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Abstract

We report the results of phase I/II studies of preoperative multidisciplinary treatment of 14 patients with soft tissue sarcoma using hyperthermia from November 1990 to April 1995. The preoperative treatment was conducted with thermo-radio-chemotherapy in 11 cases of stage III, and with thermo-radiotherapy as well as thermo-chemotherapy in three cases of stages I and II. Hyperthermia was carried out twice a week with totals ranging from 4 to 14 times (average: 8.4 times); each session lasted 60min. Radiotherapy was administered four or five times per week, and the dose was 1.8 2Gy/fraction, with a total of 30-40Gy in a four week period. Chemotherapy was mainly in the form of MAID regimen (2-mercaptoethanesulphonic acid (mesna), adriamycin, ifosfamide and dacarbazine). The tumors were surgically resected in all patients after completing the preoperative treatment. The efficacy rate, as expressed by the percentage of either tumors in which reduction rate was 50% or more, or tumors for which post-treatment contrast enhanced CT image revealed low density volumes occupying 50% or more of the total mass, was 71 % (ten of the 14 tumors). The mean tumor necrosis rate in the resected specimens was 78%. The tumor necrosis rate was significantly high ($P < 0.05$) in patients whose Time $\geq 42°C$ was of long duration. Postoperative complications were observed in six patients; among these, two patients developed wound infection that required surgical treatment as a complication of surgery performed in the early stage following the preoperative treatment. After a mean postoperative follow-up of 27 months, distant metastasis occurred in four patients resulting in three fatalities. The three-year cumulative survival rate was 64.3%. No local recurrence was observed in any patient during the follow-up, thus confirming our hypothesis that preoperative multidisciplinary treatment has an excellent local efficacy. We think that it would be valuable to conduct, at many facilities, phase III studies on the treatment of soft tissue sarcoma by a combination of surgery and preoperative multidisciplinary treatment using hyperthermia, paying close attention to the interval between these two modalities.

KEYWORDS: soft tissue tumor, hyperthermia, radiotherapy, chemotherapy

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Preoperative Multidisciplinary Treatment with Hyperthermia for Soft Tissue Sarcoma

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We report the results of phase I/II studies of preoperative multidisciplinary treatment of 14 patients with soft tissue sarcoma using hyperthermia from November 1990 to April 1995. The preoperative treatment was conducted with thermo-radio-chemotherapy in 11 cases of stage III, and with thermo-radiotherapy as well as thermo-chemotherapy in three cases of stages I and II. Hyperthermia was carried out twice a week with totals ranging from 4 to 14 times (average: 8.4 times); each session lasted 60 min. Radiotherapy was administered four or five times per week, and the dose was 1.8-2 Gy/fraction, with a total of 30-40 Gy in a four week period. Chemotherapy was mainly in the form of MAID regimen (2-mercaptoethanesulphonic acid (mesna), adriamycin, ifosfamide and dacarbazine). The tumors were surgically resected in all patients after completing the preoperative treatment. The efficacy rate, as expressed by the percentage of either tumors in which reduction rate was 50% or more, or tumors for which post-treatment contrast enhanced CT image revealed low density volumes occupying 50% or more of the total mass, was 71% (ten of the 14 tumors). The mean tumor necrosis rate in the resected specimens was 78%. The tumor necrosis rate was significantly high ($P < 0.05$) in patients whose Time $\geq 42^{\circ}C$ was of long duration. Postoperative complications were observed in six patients; among these, two patients developed wound infection that required surgical treatment as a complication of surgery performed in the early stage following the preoperative treatment. After a mean postoperative follow-up of 27 months, distant metastasis occurred in four patients resulting in three fatalities. The three-year cumulative survival rate was 64.3%. No local recurrence was observed in any patient during the follow-up, thus confirming our hypothesis that preoperative multidisciplinary treatment has an excellent local efficacy. We think that it would be valuable to conduct, at many facilities, phase III studies on the treatment of soft tissue sarcoma by a combination of surgery and preoperative multidisciplinary treatment using hyperthermia, paying close attention to the interval between these two modalities.

