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REVIEW ARTICLE

Palliative treatments for advanced osteosarcoma

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Summary

Advances in diagnostic imaging, interventional radiology, chemotherapy and surgery greatly improved the outcome of patients with osteosarcoma, and made limb salvage possible without compromising survival. In these patients, the prognosis is influenced by the site and resectability of the tumor, prior malignancy, and histological response to preoperative chemotherapy. Unfortunately, the progress has not been as significant in the treatment of advanced osteosarcoma, namely metastatic, recurrent and unresectable tumor. Yet, although advanced and forecasting a dismal prognosis, advanced osteosarcoma is not necessarily untreatable. Aggressive local and medical treatments, including surgical removal of primary and/or metastatic disease are currently available; however, yet, most treatments aim at palliation. Palliative local treatments including isolated limb perfusion, radiation therapy, embolization, chemoembolization, thermal ablation and cryoablation, all have an important role for these patients. The aim of palliative treatments is to achieve a mild response by offering the least discomfort to the patient with the minimum possible complications, and possibly increase of survival.

Key words: advanced osteosarcoma, palliative treatment

Introduction

Osteosarcoma is the most common primary malignant bone tumor in childhood and adolescence accounting for 0.2% of all malignant tumors [1,2]. Before the 1970s, amputation was the standard treatment for osteosarcoma; however, 80% of patients developed metastases, most commonly to the lungs within 6 months of diagnosis, and more than 80% developed local or distant recurrence within 2 years from diagnosis [3,4]. Over the past 40 years, advances in diagnostic imaging, interventional radiology, chemotherapy and surgery greatly improved the outcome of patients with osteosarcoma, and made limb salvage possible without compromising survival [1,5-7]. Currently, in patients with localized, nonmetastatic osteosarcoma of the extremities, the 3- to 5-year survival ranges from 60 to 80% [1,5-7]. In these patients, the prognosis is influenced by: (1) the site and resectability of the tumor (the risk of progression and death are greater in tumors of the axial skeleton than in those of the extremities) [8-10]; (2) prior malignancy (patients with osteosarcoma as a second malignant neoplasm, except radiation-induced osteosarcoma share the same prognosis as that of newly diagnosed patients if they are treated similarly) [11]; and (3) histological response to preoperative chemotherapy. Response to chemotherapy is the best predictor of long-term survival among patients with resectable tumors; patients with greater than 95% tumor necrosis after induction chemotherapy have a better prognosis than those with lesser necrosis [12,13].

Unfortunately, advances have not been as significant in the treatment of advanced osteosarcoma, namely metastatic, recurrent and unresectable tumor [14-17]. In the past, the survival of patients with metastatic or unresectable osteosarcoma was less than 20% [13,18]. At present, the 3- to 5-year survival of these patients has been up to 50% [19-22]. However, metastatic, recurrent or unresectable osteosarcoma, although advanced and forecasting a dismal prognosis, is not necessarily

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untreatable. Aggressive local and medical treatments, including surgical removal of the primary and/or metastatic disease are currently available [18]; yet, most treatments aim at palliation [23].

Definition of advanced osteosarcoma

Advanced osteosarcoma has two distinct clinical forms: (1) metastatic advanced in various organs; and (2) locally advanced, either primary or recurrent, and unresectable. Metastatic advanced osteosarcoma is usually regarded as an incurable and fatal condition that requires only palliation. The tumor tends to be chemoresistant and the prognosis is poor [23,24]. Locally advanced osteosarcoma usually involves all the compartments of the limb, or a major adjacent structure such as the neurovascular bundle, pelvic organs, chest wall, or vertebra [23]. Unresectable can be large tumors involving challenging sites such as the pelvis, the sacrum and spine, and tumors in patients who are poor surgical candidates or refuse definitive surgery [7,25,26]. Locally advanced sarcomas tend to be very symptomatic including severe pain, sepsis, tumor fungation, hemorrhage, thrombosis, pathological fractures, severe functional impairment and poor quality of life. These tumors are not amenable to limited locoregional intervention such as standard limb salvage or amputation, but necessitate a major amputative surgical procedure for a potential cure, and, even then, metastases are common and the prognosis is poor [23,24].

