Acta Medica Okayama

Volume 41, *Issue* 2 1987 *Article* 2

APRIL 1987

Therapeutic effect of hyperthermia combined with chemotherapy on vulvar and vaginal carcinoma.

Keiichi Fujiwara* Ichiro Kohno†

Kaoru Sekiba‡

*Okayama University,

†Okayama University,

‡Okayama University,

Therapeutic effect of hyperthermia combined with chemotherapy on vulvar and vaginal carcinoma.*

Keiichi Fujiwara, Ichiro Kohno, and Kaoru Sekiba

Abstract

A clinical trial was performed to investigate the efficacy of hyperthermia in combination with chemotherapy for gynecological malignancies. Sixty-nine patients with vaginal or vulvar malignancies (9 primary vulvar, 3 recurrent vulvar, 11 primary vaginal, 4 primary cervical, 40 recurrent cervical, and 2 recurrent ovarian carcinomas) were treated by thermochemotherapy (42 cases) or chemotherapy alone (27 cases). After treatment, 7 patients underwent surgery and 46 patients irradiation. The chemotherapeutic schedule was mainly a combination therapy with bleomycin and mitomycin C (B-M). Microwaves of 2.45 GHz were applied to induce local hyperthermia. The side effects of chemotherapy were not increased by hyperthermia. The rate of partial response plus complete response increased to 84% (16/19) in primary cancers and 45% in recurrent cancers by hyperthermia, compared to the respective values of 40% (2/5) and 17% (3/17) for chemotherapy alone. However, a satisfactory prognosis cannot be expected with thermochemotherapy, unless additional treatments are performed. Subsequent surgery or radiation treatment improved the progression-free interval.

KEYWORDS: hyperthermia, microwave, chemothrapy, post-thermochemothrapeutic treatment, gynecological malignancies

---

*PMID: 2438902 [PubMed - indexed for MEDLINE]

Acta Med Okayama 41 (2) 55-62 (1987)

Therapeutic Effect of Hyperthermia Combined with Chemotherapy on Vulvar and Vaginal Carcinoma

Keiichi Fujiwara, Ichiro Kohno and Kaoru Sekiba

Department of Obstetrics and Gynecology, Okayama University Medical School, Okayama 700, Japan

A clinical trial was performed to investigate the efficacy of hyperthermia in combination with chemotherapy for gynecological malignancies. Sixty-nine patients with vaginal or vulvar malignancies (9 primary vulvar, 3 recurrent vulvar, 11 primary vaginal, 4 primary cervical, 40 recurrent cervical, and 2 recurrent ovarian carcinomas) were treated by thermochemotherapy (42 cases) or chemotherapy alone (27 cases). After treatment, 7 patients underwent surgery and 46 patients irradiation. The chemotherapeutic schedule was mainly a combination therapy with bleomycin and mitomycin C (B-M). Microwaves of 2.45 GHz were applied to induce local hyperthermia. The side effects of chemotherapy were not increased by hyperthermia. The rate of partial response plus complete response increased to 84% (16/19) in primary cancers and 45% in recurrent cancers by hyperthermia, compared to the respective values of 40% (2/5) and 17% (3/17) for chemotherapy alone. However, a satisfactory prognosis cannot be expected with thermochemotherapy, unless additional treatments are performed. Subsequent surgery or radiation treatment improved the progression-free interval.

Key words: hyperthermia, microwave, chemotherapy, post-thermochemotherapeutic treatment, gynecological malignancies

Various types of therapies have been tried to improve the response to advanced or recurrent malignancies. Hyperthermic treatment for cancer has attracted our attention recently. By heating tumors to 42℃-43℃, the tumoricidal effect of irradiation or an anti-cancer drug is potentiated without damaging the normal tissues. At the present time, most hyperthermic treatment is used in combination with irradiation (1). However, there are some reports showing promising effects when hyperthermia is used in combination with chemotherapy. Particularly, Kubota *et al.* (2) reported encouraging results using localized thermochemotherapy, combined with radiotherapy, against bladder cancer. They treated bladder carcinoma patients with an infusion of heated water containing bleomycin into the bladder cavity and radiation.

