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ORIGINAL ARTICLE

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Results of surgery and radio-hyperthermo-chemotherapy for patients with soft-tissue sarcoma

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Abstract
Background. Between 1990 and 1999, we performed radio-hyperthermo-chemotherapy (RHC) in 44 patients with high-grade soft-tissue sarcomas of the limbs.
Methods. Radiotherapy involved the delivery of radiation at a dose of 2 Gy once daily on 16 days, to give a total dose of 32 Gy. Hyperthermia was conducted once a week, with a total of five sessions. Chemotherapy was performed by implanting a reservoir and administering cisplatin (3 mg/kg) three times, and pinorubin (an adriamycin derivative; 1 mg/kg) twice by intra-arterial infusion, at weekly intervals. These drugs were administered alternately during hyperthermia sessions.
Results. Tumor shrinkage was observed in 98% (43/44) of the patients. Of the 36 patients with M0 tumors, 30 were disease-free at final follow-up, 2 had no evidence of disease, 1 was alive with disease, and 3 had died of the disease. Amputation was required only in the first patient, and the affected limb was preserved in the other 43 patients. The surgical margin was wide in 9 patients and marginal in 29 patients, and intralesional excision was performed in 5 patients. There was recurrence in only 1 of the 44 patients.
Conclusion. RHC is currently the most potent and relatively safe treatment method for high-grade soft-tissue sarcomas that is available clinically.

Key words Soft-tissue sarcoma · Hyperthermia · Chemotherapy · Radiotherapy

Introduction

Soft-tissue sarcomas are relatively rare malignant tumors, accounting for about 1% of malignancies in adults. High-grade soft-tissue sarcomas have a poor prognosis, with a survival rate of approximately 50%.[1,2] Surgical resection is often performed initially, because chemotherapy and radiotherapy generally have little or no effect. Prognosis is poor if the tumor is not completely resected, and the affected limb often cannot be preserved because of the site and size of the lesion. Various adjuvant treatments have been tried in an effort to improve local disease control, reduce functional loss after resection, and increase the survival rate.[3–6] One method that has attracted attention in recent years is hyperthermia. The results of many preclinical studies (in vivo and in vitro) have indicated that hyperthermia is effective against sarcoma.[7–9] Other authors have reported both basic research and the clinical application of hyperthermia combined with chemotherapy or radiotherapy to augment the therapeutic effect.[10–12]

Here we report the results of a study in 44 patients with high-grade soft-tissue sarcomas, in whom marked improvement of local tumor control and in 5-year survival rate compared with previous findings was achieved using radio-hyperthermo-chemotherapy (RHC).

Subjects and methods

We studied 44 patients with high-grade soft-tissue sarcomas who were treated at the Department of Orthopedic Surgery of Nagoya City University Hospital between 1990 and 1999. The histological diagnosis was malignant fibrous histiocytoma (MFH) in 21 patients, liposarcoma (myxoid type, 4; round-cell type, 2; dedifferentiated type, 1) in 7 patients, synovial sarcoma in 6 patients, leiomyosarcoma in 4 patients, alveolar soft-part sarcoma in 2 patients, small round-cell sarcoma in 2 patients, epithelioid sarcoma in 1 patient, and extraosseous osteosarcoma in 1 patient. Of the 44 patients studied, 5 (3 with MFH, 1 with a primitive neuroectodermal tumor [PNET], and 1 with epithelioid sarcoma) had recurrent disease; the remaining 39 patients had primary tumors. Three patients (all with MFH) had M1 disease with pulmonary metastasis. All of the patients were informed

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about the nature of the treatment and their consent was obtained.

Infants and young children, as well as frail elderly patients, are not selected for this protocol. Infants are unable to endure the therapeutic heating for 1 h and are not able to take the insertion of a catheter in the artery. Frail elderly patients were excluded from this treatment because of pre-existing conditions. Low-grade sarcomas (such as dermatofibrosarcoma protruberans and well differentiated liposarcoma) and tumors in the pelvic and dorsal regions were also excluded from this treatment. Twenty-eight patients who did not meet the requirements for RHC were treated with surgery alone.