Key words: soft tissue tumor, hyperthermia, radiotherapy, chemotherapy

Although surgical treatment is the basic therapeutic treatment for soft tissue sarcoma, local recurrences occur in the 35-70% of patients treated with surgery alone (1). The frequency of postoperative recurrence is depending upon the surgical technique, *i.e.*, radical resection has a low recurrence rate and is therefore desirable. However, radical resection is not always possible for all patients, and preserving function of the limb in question after surgery is difficult if a radical resection is done on a sarcoma in that limb. Consequently, trials have been done using adjuvant preoperative as well as postoperative radiotherapy, and extended surgery with reasonable resection limits. These trials are aimed at preserving limb function after surgery, and preventing recurrence. Their results were very good (1-3). The role of adjuvant chemotherapy before and after surgery for soft tissue

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sarcoma has not been established yet (1, 3, 4), but many investigators have demonstrated the effectiveness of preoperative adjuvant chemotherapy. There are some reports about the usefulness of radiotherapy (5–8) or chemotherapy (8–10) in combination with hyperthermia before surgery for the treatment of soft tissue sarcoma. As yet, there are no reports concerning the results of preoperative multidisciplinary combined use of these three modalities. By carrying out preoperative multidisciplinary treatment using radiotherapy and chemotherapy combined with hyperthermia, we tried to increase the local control rate while controlling the range of tumor resection. In this paper, we report the results of phase I/II clinical studies of this multidisciplinary treatment.

Subjects and Methods

From November 1990 to April 1995, 14 patients having soft tissue sarcoma were treated with preoperative multidisciplinary treatment at Okayama University Hospital. All patients gave their informed consent before treatment. There were seven males and seven females, with a mean age of 53 years (range: 19–78 years) (Table 1). The lesions were located in the limbs in 13 patients and in the back in one. The histopathological diagnosis confirmed by preoperative incisional biopsy was as follows: malignant fibrous histiocytoma in six patients, synovial sarcoma in three, Ewing's sarcoma in one, clear cell sarcoma in one, liposarcoma in one, epithelioid sarcoma in one, and unclassified sarcoma in one. CT scanning was done in all cases before treatment to estimate the tumor volume. The tumor volume ranged from 11 to 1716 cm^3 with a mean of 251 cm^3. According to the TNM classification of The International Union Against Cancer (1987), 11 patients had stage III (stage IIIA in two and stage IIIB in nine), two had stage IIB, and one had stage IB. The preoperative treatment was conducted with thermo-radiochemotherapy in the 11 cases having stage III, and with thermo-radiotherapy or thermo-chemotherapy in the three cases having stages I and II (Table 2).

Hyperthermia was done with the BSD-1000 (BSD Medical Co., Ut, USA) in five patients, with the HEH-500C (Omron Co., Kyoto, Japan) in five, and with both machines in the same therapeutic regimen in four (Table 2). Hyperthermia was started within 30 min after irradiation, and it was carried out twice a week with a total ranging from 4 to 14 times (average: 8.4 times); each session lasting 60 min. To measure the temperature, a blind-end catheter was inserted under the guidance of CT images as deeply as possible into the tumor to monitor the temperature in the deepest parts of the tumor. To prevent dissemination of the tumor cells, the catheter was inserted into the biopsy site, or within the irradiation field if the former was not possible. Appropriate selection was made among the following three types of thermometers: thermocouple, high-resistance thermistor, and multi-point

Table 1 Patient characteristics

Case	Age	Sex	Site	Histological type	Tumor volume (cm^3)	TNM classification[a]
1	56	F	rt. thigh	Synovial sarcoma	120	Stage IIIB
2	24	F	lt. lower leg	Synovial Sarcoma	105	Stage IIIB
3	40	F	lt. thigh	Ewing's sarcoma	139	Stage IIIB
4	66	F	rt. thigh	MFH	1716	Stage IIIB
5	40	M	lt. lower leg	Unclassified sarcoma	189	Stage IIIB
6	62	M	lt. thigh	MFH	342	Stage IIIB
7	55	M	lt. thigh	Synovial sarcoma	385	Stage IIIB
8	42	M	rt. ant. forearm	Epithelioid sarcoma	11	Stage IIIA
9	59	M	rt. ant. forearm	MFH	28	Stage IIIA
10	19	F	lt. knee	Clear cell sarcoma	75	Stage IIIB
11	53	M	lt. lower leg	MFH	112	Stage IIIB
12	75	F	lt. lower leg	MFH	49	Stage IIB
13	78	M	lt. back	MFH	116	Stage IIB
14	67	F	rt. thigh	Liposarcoma	120	Stage IB

[a]: TNM classification of The International Union Against Cancer (1987). Abbreviations: F, female; M, male; rt, right; lt left; ant, anterior; MFH, malignant fibrous histiocytoma.