However, there has been no report with a sufficient number of cases of gynecological malignant tumors. In the present paper, we show a greater response of vulvar and vaginal malignant tumors to bleomycin-mitomycin C (B-M) when combined with local hyperthermia. We also show improved survival rates with combination therapy, and discuss the role of subsequent radiotherapy or surgical treatment on the progression-free interval.

Patients and Methods

Patients

From 1977 to 1983, 69 patients with vulvar and vaginal malignancies were treated at the Department of Obstetrics and Gynecology, Okayama University Medical School. There were 24 cases of primary cancer and 45 of recurrent cancer cases. Among the primary cases, there were 9 cases of vulvar cancer, 11 of vaginal cancer, and 4 of cervical cancer of the uterus with infiltration to the vaginal wall. The lesions of the recurrent cases were located in the vulva or vagina, and the original diseases were vulvar in 3 cases, cervical in 40 cases and ovarian in 2 cases. Histologically, 61 cases were squamous cell carcinoma, 2 adenocarcinoma, 4 adeno-squamous cell carcinoma and 2 undifferentiated carcinoma. The overall average age of the patients was 60.7 years (range, 38 to 80). Of the 69 patients, 42 were treated by thermochemotherapy (TC) (chemotherapy combined with local hyperthermia), and 27 patients received chemotherapy alone (CH) as the first step of treatment. Among them, 53 patients also underwent subsequent therapies as described below.

Therapies

Chemotherapy. All patients were given chemotherapy with bleomycin (BLM) or peplomycin (PLM) and mitomycin C (MMC) (Fig 1). Five milligrams of BLM or PLM diluted with 250 ml of 10% low molecular dextran was administered by intravenous drip infusion over one hour on 7 consecutive days. An intravenous bolus injection of 10 mg of MMC diluted with 20 ml of saline was given on the 8th day. This schedule was repeated 1-5 times (mean 2.7) with one-week intervals. The average doses of BLM (or PLM) and MMC were 92.7 mg and 25.9 mg, respectively.

Hyperthermia. Hyperthermia was applied while the anticancer drugs were being administered. The therapeutic temperature (42°C-43°C) was attained by irradiating 2.45-GHz microwaves, which were produced by a generator, HTS-001, a trial product and a prototype of HMS-010 from ALOKA Co. (Tokyo, Japan). The microwave applicator was in direct contact with the tumor. The temperature was measured with a copper-constantan (C-C) thermocouple attached to the tip of the applicator.

In order to determine the characteristics of this hyperthermic apparatus, the thermal distribution and temperature curve were examined using rabbit skin prior to clinical use. The thigh of a rabbit was shaved and the applicator was attached to the skin directly. In order to measure the temperature continuously, several elastic needles were inserted into the subcutaneous tissue, the inner needles were removed and the C-C thermocouple was inserted through the outer tubes.

Subsequent therapies. Of the 42 TC patients, 6 were treated by thermochemotherapy alone, 2 underwent surgery after TC, and 34 underwent subsequent irradiation. In the CH group, 10 patients were treated by chemotherapy alone, and 5 patients were treated by surgery following chemotherapy, and 12 by irradiation.

Evaluation of results

The therapeutic effects were evaluated on the basis of the chemotherapeutic response, survival rate, and progression-free interval. The chemotherapeutic response was evaluated based upon the criteria of the direct chemotherapeutic response of solid cancers as standardized by the Japan Society for Cancer Therapy. The response rate was calculated by the following equation, and compared between the TC and CH groups.

$$\text{Response rate (\%)} = \frac{\text{number of (CR+PR)} \times 100}{\text{number of (CR+PR+MR+NC+PD)}}$$

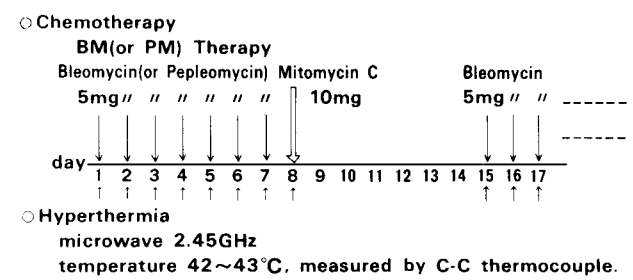

Fig. 1 Therapeutic schedule of bleomycin (or pepleomycin)-mitomycin C therapy alone or with hyperthermia. Bleomycin or peplomycin was administered by intravenous drip infusion over 1 h at 5 mg/day on 7 consecutive days and 10 mg of mitomycin C by bolus intravenous injection on the 8 th day.

where CR : complete response, PR : partial response, MR : minor response, NC : no change, and PD : progressive disease. Kaplan-Meier's accumulative survival rates (3) of the two groups were also compared.