Before RHC, angiography was performed, after which an arterial catheter was inserted and a reservoir was implanted. If the tumor was in the lower extremity, the catheter was inserted via the femoral artery on the affected side and the contralateral side, and the reservoir was implanted in the inguinal region or in the lower abdomen. If the upper extremity was affected, the catheter was inserted into the brachial artery and the reservoir was implanted in the precordial region. Chemotherapy was given by intra-arterial infusion, using the reservoir, and consisted of cisplatin (3 mg/kg) with the first, third, and fifth hyperthermia sessions and pinorubin (an adriamycin derivative; 1 mg/kg) with the second and fourth hyperthermia sessions. Two weeks after five sessions of RHC had been performed, the patients received systemic chemotherapy, (primarily with ifosfamide), followed by surgery. The chemotherapy agents were administered continuously via the reservoir from the start of hyperthermia until approximately 1.5 h after hyperthermia was completed. Radiotherapy involved the delivery of radiation, at a dose of 2 Gy, on 5 days per week, with 16 sessions, giving a total dose of 32 Gy. Irradiation was performed immediately before hyperthermia and chemotherapy. Hyperthermia was done using an 8-MHz radiofrequency capacitive heating system (Thermotron RF-8; Yamamoto Vinyter, Osaka, Japan). The temperature was measured by inserting a hyperthermia needle into the tumor and inserting a thermocouple thermometer (0.64-mm f) into the space. The objective of the treatment was to achieve a temperature of 42.5°C or more for 60 min (Fig. 1).

The treatment protocol comprised a total of five sessions, consisting of four sessions of RHC followed by one session of hyperthermia and chemotherapy. However, patients also underwent several extra sessions of hyperthermia alone if the optimum temperature was not obtained during the scheduled hyperthermia sessions. Surgical resection was carried out between 2 and 4 weeks after systemic chemotherapy. Amputation was performed only in the first patient. It was possible to preserve the affected limb in all the other patients.

In regard to using the general rules of the Japan Society of Clinical Oncology, because the size of the tumor is not reduced easily when treated by therapeutic heating, the criterion of effect was originally established by the Hyperthermia Academy. However, this criterion cannot be applied to this treatment because the hyperthermia, radiotherapy, and chemotherapy were done at same time.

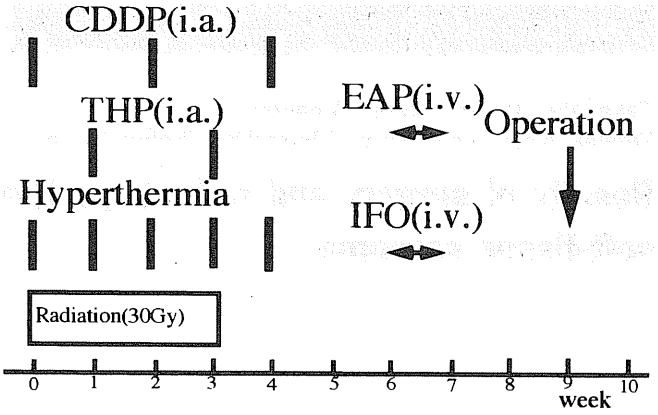

Fig. 1. Radio-hyperthermo-chemotherapy. *CDDP(i.a)*, Cisplatin (intra-arterial infusion); *THP(i.a.)*, pirarubicin (intra-arterial infusion); *hyperthermia*, 42.5° 1 h; *radiation*, 2 Gy/day; *EAP*, etoposide (VP16), adriamycin, CDDP (intravenous infusion); *IFO*, ifosfamide (intra-arterial infusion)

We relied on magnetic resonance imaging (MRI) and dynamic MRI findings to determine the efficacy of RHC. Our surgical goal was to minimize invasion and limit the extent of surgical resection. Dynamic MRI, computed tomography (CT), and angiography were performed before surgery to assess the effects of preoperative therapy, and the extent of surgical resection was decided on the basis of the findings. The surgical margin ranged from 1 cm to marginal in most of the patients.[13] In 2 patients, marginal resection had been performed by another surgeon and only the surgical scar tissue was resected after RHC at our department (second-look operation). Some patients required skin grafts to cover defects.

The efficacy of RHC therapy was assessed from the extent of histological necrosis on the largest cut section of the resected tumor.

The patients were followed up for a mean of 5 years after surgery (range, 1.4 to 10.3 years).