Table 2 Treatment methods

Case	Hyperthermia		Radiotherapy	Chemotherapy
	Heating device	Sessions		
1	HEH-500C	10	40 Gy	ADM, VCR, CDDP
2	BSD-1000, HEH-500C	14	40 Gy	IFM
3	BSD-1000	8	40 Gy	IFM
4	BSD-1000	8	40 Gy	CBDCA
5	HEH-500C, BSD-1000	9	40 Gy	ADM, IFM, DTIC
6	HEH-500C, BSD-1000	9	40 Gy	ADM, IFM, DTIC
7	HEH-500C, BSD-1000	9	40 Gy	IFM
8	HEH-500C	9	40 Gy	ADM, IFM, DTIC, CDDP
9	HEH-500C	8	40 Gy	ADM, IFM, DTIC
10	HEH-500C	8	32 Gy	ADM, IFM, DTIC
11	BSD-1000	6	30 Gy	ADM, IFM, DTIC, CBDCA
12	BSD-1000	8	40 Gy	—
13	BSD-1000	8	40 Gy	—
14	HEH-500C	4	—	ADM, IFM, DTIC

Abbreviations: ADM, adriamycin; VCR, vincristine; CDDP, cis-platinum; IFM, ifosfamide; CBDCA, carboplatin; DTIC, dacarbazine.

fiberoptic thermometer. For each temperature measurement, the temperature in the deepest part of the tumor was monitored. In the early phase of this study, single point temperature measurement was done in four patients, but later the distribution of temperature inside the tumor was measured by the pull-out technique or with a multipoint thermometer. Hyperthermia was conducted so as to raise the temperature of the entire tumor to more than 42 °C. Based on the data of temperature measurement, we calculated the following hyperthermia treatment parameters in each patient: Time $\geq$ 42 °C (min), Taverage (°C), Tmax (°C), and Tmin (°C). Time $\geq$ 42 °C represents the total time in each patient during which the temperature inside the tumor at any measuring point reached 42 °C or more during the therapeutic course. Taverage, Tmax, and Tmin represent the means of the average temperature, maximum temperature, and minimum temperature, respectively, after estimating these temperatures at each measuring point inside the tumor during the therapy time of each cycle throughout the treatment course for each patient.

Radiotherapy was administered four or five times per week, and the dose was 1.8-2 Gy/fraction, with a total of 30-40 Gy for four weeks (Table 2). The machine used was a MEVATORON-77 (Toshiba Medical Co., Tokyo, Japan) which administered 6 MV X-ray and 6 MeV electron. When setting the radiation fields, the normal tissue margin included in the long axis of the extremity was 5-10 cm for stage I, IIA and IIIA, and 10-15 cm or more for stage IIB and IIIB sarcomas. The normal tissue margin included in the cross-section of the extremity was determined by MRI or contrast CT studies. The radiation fields were set to contain the boundary of the tumor which was formed by major fascial planes, interosseous membrane and bone.

Chemotherapy was mainly in the form of MAID regimen [adriamycin 15 mg/m^2, ifosfamide 1.5 g/m^2, and dacarbazine 200 mg/m^2 on days 1-4, in addition to 2-mercaptoethanesulphonic acid (mesna) 900 mg/m^2 on days 1-6]. In some cases, vincristine, cis-platinum, and/or carboplatin were also used (Table 2). The chemotherapy was used in combination with hyperthermia by administering the chemotherapeutic agents either by intravenous infusion before and during heating, or by intra-arterial injection directly before heating.

The tumors were surgically resected in all patients after completing the preoperative treatment. Surgery was done on the 22nd day on the average (range: 9-41 days) after completing the preoperative treatment. The surgically resected specimens were fixed in formalin and stained. The histological specimens in the largest tumor sections were examined by expert histopathologists who then calculated the necrosis rate inside the tumor.