To clarify the role of the additional treatment after thermochemotherapy, the progression-free interval was calculated. With respect to patients who experienced recurrence following remission, the duration until recurrence was adopted instead of the survival period. For patients who did not obtain remission, the survival period was adopted and calculated according to Kaplan-Meier's method.

Results

Preliminary experimentation. The thermal distribution produced in rabbit skin by the applicator is shown in Fig. 2. When the surface of the applicator was heated to 43°C, the temperature was 43°C at a depth of 3 mm, 41°C at 10 mm, 40°C at 15 mm and 38°C at 30 mm. The temperature decreased with the distance from the center of the skin surface attached to the applicator. The temperature remained 43°C at a distance of 2 mm from the center, but decreased to 40°C at 5 mm and 38°C at 10 mm. When the skin was not heated, the temperature in the subcutaneous tissue deeper than 8 mm from the skin surface was 38°C at room temperature (20°C). These results suggest that 2.45-GHz microwaves can heat superficial lesions, but are not adequate for heating deep tissues.

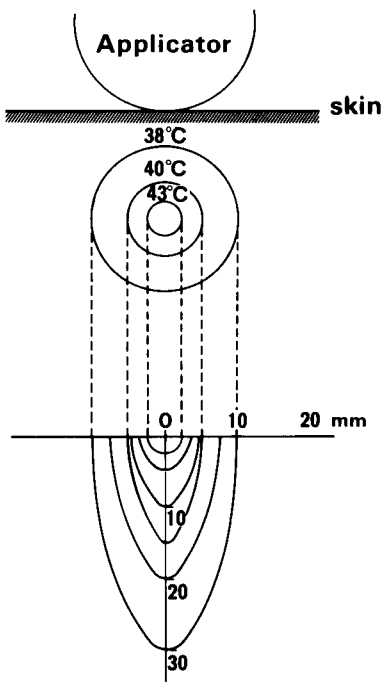

Fig. 2 Thermal distribution produced by 2.45-GHz microwaves. The power was 10 watts, and room temperature was 20°C.

When the apparatus was operated at 10 watts, the temperature of the subcutaneous tissue rose to the therapeutic temperature (42°C-43°C) within 10 min. The temperature was controlled with a microcomputer during the treatment. The temperature fell rapidly when the power was turned off.

Clinical investigations. Since the patients were not randomly selected, it was difficult to evaluate statistical differences of the clinical results between the TC group and the CH group. Actually, these two groups differ in some factors, *e.g.*, the mean dose of BLM, number of primary and recurrent cases and use of additional therapies. It was also difficult to compare the statistical differences between the TC and CH groups of the primary tumor group, because the number of cases was considerably different, *i.e.* 19 cases were treated with thermochemotherapy and only 5 with chemotherapy alone. However, in the recurrent group, these two (TC and CH) groups of patients were similar in age, chemotherapeutic dose of BLM and MMC, course of chemotherapy and use of additional therapies (Table 1). Therefore, only the results from the recurrent cases were statistically analyzed.

The response of cancer to B-M therapy is summarized in Table 2. Of the 42 pa-

Table 1 Demographic comparison between thermochemotherapy and chemotherapy groups of recurrent cases

Item	Mean value (range) or number of cases		p[a]
	Thermochemotherapy group	Chemotherapy group	
Patients' age (y)	58.5 (43-72)	59.3 (33-72)	N. S.[b]
Amount of BML or PLM administered (mg)	87.5 (35-104)	101.1 (35-175)	N. S.
Amount of MMC administered (mg)	25.5 (10-40)	27.5 (10-50)	N. S.
Frequency of therapy	2.5 (1-4)	2.9 (1-5)	N. S.
Number of cases			
with additional therapy	20	14	
without additional therapy	3	8	N. S.

a: Calculated by Student's *t*-test or χ^2 test.
b: Not significant; the lack of any significant difference between the above two groups.