Results

The mean age of the patients was 49.1 years (range, 13 to 74 years). The primary tumor site was the forearm in 5 patients, the upper arm in 3 patients, the shoulder in 1 patient, the gluteal region in 1 patient, the thigh in 24 patients, and the leg in 10 patients. RHC could not be completed in 3 patients (2 patients with MFH and 1 patient with extraosseous osteosarcoma). Failure to complete therapy was due to serious side effects of chemotherapy. Of the 3 patients in whom RHC could not be completed, 1 patient with MFH died of another disease and the other 2 patients died of pulmonary metastasis. The side effects of chemotherapy in almost all of the patients included a decreased white blood cell count and a decreased platelet count. One patient died of septicemia. However, in the other patients, these side effects were successfully controlled with granulocyte colony-stimulating factor and platelet transfusions. In

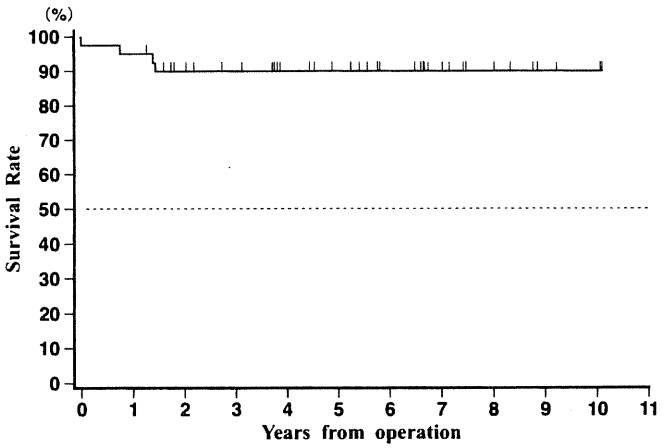

Fig. 2. Overall survival rate (Kaplan-Meier estimates) after surgical treatment of soft-tissue sarcoma in 41 patients (3 patients in whom radio-hyperthermo-chemotherapy (RHC) could not be completed were excluded)

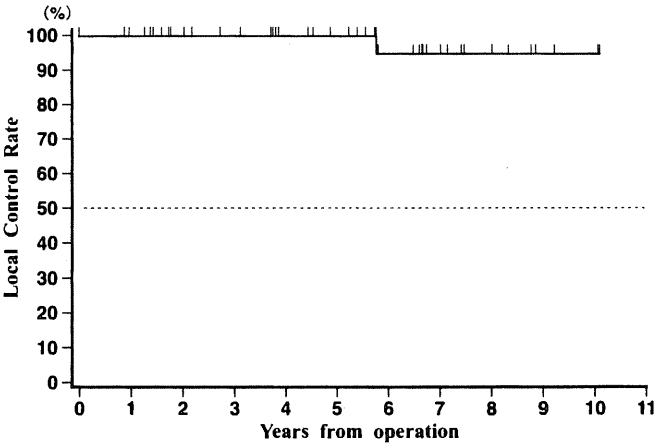

Fig. 3. Local control in 41 patients treated by RHC was 97.7% at 5 years

approximately two-thirds of the patients, the fifth treatment session had to be postponed. Second-degree burns were caused by hyperthermia in 3 patients. Dehiscence of the skin wound and delayed healing occurred in one-third of the patients, while fat necrosis was seen in 3 patients; however, none required amputation. Fat necrosis could not be distinguished from recurrence at the early stage, but differentiation was possible when dynamic MRI was employed.

The antitumor effect was evaluated mainly with dynamic MRI. There was a decrease of the time-intensity curve in all of the patients in whom RHC was completed. Shrinkage of the tumor was evident in 43 patients (98%), and overall survival was good (Fig. 2). At final follow up, of the 18 patients with M0 MFH, 16 remained disease-free. Two of the 3 patients with M1 tumors died of their disease, and 1 remained alive with disease. All 7 patients with liposarcoma were disease-free at final follow-up. Of the 6 patients with synovial sarcomas, 2 died of their disease, 1 had no evidence of disease, and 3 were disease-free. Of the 4 patients with leiomyosarcoma, 1 died of disease, 1 had no evidence of disease, and 3 were disease-free. Of the 36 patients with M0 tumors in whom RHC was completed, 30 were disease-free, 2 had no evidence of disease, 1 was alive with disease, and 3 had died of the disease. Of the 2 patients with alveolar soft-part sarcoma, 1 is alive with disease and the other is disease-free. Of the 5 patients with recurrent disease, 3 had no evidence of disease and 2 died of the disease (1 with PNET and 1 with epithelioid sarcoma). Two of the 3 patients with M1 tumors died of the disease and 1 remained alive with disease.