Results

Of a total of 118 heat treatments, burns occurred as a side effect during preoperative treatment in 18 treatments (11 %) (Table 3). In 16 of these treatments, first degree burns (cutaneous erythema and subcutaneous burns) occurred, and second degree burns involving blistering occurred in the remaining two treatments. All these manifestations were cured by symptomatic treatment alone and had no effect on the continuation of our therapy. Otherwise, there were no adverse reactions that postponed or mandated discontinuation of the preoperative multidisciplinary treatment.

Table 3 shows the local therapeutic effect of the preoperative treatment. The percentage of reduction in tumor volume, as calculated from the CT images before and after treatment, was CR (reduction rate (RR): 100 %) in no cases, PR (RR: 50 %-99 %) in three, MR (RR: 25 %-49 %) in three, and NC (RR: 25 %-24 %) in eight. Furthermore, estimating the percentage of volume occupying by low density areas (LDV) inside the tumor from the contrast enhanced CT images after treatment revealed CRh (LDV occupying 80 % or more total volume) in no cases, PRh (LDV occupied 50 %-79 %) in eight, and NCh (LDV occupying less than 50 %) in six. The efficacy rate, as expressed by the percentage of CR, CRh, PR, and PRh in all cases, was 71 % (ten of the 14 patients). On the other hand, the necrosis rate inside the tumors as observed in the surgically resected specimens ranged from 10 % to 100 % with a mean of 78 %, and it was 90 % or less in seven cases, and 91 % or more in the other seven. The results of the various treatment parameters of hyperthermia are shown in Table 3. These results were compared with the necrosis rate inside the tumors in the surgically resected specimens (Fig. 1). There were no significant differences in the number of treatments, Taverage, Tmax and Tmin be-

Table 3 Hyperthermia treatment parameters, side effects and local treatment results

Case	Hyperthermia treatment parameters				Side effects and local treatment results			
	Time ≥ 42 °C[a] (min)	Taverage[b] (°C)	Tmax[c] (°C)	Tmin[d] (°C)	Side effect	Volume reduction[e] (%)	Low density volume %[f]	Necrosis %[g]
1	363	41.5	42.3	39.3	Burn (2/10)	NC (0)	68	60
2	471	43.4	44.5	41.1	Burn (1/14)	PR (53)	62	99
3	345	44.1	44.9	41.9	Burn (1/8)	MR (30)	49	98
4	252	40.1	40.9	38.2	Burn (4/8)	NC (22)	53	80
5	229	41.3	43.3	38.7	Burn (2/9)	NC (-1)	39	98
6	421	43.8	44.2	41.9	Burn (1/9)	NC (-22)	57	99
7	0	40.1	40.7	39.7	—	PR (56)	9	40
8	449	41.0	41.8	40.1	—	NC (-22)	58	99
9	272	40.5	43.6	37.7	Burn (1/8)	PR (88)	0	100
10	0	38.9	39.2	38.7	—	MR (34)	19	10
11	268	43.9	44.3	42.5	—	NC (-13)	64	70
12	363	47.8	50.2	45.7	—	MR (47)	75	100
13	359	43.5	44.5	42.5	—	NC (19)	10	50
14	136	41.3	43.0	39.7	Burn (1/4)	NC (3)	61	90

a: The heating time in each patient when the temperature inside the tumor at any measuring point reached 42 °C or more during the therapeutic course.

b: The means of the average temperature after estimating these temperatures at each measuring point inside the tumor during the therapy time of each cycle throughout the treatment course for each patient.

c: The means of the maximum temperature after estimating these temperatures at each measuring point inside the tumor during the therapy time of each cycle throughout the treatment course for each patient.

d: The means of the minimum temperature after estimating these temperatures at each measuring point inside the tumor during the therapy time of each cycle throughout the treatment course for each patient.

e: Post-treatment reduction rate (%) of tumor volume calculated with pre-and post-treatment CT images.

f: Rate (%) of volume of low density area inside of the tumor on post-treatment CT images.

g: Rate (%) of pathological tumor necrosis observed on the largest section of the post-treatment resected tumor.

Abbreviations: NC, no change; PR, partial response; MR, minor response.

tween the group with tumor necrosis rate of 90 % or less and the group with tumor necrosis rate of 91 % or more. Nevertheless, the Time $\geq$ 42 °C was 197 and 364 min, respectively, and this difference was statistically significant (Student t-test, $P < 0.05$).