Metastatic advanced osteosarcoma

Osteosarcoma may metastasize within the same extremity, or systemically to other organs. Systemic metastases have a predilection for the lungs, followed by the bones, liver and brain. Regional lymph node metastases are rare [1]. The prognosis of patients with advanced metastatic osteosarcoma is poor with a 3- to 5-year survival ranging from 10 to 50% [19-22]. Numerous drug combinations have been assessed for metastatic osteosarcoma. Combination of cisplatin, doxorubicin, methotrexate and ifosfamide remains the gold standard for first-line chemotherapy for metastatic primary osteosarcoma [19,23]. However, reports regarding second-line chemotherapy for patients with metastatic advanced osteosarcoma are conflicting, and meaningful options for second-line chemotherapy are limited [14,16,26-28]. Second-line chemotherapy includes drugs not used in the first-line treatment, or previously used drugs in higher doses [28]. If there has been a long disease-free interval, it is common practice to prescribe the same drugs that were used for first-line induction and postoperative chemotherapy, provided there was not any chemotherapy-induced toxicity, and the bone marrow reserves are adequate [23]. High-dose methotrexate plus folinic acid is commonly used, however it is associated with substantial morbidity. Ifosfamide may be given as a single-agent or in combination with etoposide plus mesna uroprotection, however the response rate is low and of short duration [29,30]. In a study, the likelihood of response was 30% among previously untreated patients but only 10% among those who had recurrent or refractory disease after first-line chemotherapy [29]. Gemcitabine was shown to be promising. In a small series of 7 patients who failed to respond to doxorubicin and ifosfamide-based chemotherapy, gemcitabine achieved prolonged disease stabilization in 5 of them [31]. It is also accepted as ethical to enroll patients with metastatic advanced osteosarcoma into trials using experimental agents or drug combinations such as modulators of multidrug resistance proteins or genes [23,31].

Patients with metastatic advanced osteosarcoma confined to the lungs should be assessed for surgical resection of the lung metastases, with or without second-line chemotherapy [32-34]. The ability to achieve complete resection of metastatic disease is the most important prognostic factor at the first relapse, with a 3- to 5-year survival of 20-40% following complete resection of lung deposits [35]. Factors that suggest a better outcome include 4 or fewer lung nodules, unilateral lung involvement, and long metastases-free interval from the primary tumor resection [36]. Patients with bone metastases fare worse than those with lung metastases, and survival also appears to inversely correlated with the number of bone metastases and the metastases-free interval [14,16,21,37,38]. Brain metastases of osteosarcoma are rare, usually solitary, follow lung and bone metastases, and can arise long after resection of the primary tumor [39-41]. Resection has been reported, but there is little clinical benefit [41].

Locally advanced osteosarcoma

Locally advanced osteosarcoma may be primary or recurrent, and unresectable. The incidence of primary or recurrent unresectable tumors is 2.3%; unresectable are more commonly high-grade osteosarcomas of the pelvis [42]. Local recurrence will develop in 2-3% of patients with osteosarcoma after amputation and 5-7% after limb salvage [22,43]. The incidence of local recurrence is related to the achieved surgical margins and the response to induction chemotherapy [14,16,38]. Local recurrence is a very ominous event, as it is usu-

ally accompanied or followed by metastatic spread that significantly deteriorates the prognosis [43]. The 5-year survival of the patients with locally advanced osteosarcoma ranges from 23 to 29%, and depends on the occurrence and number of metastases at the time of recurrence, and the recurrence-free interval [14,16,38].

Local control of the primary or advanced osteosarcoma is absolutely critical concerning survival, both in the absence or presence of systemic metastases. Amputations performed for the first local recurrence do not appear to provide significant survival benefit [44]. However, palliative major amputation of the involved limb including forequarter amputation and standard or extended hemipelvectomy should be considered to improve the outcome of patients with locally advanced recurrent osteosarcoma [14,45,46]. The indications for palliative major amputations include: (1) involvement of a proximal limb or a major joint, accompanied by intractable pain, sepsis, tumor fungation, hemorrhage, vascular thrombosis, pathologic fractures, radiation-induced necrosis; and/or (2) a limb with severe functional impairment [45]. The presence of metastases is not in itself a contraindication for palliative major amputation.[23,45]. The success of palliative major amputation can be assessed by the improvement in performance status and local control of the clinical symptoms, reduction of tumor volume, extent of rehabilitation, and lack of complications [23,46]. However, palliative major amputation is associated with a perioperative mortality and morbidity rates of 1-7% [45,46]. Adding complications to severely ill and debilitated from cancer patients seems unwarranted, especially if without any obvious improvement in life expectancy.