Actuarial local control is shown in Fig. 3. The surgical margin was wide in 9 patients (3 cm in 2 patients and 1 cm in 7 patients) and was marginal in 29 patients. Intralesional excision was performed in 5 patients (second-look operations in 2 patients), and 1 patient required amputation. In the 5 patients with intralesional excision, none relapsed. One of the 9 patients with a wide surgical margin had a recurrence. In this patient, the optimum temperature of 42.5°C or higher was never achieved, despite seven sessions of hyperthermia. In the patients with intralesional excision, this was done to preserve the femoral artery and vein, as well as the sciatic nerve. The second-look operations were performed in patients who had changed hospitals after another surgeon had excised the tumor with an inadequate margin. In these patients, the scar tissue was resected in a piecemeal fashion after RHC, and no residual tumor was found.

We examined differences in recurrence and survival related to tumor size, location, and histology. In the patient who experienced recurrence, the tumor was large (more than 10 cm in diameter) and extended from the medial aspect to the back of the left thigh. The histological therapeutic effects were as follows. Of the 13 patients with tumors 10 cm or more in diameter, 1 showed a complete response (100% necrosis) and 12 showed a remarkable effect (necrosis of two-thirds or more). Seven of the 21 patients with MFH showed a complete response; 3 of the 7 patients with liposarcoma showed a complete response; 1 of the 4 patients with leiomyosarcoma showed a complete response; and 1 of the 6 patients with synovial sarcoma showed a complete response. Six of the 21 patients with MFH were 10 cm or more in diameter, and 3 of them had M1 disease.

Discussion

Historical data show that local control of soft-tissue sarcomas can be achieved with wide excision in 40% of patients and with local excision in 10%,[14] but the prognosis is poor if curative resection is not possible. However, extensive resection necessitates the sacrifice of nerves, blood vessels, and important muscles, often resulting in severe functional impairment.[15–18] Good results have been reported with the use of radiotherapy before surgery to increase limb preservation and decrease local recurrence.[19–24] However, more effective forms of chemotherapy need to be developed,

because distant metastasis (mainly pulmonary) occurs in 40%–50% of patients with high-grade tumors.[25,26] The role of adjuvant chemotherapy is still unclear. Most studies present equivocal or negative results, and therefore the role of adjuvant chemotherapy in high-grade sarcomas remains under investigation. In the period 1965 to 1975, at Roswell Park Memorial Institute, 251 patients with localized soft-tissue sarcomas were treated with surgery alone. Of the patients with extremity sarcomas, 40% underwent amputation. The incidence of local recurrence at 5 years was 65% with local excision, 36% with wide excision, and 8% with amputation. The 5-year survival rate was 45% for lesions in all anatomic locations and 50% for sarcomas in the extremities.[27]

In 1985, Eilber et al.[28] reported limb preservation in 96% of patients and a local recurrence rate of 4% after radiotherapy combined with intra-arterial doxorubicin. Temple et al.[29] were able to reduce side effects without decreasing local tumor control by using a modification of Eilber's protocol.

Long-term studies have also investigated the usefulness of adjuvant chemotherapy, but many authors have reported negative results for high-grade soft-tissue sarcomas other than small round-cell tumors. Although hyperthermia with radiation and/or chemotherapy is an established method of treating cancer, there have not been many studies on the use of hyperthermia for soft-tissue sarcoma where the primary tumor is in a limb. Recently, Wiedemann et al.[30] reported an efficacy rate of 63% for metastatic sarcoma, using whole-body hyperthermia in combination with ifosfamide, carboplatin, and etoposide.

In a study of hyperthermia aimed at local control in 12 patients with soft-tissue sarcomas (3 with liposarcoma, 2 each with rhabdomyosarcoma, leiomyosarcoma, and neurofibroma, and 3 with other sarcomas), Storm et al.[31] reported a histological efficacy rate of 75% (9/12 patients) at a temperature of 45°C or higher, 50% (6/12 patients) at 50°C or higher, and 90% in patients who underwent hyperthermia at 45°C or higher for 10 days. Cancer cells are damaged by 42°C temperatures, while surrounding normal cells are not damaged by 42°C temperatures. We chose a temperature of 42.5°C as the optimal temperature for therapeutic heating so that we might reduce the damage to the surrounding skin, blood vessels, and nerves.