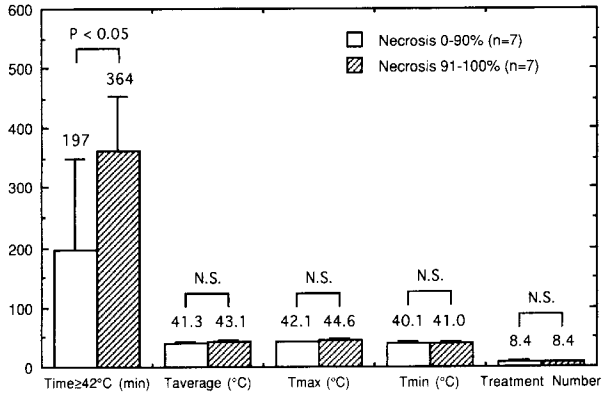

Fig. 1 Comparison between hyperthermia treatment parameters and necrosis rate. The following hyperthermia treatment parameters were determined for each patient: Time $\geq$ 42 °C (min), Taverage (°C), Tmax (°C), and Tmin (°C). Time $\geq$ 42 °C is the total time in each patient when the temperature inside the tumor at any measuring point reached 42 °C or more during the therapeutic course. Taverage, Tmax, and Tmin represent the means of the average temperature, maximum temperature and minimum temperature, respectively after estimating these temperatures at each measuring point inside the tumor during the therapy time of each cycle throughout the treatment course for each patient. The vertical axis represents the mean values (min, °C or times) of these reatment parameters among each group of different necrosis percentages.
Abbreviations: N.S., not statistically significant.

Table 4 shows the outcome of surgery and postoperative course. Amputation was done in one case, and wide resection of the tumor was performed in the other 13. Postoperative complications were seen in six patients. Hematoma formation and delayed wound healing occurred in two patients each, and were cured by symptomatic treatment alone. Wound infection was a complication in two patients who underwent surgery on the ninth day after completion of the preoperative multidisciplinary treatment. Surgical intervention was done in both cases; one of them was cured while the other case required amputation four months after the preoperative treatment. Until March 1996, after a postoperative follow-up of 8 to 61 months with a mean of 27 months, four patients (29 %) had developed distant metastasis (pulmonary metastasis in three, and brain metastasis in one) which resulted in three fatalities. Calculated with the Kaplan-Meier's method, the three-year cumulative survival rate was 64.3 %. No local recurrence was observed in any patient during the follow-up, nor was any postoperative functional impairment attributable to the preoperative multidisciplinary treatment.

Discussion

The sensitivity of soft tissue sarcoma to radiotherapy

Table 4 Treatment outcome

Case	Surgery	Wound complication	Follow up (months)[a]	Status	Local recurrence	Metastasis
1	WR	—	61	CDF	—	—
2	Amputation	—	42	CDF	—	—
3	WR	Hematoma	29	DOD	—	Lung
4	WR	Hematoma	36	CDF	—	—
5	WR	Delayed healing	8	DOD	—	Lung
6	WR	Wound infection	32	AWD	—	Lung
7	WR	Wound infection	32	CDF	—	—
8	WR	—	14	DOD	—	Brain
9	WR	—	28	CDF	—	—
10	WR	Delayed healing	21	CDF	—	—
11	WR	—	13	CDF	—	—
12	WR	—	11	CDF	—	—
13	WR	—	23	DOO	—	—
14	WR	—	30	CDF	—	—

[a]: Observed till March 1996. Abbreviations: WR, wide resection; CDF, continuously disease free; DOD, died of disease; AWD, alive with disease; DOO, died of other disease.

and chemotherapy is generally low. Thus, surgical treatment is the primary therapeutic approach for this disease (2, 3). However, the local recurrence rate is high after surgery alone. The combined use of surgery and radiotherapy is useful in preventing local recurrence, and the current standard therapy consists of a combination of surgical resection of the tumor and radiotherapy. Compared with postoperative radiotherapy, preoperative radiotherapy has the following advantages: a) the irradiation field is smaller, and b) the irradiation dose is lower (1-3). The local recurrence rate after a combined treatment with preoperative radiotherapy is 13%, while that with postoperative radiotherapy is 17% (3). Combining hyperthermia with preoperative radiotherapy reduced the local recurrence rate to 11% (6-8). Tumors larger than 5 cm in diameter and those with high histological grades commonly metastasize, and this metastasis is difficult to control in 50%-60% of cases, with resultant bad prognoses (1, 11). Although some inhibition of local recurrence is achieved with the combined use of surgery and radiotherapy, metastasis still occurs in up to 60% of patients with high grade tumors (3).