Table 2 Response of 69 vulvar and vaginal malignancies to bleomycin-mitomycin C therapy alone or in combination with hyperthermia

Group	Number of cases showing						Total no. of cases
	Complete response	Partial response	Minor response	No change	Progressive disease	Could not be evaluated	
Thermo-chemotherapy group	6	20	2	10	3	1	42
Chemotherapy group	0	5	1	16	4	1	27

Table 3 Response of primary vulvar and vaginal malignancies to bleomycin-mitomycin C therapy alone or in combination with hyperthermia

Group	Number of cases showing						Total no. of cases
	Complete response	Partial response	Minor response	No change	Progressive disease	Could not be evaluated	
Thermo-chemotherapy group	5	11	1	1	1	0	19
Chemotherapy group	0	2	0	3	0	0	5

Table 4 Response of recurrent vulvar and vaginal malignancies to bleomycin-mitomycin C therapy alone or in combination with hyperthermia

Group	Number of cases showing						Total no. of cases
	Complete response	Partial response	Minor response	No change	Progressive disease	Could not be evaluated	
Thermo-chemotherapy group	1	9	1	9	2	1	23
Chemotherapy group	0	3	1	13	4	1	22

tients with vulvar or vaginal malignancies treated by TC, 26 patients showed a positive response, including 6 who showed a complete response. The response rate was 26/41 (63%). This rate is higher than that of the CH group, 5/26 (19%). With primary cancers. the positive response rate was 84% (16/19) in the TC group compared with 40% (2/5) in the CH group (Table 3). With recurrent cases, the positive response rate was significantly higher in the TC group (45%) than in the CH group (17%) ($p < 0.05$) (Table 4). These results show that hyperthermia enhances the chemotherapeutic effect. A striking improvement in the response rate was obtained for both primary and recurrent cancers.

The long-term survival curve of 69 patients is shown in Fig. 3. With the TC group, strikingly better results were obtained than with the CH group at any time after treatment. In the recurrent cases, the survival rate of the TC group was significantly higher than that of the CH group (Fig. 4).

When the survival curves in the thermochemotherapy group were compared with regard to the use or nonuse of additional treatments, there was not much difference between the curves (Fig. 5). There were some patients who were surviving because the treatment after recurrence was effective. Therefore, we compared the progression-free rate to exclude the influence of secondary treatments after recurrence (Fig. 6). These curves demonstrate that earlier recurrence was observed in the patients without additional therapy than in the patients who received treatment after TC therapy. These findings imply that subsequent treatment plays an important role in obtaining

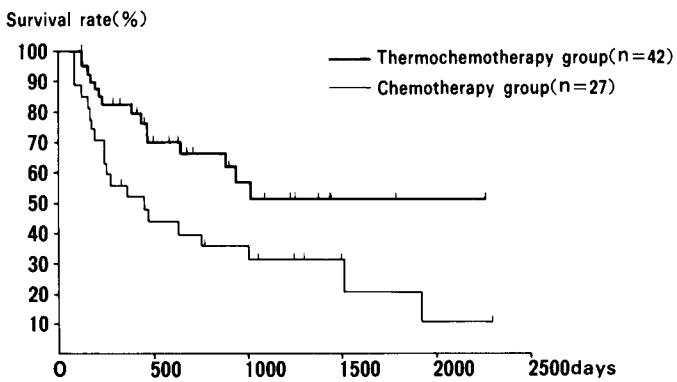

Fig. 3 Comparison of survival curve of 69 patients with vulvar or vaginal malignancies treated by thermochemotherapy or chemotherapy. The survival rate was calculated by Kaplan-Meier's method. A better survival rate was obtained in the thermochemotherapy group.