Locally advanced unresectable osteosarcoma is usually an incurable condition [14,16]. Although patients with unresectable osteosarcomas are generally excluded from large clinical trials [14,16,47], the role of second-line chemotherapy for metastatic advanced osteosarcoma is important [15,30,38]. Moreover, palliative major amputation is usually not feasible for patients with locally advanced unresectable osteosarcoma. In this setting, the role of conservative local treatments, including isolated limb perfusion, radiation therapy, embolization, chemoembolization, thermal ablation and cryotherapy is important. These treatments are mostly aimed at palliation. The aim of palliative treatment is to achieve the best possible response by offering the least discomfort to the patient with the minimum possible medical risks.

Isolated limb perfusion

Isolated limb perfusion with tumor necrosis factor-alpha (TNFa) plus melphalan is often considered as a treatment option for patients with advanced primary or recurrent soft tissue sarcomas [40,48]. It may also induce significant tumor response and allow limb salvage as an alternative to palliative major amputation for locally recurrent and advanced bone sarcomas, such as osteosarcoma, without systemic spread [23,40].

Radiation therapy

Radiation therapy has a limited role in the management of osteosarcoma because of the relative radioresistance and the need for a large dose of radiation (up to 70 Gy) to achieve a clinical response [19,23,49]. However, it could be used as a palliative treatment combined with chemotherapy for unresectable osteosarcoma [50,51]. Chemotherapeutic agents including ifosfamide, cisplatin, high-dose methotrexate or gemcitabine combine systemic osteosarcoma control and increase the effectiveness of radiation therapy [51,52]. Whole-lung radiation therapy seems to have some effect against osteosarcoma metastatic to the lung, but does not give any advantage when added to conventional chemotherapy [53]. Radiation therapy can be used as an effective palliative treatment for multiple or unresectable painful bone metastases [50]. Samarium-153 ethylene diamine tetramethylene phosphonate (153Sm-EDTMP) is a bone-seeking radiopharmaceutical designed to selectively deliver radiation to osteoblastic bone metastases, [49] and can be used for palliation of painful bone metastases and micrometastatic disease [49,54,55]. Because of the heterogeneity of the isotope deposition in bone-forming osteosarcoma tumors, 153Sm-EDTMP seems to be most effective when used in combination with external-beam radiation and radiosensitizing chemotherapy, usually gemcitabine [49,52]. However, the risk of radiation-induced complications is high and prospective studies are necessary to evaluate the role of radiation therapy for inoperable osteosarcomas. Proton therapy plus heavy ion carbon therapy seems to offer a new promising therapeutic option in patients with unresectable osteosarcoma [47,56,57].

Embolization

In surgically complex cases, biplanar angiography accurately determines the vascular mapping and the hemodynamic status of the tumor, along with the vascular displacement that occurs in the anatomic region with a large soft tissue component [1,58]. In addition, angiography can assist in the surgical planning and in estimating the tumor response to induction chemotherapy [59];

