, but its imaging contrast is poor, quantitative temperature measurement is impossible, and the accuracy of postoperative evaluation is not high.[141] MRI-guided ultrasound has good imaging quality and high resolution, but the imaging speed is relatively slow and can be easily affected by patients' breathing movements.[142] Patients with cardiac pacemakers and metal parts are prohibited, and the cost is high.

HIFU has unique advantages when treating malignant bone tumors. Because it is noninvasive or minimally invasive, it reduces complications such as bone nonunion and infection that may result from invasive surgery. Further, it does not require functional reconstruction and it can enhance the immune function of the body. The treatment is rapid and has high accuracy. As one of the comprehensive treatment methods for tumors, HIFU can effectively relieve pain and improve patients' quality of life.[143] However, there is no unified standard for the treatment dose of HIFU for tumors of different pathological types at different sites. Practices need to be adjusted based on intraoperative real-time feedback. Newer HIFU technologies such as ultrasound microbubble angiography still need to be evaluated for their usefulness in treating osteosarcoma.[144]

Furthermore, RFA and cryoablation are other ablation techniques recommended for the treatment of osteosarcoma metastasis. However, there are differences between the two because of their different mechanisms of action.[145] RFA is not strong enough to easily penetrate bone, so it is often used to treat lung metastasis, whereas a cold probe can penetrate deep bone tissue, so it can be used in bone metastases. Saumet et al[133] employed RFA to treat 10 patients with lung metastases of osteosarcoma under the age of 25 years. The results showed that 7 patients were completely relieved and no metastasis occurred at the treatment site.

Stem Cell Therapy

Osteosarcoma occurs when genetic or other factors interfere with the normal process by which mesenchymal stem cells differentiate into bone cells. Because mesenchymal stem cells can transform into tumor stem cells (TSCs), there is an opportunity to study the relationship between TSCs and osteosarcoma.[146] TSCs are closely related to tumorigenesis, proliferation, recurrence, and chemotherapy resistance.[147] Therefore, the study of TSCs can help solve the problem of recurrence and metastasis of osteosarcoma at the source.

Based on isolating TSCs and identifying different specific surface antigens expressed by osteosarcoma stem cells, researchers can create a targeted neutralizing antibody to inactivate TSCs and block the development of osteosarcoma.[148] It has been found that in a hypoxic environment, TSCs can activate lysine oxidase by upregulating the expression of hypoxia-inducible factors and promoting the formation of metastatic tumors.[149] This suggests that changing the microenvironment in which TSC survives may be another way to treat osteosarcoma. In summary, the introduction of TSC research has elevated the diversification of osteosarcoma treatment to a new height.

Outlook

The clinical treatment of osteosarcoma has gone through a long period of exploration and development. So far, great progress has been made and treatment techniques have matured. The application of high-dose chemotherapy increases the intensity of action on tumor tissues so that the patient's prognosis is greatly improved. Neoadjuvant chemotherapy combined with extensive resection of tumors not only improves the survival rate of patients but also preserves better limb function. The popularity of large-scale medical testing instruments, such as MRI and radionuclide scanners, has made early detection, early diagnosis, and early treatment of osteosarcoma possible.

Great progress has been made in the reconstruction of bone materials suitable for bone tumor salvage surgery. Extensive resection of the tumor has become possible, resulting in a significantly prolonged local tumor-free period, improved quality of life, and prolonged life expectancy for the patient. Finally, the study and application of new technologies such as radiotherapy, molecular targeted therapy, immunotherapy, ablation, and stem cell therapy have brought new hope in controlling local recurrence and distant metastasis.

Conclusion

Osteosarcoma, one of the most common malignant tumors in the skeletal system, occurs primarily in children and adolescents and most cases involve rapid tumor development and early blood metastasis. Since 80% of patients have metastasis at the time of initial diagnosis, the prognosis is extremely poor regardless of the treatment taken by 20% to 30% of patients. In recent years, research has grown in the areas of molecular biology, biological materials, imaging medicine, applied anatomy, biomechanics, surgical techniques, and comprehensive treatment of tumors. With developments in molecular biology and tissue bioengineering, treatment methods have also made

great progress, especially in comprehensive limb salvage treatment, which significantly enhances the quality of life after surgery and improves the 5-year survival rate of patients with malignant tumors. Improving the treatment efficacy and survival rate of patients with osteosarcoma remains an urgent issue to be solved in clinical practice.

Author's Contribution

YSM, ZYJ, and DF designed and supervised research. All authors interpreted the data and contributed to the final version of the manuscript.

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Availability of Supporting Data

The datasets supporting the conclusions of this article are included within the article.

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