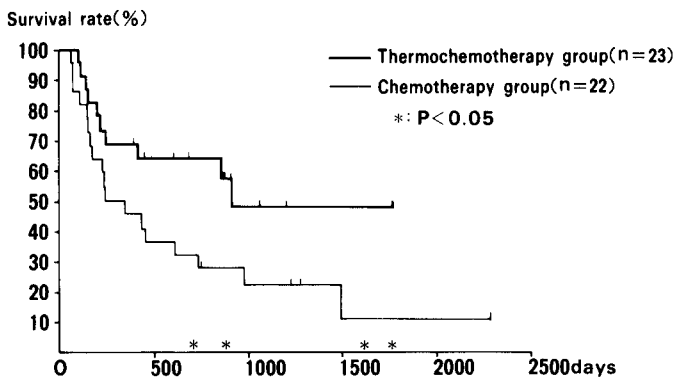

Fig. 4 Comparison of survival curve of 45 patients with recurrent vulvar or vaginal malignancies treated by thermochemotherapy or chemotherapy. Calculated by Kaplan-Meier's method. The survival rate was significantly better (*: $p < 0.05$) in the thermochemotherapy group than in the chemotherapy group.

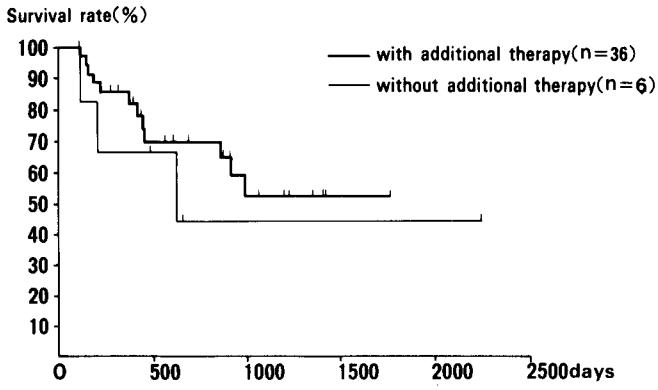

Fig. 5 Comparison of survival curve of 42 patients with vulvar or vaginal malignancies treated by thermochemotherapy with or without additional therapies. The survival rate was not different between the two groups.

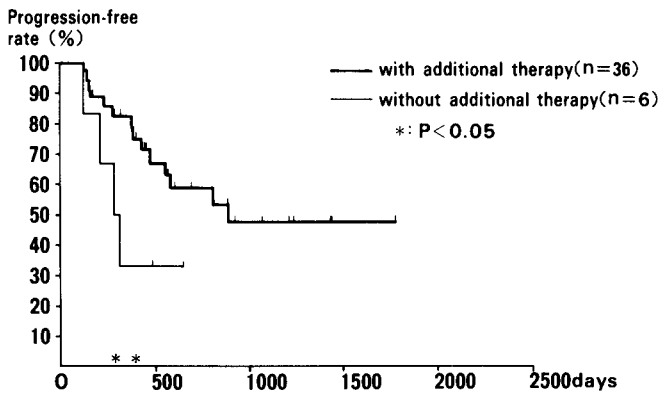

Fig. 6 Progression-free rate of 42 patients with vulvar or vaginal malignancies treated by thermochemotherapy with or without additional treatment. Earlier recurrence was noted in the patients without additional treatments compared to the patients who received additional therapy following thermochemotherapy (*: $p < 0.05$).

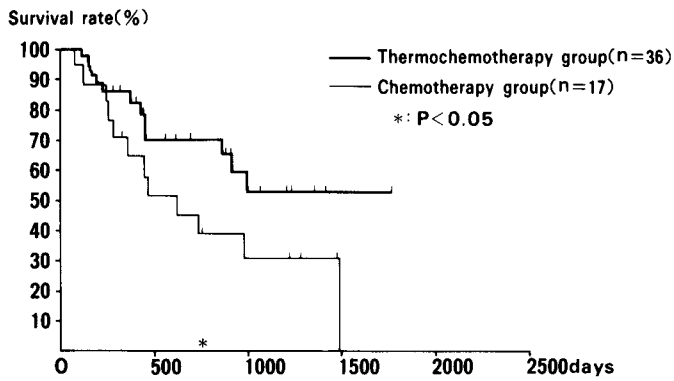

Fig. 7 The survival curve of 53 patients who received subsequent therapies after thermochemotherapy or chemotherapy. A significantly better survival rate was obtained by thermochemotherapy with additional treatments (*: $p < 0.05$).

good results. The survival curve of the patients with additional therapy was compared between the TC and CH groups. The TC group showed significantly better results than the CH group (Fig. 7).