complete disappearance of tumor vasculature after preoperative chemotherapy correlates with good response to treatment [59,60]. Following angiography, transcatheter arterial embolization selectively and superselectively occludes the pathological tumor vessels and obstructs the arterial flow to the tumor, resulting in pain reduction, tumor necrosis and reduction of tumor size [61-63]. Reduction of pain is considered to be related to the decompression of the periosteum with or without reduction of the tumor volume [64,65] and suppression of the nociceptor activation by reducing the production of algesic chemicals [64,65]. Pain relief occurs from 12 hours to several days after embolization, usually within 1 week [65]. Alternative treatment methods, such as chemotherapy and radiotherapy, are not able to provide a response in such a short period of time. The duration of pain relief is related to the completeness of the occlusion, the availability of collateral circulation, and use of the appropriate embolic agent [65]. Potential ischemic complications of embolization depend on the arterial territory of the anatomic region being embolized and the embolic agent used [66]. The usual contraindications to intravascular procedures apply, with attention to the presence of coagulopathy, thrombocytopenia or anemia [64]. Considerations for choosing an embolic agent are speed and reliability of delivery, duration of occlusive effect, preservation of normal tissue, and operator's experience. Currently available embolic agents include gelfoam, polyvinyl alcohol (PVA) particles, liquid (absolute alcohol), coils, tissue adhesives, ethanol, microfibrillar collagen and autologous blood clot [63,64,67]. For multiple lesions, distal location, or lesions supplied by numerous feeding vessels, particles can be used [64]. Embosphere particles (Biosphere Medical, Rockland, Maryland) are clear acrylic copolymer (trisacryl) microspheres that were previously used as a microcarrier for cell culture. Their advantages include that they are compressible, allowing easy passage through a microcatheter with a luminal diameter smaller than that of the spheres, and are more uniform in size than PVA, and the particle size does not change in liquids [64]. However, particles may be difficult to deliver through small microcatheters or tortuous anatomy. In addition, the particles themselves are not radiopaque, making exact documentation via radiography of their site of occlusion impossible [58,68]. Gelatin sponge is a dissolvable sponge-like material that comes in small flat rectangular blocks that can be cut with scissors into elongated rectangles and rolled into pledgets, which can then be injected by catheters or microcatheters. It is considered a temporary occluding agent, with the occluded vessel recannalizing in 2-4 weeks [69]. Once stasis or near stasis has been achieved with Gelfoam, and many interventional radiologists use coil embolization for final and complete vessel occlusion [64]. Stainless steel fibered and platinum coils are usually reserved for single and large vessel occlusion. Prior to particulate or liquid embolization, coils may be placed to protect the distal vasculature from these agents [64]. Liquid embolic agents including absolute alcohol, N-2-butyl cyanoacrylate (NBCA), Ethibloc (Ethicon, Norderstedt, Germany), sodium tetradecyl sulfate and Onyx (Microtherapeutics, Irvine, California) offer the advantages of low viscosity for easy injection through small catheters or catheters with many bends through tortuous blood vessels [63,67]. NBCA or "liquid glue" is a liquid embolic agent that spreads according to its polymerization time and the vascular flow. Although NBCA can pass through bent catheters navigating tortuous blood vessels, it does not permeate all the way to the capillary level, and therefore does not cause tissue death. Another distinct advantage of NBCA with lipiodol compared with particles is its dense radiopacity. In addition, NBCA can be used in patients with clotting pathologies [58,63,67,68].

In oncology, embolization has been reported for facilitating surgery through hemorrhage control, for tumor size reduction before surgery, for the treatment of life-threatening situations, and for palliation of pain and bleeding [63,66,70]. Subsequently, it was used for the control of tumor growth most commonly for bone metastases from various carcinomas, benign bone tumors such as giant cell tumors and aneurysmal bone cysts, and rarely for palliative treatment of bone sarcomas. Embolization of solid tumors is not a standard management. Indications may include: (1) difficult surgery of a highly vascularized or very fragile mass; (2) life-threatening bleeding or chance of bleeding; (3) failure of other treatments to control the symptoms or to stop the progression of the disease; and (4) the site of the tumor, general condition, or coagulation tests make embolization possible [66]. However, palliative embolization may be a therapeutic alternative or a complementary treatment for local control of locally advanced unresectable osteosarcoma, osteosarcoma with too many bone metastases to easily resect, and pelvic or axial osteosarcoma with lung metastases (Figure 1) [7,66]. Osteosarcomas are hypervascular tumors due to extensive neovascularization, and thus enhance with contrast medium in angiography [60,71]. This enhancement, referred to as "tumor blush," usually reflects viable tumor (Figure 2). Osteosarcomas' pathological vessels' blush can be reduced by more than 90% with embolization [60,71].