The role of combined treatment using preoperative and/or postoperative adjuvant chemotherapy in improving the survival rate has not yet been established (1, 3, 4). Nevertheless, in some patients who showed a histological improvement after the preoperative adjuvant chemotherapy, the inhibition of local recurrence was partially achieved and the metastasis decreased (1).

In the present study, we conducted a preoperative multidisciplinary treatment by combining hyperthermia with radiotherapy and chemotherapy. The results revealed that the tumor necrosis rate after treatment was high (mean: 78%), and that local recurrence did not occur in any case after a mean follow-up of 27 months. Thus, this preoperative multidisciplinary treatment was useful in improving the post-treatment local tumor control. Excluding the surgical wound infection, which occurred in two cases, no serious complications were observed in our study. In these two cases, surgery was performed in the early stage, on the ninth day, following the preoperative multidisciplinary treatment, whereas no complications occurred in the other cases of the same protocol where surgery was performed 13-41 days after the preoperative treatment. Accordingly, we suggest leaving an interval of 2.5-4 weeks (2, 8) after finishing the preoperative treatment to prevent any acute reactions.

The local therapeutic efficacy of the preoperative multidisciplinary treatment was evaluated for tumor necrosis rate in the resected specimens, and the treatment parameters of hyperthermia were investigated. The mean number of hyperthermia treatments in the group with high tumor necrosis rate was the same as that in the group with low tumor necrosis rate, and all the heating parameters tended to be high in the former group. However, there were no significant differences in the parameters reflecting only intra-tumor temperature, *i.e.*, Taverage, Tmax, and Tmin. On the other hand, Time $\geq 42^{\circ}C$, which is a parameter reflecting the temperature inside the tumor and the heating time, was significantly higher in the group with high tumor necrosis rate. This indicates that the effect of heating is determined not only by the temperature but also by the heating time, and that elevating the temperature as well as prolonging the heating time are important in potentiating the local therapeutic efficacy. To demonstrate the therapeutic importance of increasing the temperature inside the entire tumor as well as the heating time to a satisfactory level, Leopold *et al.* (5, 12) used a heating parameter of cumulative equivalent minutes at a T_{90} converted to $43^{\circ}C$ (CEM 43 T_{90}), which reflects both concepts of the thermal dose (13) and thermal parameters, such as T_{90} (7), which reflects the temperature distribution inside the tumor. We think that in preoperative multidisciplinary treatment using hyperthermia, satisfactory heating of the entire tumor by means of excellent heating machines is important in determining the local therapeutic outcome.

A massive coagulation necrosis is generally observed inside the tumor after hyperthermia (14). Estimation of therapeutic efficacy by tumor reduction rate might be difficult after hyperthermia if these necroses obstruct tumor shrinkage (14). Coagulation necrosis is visible as the low density area inside the tumor on the contrast enhanced CT images after hyperthermia (15). In this study, necrosis percentage was estimated as being lower using LDV on the post-treatment CT (Table 4). Perhaps these estimates are falsely low due to inflammation present around in the tumor following hyperthermia, as our CT examinations were performed for an average of only 8 days after treatments. As inflammation around the necrosis was observed in the former histopathological analysis (16), we think that the necrosis percentages that we generated using CT analysis were falsely low due to the presence of this inflammation resulting from hyperthermia treatment. In future studies, it would be best to lengthen the time between treatment and CT examination to allow

for an accurate estimation of necrosis rate (16).

In the present study, with a small number of patients, limb-sparing operations could be performed in 12 of 13 patients (92 %) with soft tissue sarcoma of the limbs, no local recurrence occurred in any patient, and the superior local efficacy of the preoperative multidisciplinary treatment was confirmed. We think that it would be worthwhile to conduct, at many facilities, phase III studies on the treatment of soft tissue sarcoma by a combination of surgery and preoperative multidisciplinary treatment using hyperthermia, paying close attention to the interval between these two modalities.

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