Toxicity of anti-cancer agents. Side effects, such as general fatigue, nausea or vomiting, fever, aphthous stomatitis, acrocyanosis, exanthema, lung fibrosis, anemia, leukocytopenia, thrombocytopenia and elevation of GOT and GTP have been observed to accompany B-M therapy. However, no significant differences in these side effects were observed between the TC and CH groups.

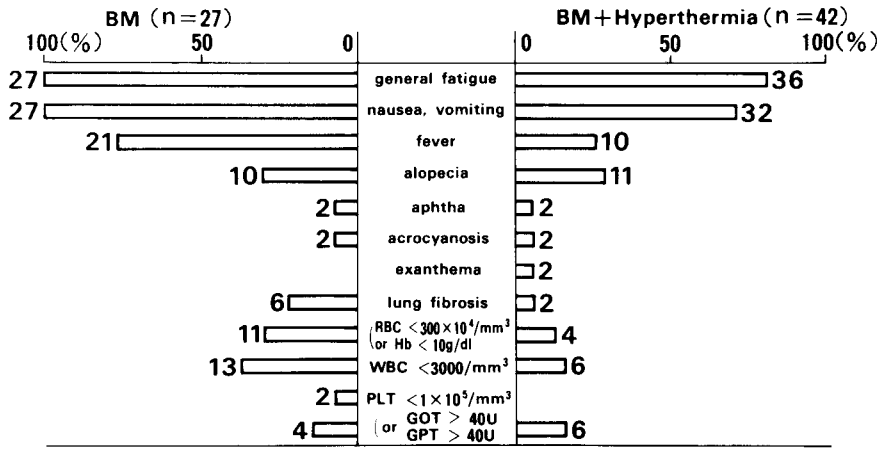

Fig. 8 Frequency of side effects of bleomycin-mitomycin C therapy. Mean dosage of bleomycin was 85.8 mg in the thermochemotherapy group and 104.4 mg in the chemotherapy group, and that of mitomycin C was 24.5 mg and 28.3 mg, respectively. Hyperthermia did not increase the frequency of side effects except for local exanthema.

With the exception of regional exanthema, which seemed to result from local heating, a slightly higher incidence of side effects was seen in the CH group. This may be attributable to the fact that the total doses of the chemotherapeutic agents were larger in the CH group than in the TC group (Fig. 8).

Discussion

When 2.45-GHz microwaves were used to induce hyperthermia, it was difficult to obtain satisfactorily high temperatures in the deep tissue away from the skin surface. However, microwave hyperthermia is easily applied to vulvar and vaginal malignancies, because most of the tumors are superficial and can be heated directly by the applicator. Margin *et al.* (4) reported the effect of local hyperthermia which was produced with a 2.45-GHz microwave apparatus. The local hyperthermia reduced the size and retarded the growth of treated tumors of tumor-bearing mice in comparison with the control tumors.

Since it is difficult to completely remove advanced or recurrent malignancies of the vulva and vagina by surgery, various adjuvant therapies, including chemotherapy (especially using bleomycin) have been proposed (5, 6). However, treatment with chemotherapy alone has often given poor results (5, 6) as shown in the present paper. When hyperthermia was combined with B-M therapy, the chemotherapeutic response was strikingly improved in both primary and recurrent cancer patients. Similar findings have been reported in several experimental and clinical studies (7-11).

Although the long-term survival rate was also improved with B-M therapy combined with hyperthermia, compared to B-M therapy alone, recurrence often occurred in the early stage of the follow-up period if additional treatment was not performed. Therefore, we must consider the importance of surgery or irradiation after the initial treatment (TC or CH), as indicated by the experimental studies of Urano *et al.* (12) and Kai *et al.* (13). Urano *et al.* (12) reported that the TCD-50 following a single-dose irradiation was reduced when thermochemotherapy (200 mg/kg cyclophosphamide and heat at 42.5°C for 30 min) was given 24 h before irradiation to a spontaneous murine fibrosarcoma.