Chemoembolization

Chemoembolization consists of direct administra-

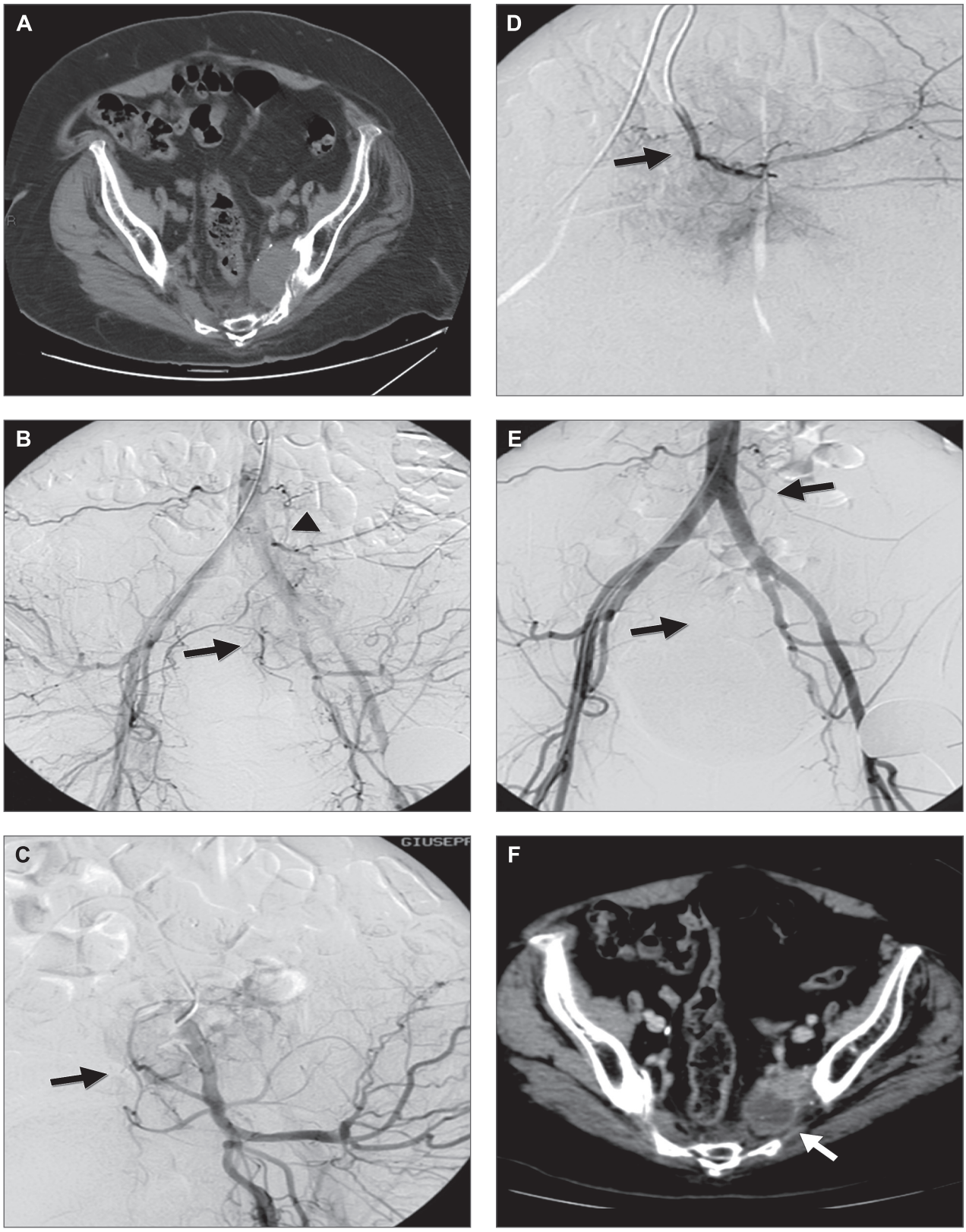

Figure 1. (A): Axial computed tomography scan of the pelvis of a 57-year-old female patient with a locally advanced, recurrent osteosarcoma of the sacrum and pelvis. The patient had second-line chemotherapy and palliative embolization with NBCA because of extreme pain. **(B):** Panoramic aortography shows the pathological feeding vessels originating from two left lateral sacral arteries (arrows) and the left L5 lumbar artery (arrowhead). Superselective catheterization of the **(C)** lateral sacral arteries (arrow) and the **(D)** L5 lumbar artery (arrow). **(E):** Post-embolization aortography shows complete occlusion of the pathological tumor vessels with NBCA (arrows). **(F):** Post-embolization computed tomography scan of the pelvis shows tumor necrosis (arrow). The patient experienced pain relief within 3 days post-embolization. She developed lung metastases and died 3 years later.