Studies of hyperthermia combined with radiotherapy, using cultured cells and tumors in laboratory animals, have yielded the following results: (1) The G1/S transition and the G2 + M phase of the cell cycle are highly sensitive to radiation, while late S phase is highly sensitive to heat. (2) Radiation has the most lethal effect on normooxic cells, and hyperthermia has the most lethal effect on hypoxic cells. (3) After irradiation, recovery from sublethal damage and potentially lethal damage to cells is inhibited by the combined use of hyperthermia.[32] However, Prosnitz et al.[33] found that, while preoperative thermoradiotherapy for high-grade soft-tissue sarcomas of the limbs was useful for local control, postoperative adjuvant chemotherapy was also required, because this preoperative therapy did not improve prognosis. Bistolfi et al.[34] reported that combined radiotherapy and hyperthermia was effective against synovial sarcoma, malignant fibrous histiocytoma, malignant schwannoma, and chondrosarcoma. Nakano et al.[35] found no correlation between the reduction of tumor size and the histological response after combined radiotherapy and hyperthermia. This was because the characteristic coagulative necrosis and edema produced by hyperthermia led to a delay in reduction of the tumor size.

Tsukiyama et al.[36] and Egawa et al.[37] recommend that the therapeutic effect of hyperthermia be assessed using CT.[36,37] They found a correlation between hypodense areas on CT scans and necrosis, and stated that hypodense areas, as well as absolute tumor size, should be evaluated. With the improvements in MRI in recent years, gadolinium-enhanced MRI and dynamic MRI are now established methods for evaluating treatment. We also assessed the outcome of treatment using dynamic MRI, time-intensity curves, and subtraction MRI, as well as conventional angiography and contrast-enhanced CT.

It is known that the combination of chemotherapy and hyperthermia increases the uptake of anticancer drugs by tumor cells and is also effective against drug-resistant cancer.[38] We have also confirmed that performing hyperthermia concurrently with chemotherapy increases the therapeutic effect. In other words, intra-arterial infusion of anticancer drugs during hyperthermia has proven to have the greatest therapeutic effect. Studies conducted to date have shown that hyperthermia enhances the effects of anticancer drugs such as cisplatin, adriamycin, ifosfamide, and 5-fluorouracil.[39]

The advantage of RHC used in the present study is that the implantation of a reservoir allows repeated intra-arterial infusion of anticancer drugs without greatly interfering with the patients daily life. In addition, a systemic therapeutic effect can be expected with intra-arterial chemotherapy given at the same doses as those used for intravenous systemic administration. The outcome was particularly good for MFH when the tumor was only M0, with 16 of our 18 patients with M0 MFH being disease-free and 2 patients being alive with disease. All 7 of our patients with liposarcoma were also disease-free. The survival rates for these groups are better than any others reported to date. However, the prognosis was poor for patients with obvious metastasis at initial presentation, and more effective treatment methods need to be developed for such patients. Good results were obtained in the 36 patients in our study who had M0 tumors, with 30 being disease-free, 2 having no evidence of disease, 1 being alive with disease, and 3 dying of their disease. We have stated above that the survival rates for our patients with MFH and liposarcoma were better than those in other reports. We relate these results to: fewer relapses, the intra-arterial injection of the anticancer agent also being very effective for micrometastasis, cancer cells that had spread in the vein near the tumor being killed by the RHC treatment, and individual immunoreactions to the treatment.

This outcome, plus the fact that preservation of the affected limb was possible in all but the first patient, indicates

that hyperthermia should be attempted in patients with high-grade soft-tissue sarcomas.

We did not do a another (wide) resection for tumors excised by inadequate resection, but RHC treatment and excision of scar tissue were performed. These patients have had no recurrence and no functional disturbance. We believe we can employ this second operation (combination therapy of marginal resection and excision of scar tissue after RHC) in the future. A possible future application of RHC would be to perform initial marginal resection of the tumor by excisional biopsy, followed by RHC. Then a second-look operation could be done to resect the scar tissue and to detect residual tumor cells, after which the patient could be followed up. This procedure would minimize functional defecits.

The side effects of RHC include burns, fat necrosis, and pain caused by hyperthermia; dermatitis and secondary malignant tumors caused by the radiotherapy; and a decreased white blood cell count, decreased platelet count, anemia, nausea, and vomiting caused by the anticancer drugs. The scheduled protocol could not be completed in 3 of our 44 patients. The use of steroids, and improvements in the technique of operating the machine and in the positioning of the catheter tip, as well as the use of antiemetic drugs and hyperleukocytosis agents may help to prevent these side effects. However, in the future we hope that the hyperthermia equipment will developed to the point where only the tumorous area is affected. We limited the radiation dose to 30–32 Gy, because higher doses can cause secondary cancer.

RHC for high-grade soft-tissue sarcomas achieves the best local disease control of any method currently available. This technique also allows surgery to be minimized, producing a better cosmetic and functional outcome. Furthermore, RHC appears to increase the survival rate in patients with MFH and liposarcoma.

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