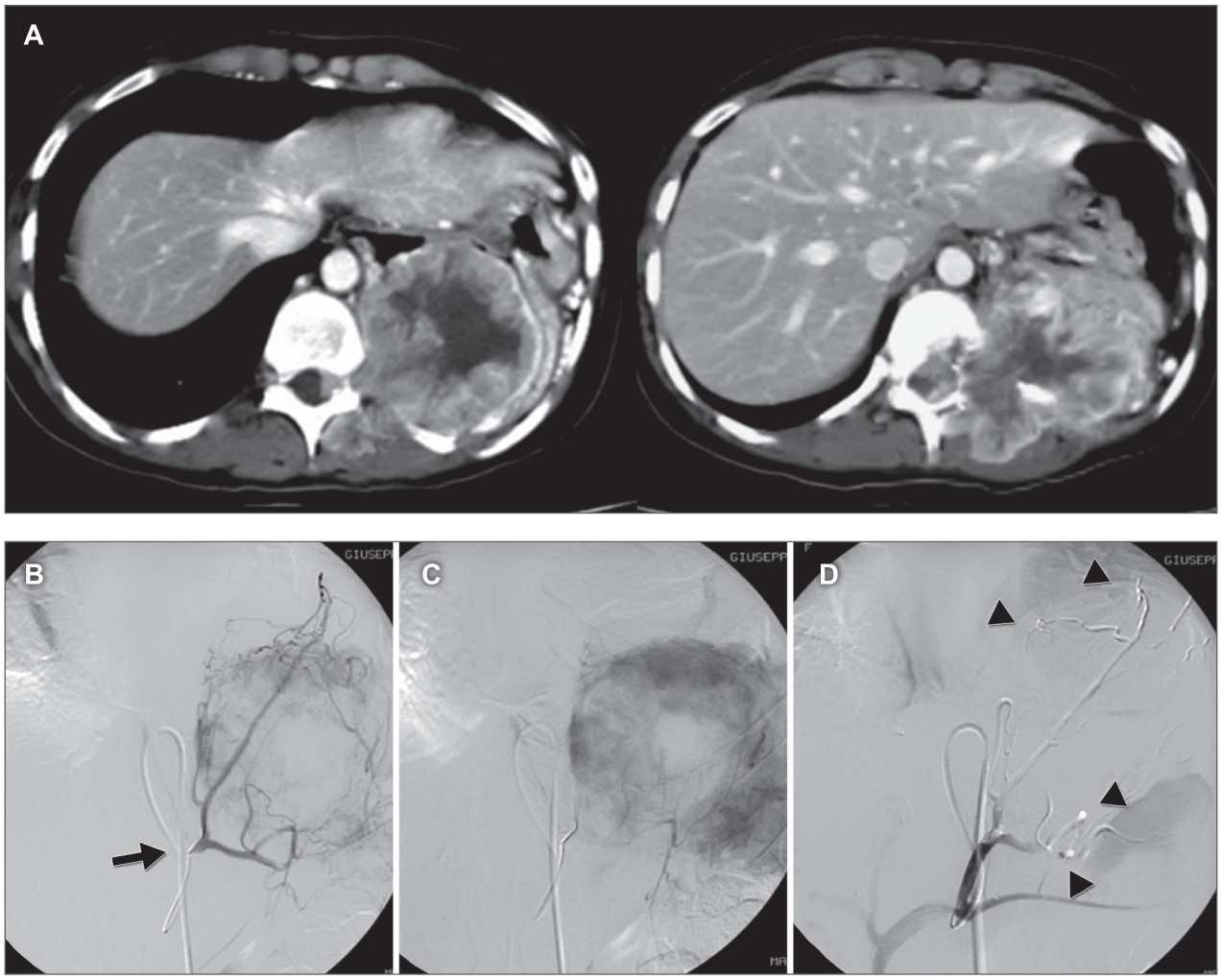

Figure 2. (A): Axial computed tomography scans of the chest and abdomen of a 19-year-old female patient with a locally advanced, unresectable osteosarcoma originating from the T12 vertebra. The patient had first-line chemotherapy and palliative embolization with NBCA because of extreme pain. **(B):** Digital subtraction angiography shows selective and superselective catheterization of the left diaphragmatic artery (arrow). **(C):** Late-phase angiography shows the pathological tumor blush. **(D):** Post-embolization angiography shows complete occlusion of the pathological tumor vessels with NBCA (arrowheads). The patient experienced pain relief within the first week post-embolization, however, she died from disease 3 months later.

tion of chemotherapeutic agents into the tumor through selective catheterization of the tumor feeding vessels, followed by conventional embolization with an embolic agent [60,66]. Intra-arterial chemotherapeutic increases the chemotherapy drug concentration and the dwell time in the tumor, thereby resulting in improved efficacy and tumor response compared to systemic intravenous chemotherapy in patients with osteosarcomas [60]. The local blood drug concentration obtained from intra-arterial chemotherapy is up to 5-6-fold higher than that obtained with intravenous infusion of the same drug dosage [72,73]. In addition, the drug can exert its cytotoxic effect in its molecular prototype form on the tumor without being inactivated by the liver, thus raising the antitumor efficacy of the drug. As part of the drug may reach the whole body through blood circulation, it is also helpful in controlling metastatic microfoci and subclinical foci by acting as systemic chemotherapeutic agent [74]. Subsequent embolization occludes the blood supply resulting in ischemic necrosis of the tumor, which acts synergistically with the cytotoxic effect of intra-arterial chemotherapy [60]. The completeness of terminal tumor vessel embolization is also positively correlated with the degree of tumor necrosis [75,76]. When the same drug is delivered by arterial balloon occlusion infusion, the tissue drug uptake increased 20-30 times compared with intravenous administration [77]. Chemoembolization using microencapsulation of a chemotherapeutic agent has also been reported [78,79].

Chemoembolization has been reported safe and effective for neoadjuvant chemotherapy for osteosarcoma, especially before limb-salvage surgery, inducing

tumor necrosis without major complications; however, the tumors of the patients in the related series were not advanced osteosarcomas [60,62,66,71,80]. Krauel et al. [66] treated a 12-year-old patient with locally advanced undifferentiated skull osteosarcoma after systemic chemotherapy with methotrexate, doxorubicin, ifosfamide and cisplatin, and tumor and skull resection, with chemoembolization for palliation. Intra-arterial chemotherapy given was topotecan; embolization was done with 300 μm Embospheres. Tumor devascularization was accomplished; the patient survived for 2 years after chemoembolization [66]. Chu et al. [71] used preoperative intra-arterial chemotherapy and embolization in 32 patients with primary osteosarcoma of the extremities. Angiography showed that the tumors were hypervascular. A 3-drug intra-arterial chemotherapy regimen was given including methotrexate (1-2 g), epidoxorubicin (30-50 mg), and cisplatin (60-100 mg); the embolic agents used were doxorubicin gelatin microspheres, anhydrous alcohol, common bletilla tuber, or gelatin sponge particles. Limb salvage was performed 10-14 days after chemoembolization. Large areas of necrosis were found histologically in 85.5% of the tumors. Doxorubicin microspheres, anhydrous alcohol, and common bletilla tuber had better clinical effects than gelatin sponge particles. Major complications were not observed. All patients received postoperative multidrug combination chemotherapy consisting of high-dose methotrexate (8 g/m^2) with folinic acid rescue, epidoxorubicin (50-80 mg/m^2), and cisplatin (100 mg/m^2) over a period of 4-6 weeks for about 1 year. Patients' overall survival after chemoembolization at 1, 2, and 5 years was 95.5%, 72%, and 42% respectively [71]. In a more recent similar study, Zhang et al. [60] used preoperative intra-arterial chemotherapy and embolization in 47 patients with primary osteosarcoma of the extremities. Angiography showed that the tumors were hypervascular. Intra-arterial chemotherapy given was pirarubicin 30-50 mg/m^2, and cisplatin 40-80 mg/m^2; the embolic agent used was gelatin sponge particles. Chemoembolization successfully resulted in substantial reduction or complete disappearance of the tumor blush in all patients, without major complications. Curettage or wide resection and reconstruction was performed 3-7 days after chemoembolization in all patients; transfusion requirements during surgery were reduced, and formation of a false capsule around the tumor facilitating surgical excision of the tumors was observed. Tumor necrosis by chemoembolization ranged from 70.2 to 94.2% (mean 82.9%). In 24 cases, angiography performed for a second intra-arterial perfusion chemotherapy within 2-5 weeks after the surgical operation did not show significant tumor blush. Complications included some exacerbation of local tumor site pain during and immediately after embolization that was treated with opioids and alleviated within 24-36 h after the intervention, local skin redness, swelling, burning sensation and a blister-like change in the skin that was relieved 12-36 h after symptomatic treatment. Postembolization syndrome was mild and subsided completely within 3-5 days after embolization [60].

Thermal ablation

Thermal ablation refers to the local destruction of a tumor by local application of either chemical agents such as ethanol and acetic acid, or some form of energy such as radiofrequency, laser, microwave, ultrasound, or cold. It is a palliative treatment to control tumors locally in patients who cannot tolerate a major surgical procedure because of multiple comorbidities or multiple metastatic lesions [81]. There is little published data on the use of thermal ablation for the treatment of lung and bone osteosarcoma lesions [15,82-85]. Patients are offered local ablation treatments for painful metastases when they experience moderate or severe pain, which is limited to one or two sites. Patients with lower pain scores or numerous painful lesions are not treated with these techniques because this type of pain is better treated with a systemic approach rather than local. Moreover, tumors close to neurovascular bundles or the skin cannot be adequately ablated because of the risk of nerve and vascular injury, or wound breakdown [86]. The most widely favored techniques for local ablation of musculoskeletal tumors are radiofrequency ablation and cryoablation [82]. Both have shown effective and durable results in the treatment of bone and soft-tissue metastases, with minor complications. Additionally, these treatments are repeatable, as needed in cases of recurrent or metastatic bone and soft-tissue tumors [82,84].

Radiofrequency energy poorly penetrates sclerotic bone. Therefore, it can be used for lung metastases, but not for bone metastases from osteosarcoma [83,84,87-89]. Radiofrequency ablation is best used in patients with a limited number of small (< 3 cm) slow-growing metastases. The best results in terms of complete tumor ablation are achieved in patients with small lesions no larger than 3 cm in diameter, and slow-growing metastases. Although preliminary survival data are encouraging, definitive evidence supporting the use of radiofrequency to prolong survival is still lacking [90]. Up to 80% of the patients experience recurrences of the lung metastases; more than 80% of these patients can be retreated with lung radiofrequency ablation. Although common in nearly all patients, pneumothoraces rarely (<20%) require treatment with needle aspiration or chest tube

placement. Postprocedural small pleural effusions after the treatment of peripheral lesions are self-limited [84].

Cryoablation uses repetitive freezing and thawing of tissue to produce necrosis [91]. It has been reported as safe and effective treatment for the palliation of painful bone metastases in which standard therapies are contraindicated [82,87,90]. In contrast to radiofrequency ablation, cryoablation may be used in osteoblastic bone metastases; using bone-biopsy techniques or a bone drill to provide a path to the tumor, ice is able to penetrate deeply into bones [86-88]. However, the target lesion must be accessible percutaneously and be sufficiently distant from the spinal cord, the Adamkiewicz artery, major motor nerves, the brain, the bowel and the bladder [82].

Conclusion

Metastatic, recurrent or unresectable osteosarcoma, although advanced and forecasting a dismal prognosis, is not necessarily untreatable. Palliative local treatments including isolated limb perfusion, radiation therapy, embolization, chemoembolization, thermal ablation and cryoablation have an important palliative role in these patients. The aim of palliative treatments is to achieve a mild response by offering the least discomfort to the patient with the minimum possible complications, and possibly to increase survival. Although current experience is limited, intra-arterial chemotherapy and embolization are promising as an adjunct to surgery, or for palliation when other treatments have failed and for patients with advanced tumors for temporary improvement of their quality of life.

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