Kai *et al.* (13) studied the effectiveness of a combination of 3 modalities : hyperthermia, chemotherapy (bleomycin) and irradiation in tumor-bearing mice. These studies, as well as ours, demonstrated that the combination of hyperthermia with anticancer drugs could be an effective treatment when followed by irradiation.

No serious side effects of B-M therapy were produced by hyperthermia. Local exanthema was seen in 2 cases. This is assumed to result from dilatations of local capillaries due to high temperature, but it was not a dose limiting factor. The incidence of other side effects was higher in the CH group than in the TC group, probably due to lower doses of chemotherapeutic agents in the TC group than in the CH group. In other words, we can say that a better response was obtained with a smaller drug dose by combining chemotherapy with hyperthermic treatment.

The results of this study suggest that a three-stage approach, surgery or irradiation after reduction of tumor size by thermochemotherapy, is a new and safe treatment for advanced or recurrent vulvar and vaginal malignancies.

Acknowledgment. This study was supported in part by a Grant-in-Aid for Scientific Research (59579711) from the Japanese Ministry of Education.

References

1. Landberg T: Hyperthermia and cancer chemotherapy clinical results. A literature review. Proc the 4th International Symposium on Hyperthermic Oncology (1984) **2**, 169-179.
2. Kubota Y, Shuin T, Miura T, Nishimura R, Fukushima S and Takai S: Treatment of bladder cancer with a combination of hyperthermia, radiation and bleomycin. Cancer (1984) **39**, 199-202.
3. Kaplan EL and Meier P: Nonparametric estimation from incomplete observation. Am Stat Assoc J (1958) **53**, 457-481.
4. Magin RL and Jonson RK: Effects of local tumor hyperthermia on the growth of solid mouse tumors. Cancer Res (1979) **39**, 4534-4539.
5. Sekiba K and Kohno I: Vaginal cancer, Chemotherapy for Gynecologic Cancer. Sanfujinka Series (1982) **32**, 260-273 (in Japanese).
6. Sugawa T and Umesaki N: Vulvar cancer, Chemotherapy for Gyneclogic Cancer. Sanfujinka Series (1982) **32**, 274-293 (in Japanese).
7. Miyao J: Experimental studies on thermochemotherapy. Acta Obstet Gynecol Jpn (1982) **34**, 1691-1698 (in Japanese).
8. Marmor JB, Kozak D and Hahn GM: Effects of systemically administered bleomycin or adriamycin with local hyperthermia on primary tumor and lung metastases. Cancer Treatment Reports (1979) **63**, No. 8, 1279-1290.
9. Arcangeli G, Cividalli A, Mauro F, Nervi C and Pavin G: Enhanced effectiveness of adriamycin (ADM) and bleomycin (BLM) combined with local hyperthermia in neck node metastases from head and neck cancer. Tumori (1979) **65**, 481-486.
10. Arcangeli G, Cividalli A, Lovisiolo G, Mauro F, Creton G, Nervi C and Pavin G: Effectiveness of local hyperthermia in association with radiotherapy or chemotherapy: Comparison of mutimodality treatments on multiple neck node metastases. Proc the lst Meeting of European Group of Hyperthermia in Radiation Oncology (1980) 259-265.
11. Storm FK, Kaiser LR, Goodnight JE, Harrison WH, Elliott RS, Gome AS and Morton DL: Thermochemotherapy for melanoma metastases in liver. Cancer (1982) **49**, 1243-1248.
12. Urano M and Kahn J: Thermochemotherapy as an adjuvant to radiotherapy. Proc the 4th International Symposium on Hyperthermic Oncology (1984) **2**, 461-464.
13. Kai H, Inokuchi K, Sugimachi K and Matsufuji H: Hyperthermochemo-radiotherapy for Ehlrich ascites tumor. Proc the 4th International Symposium on Hyperthermic Oncology (1984) 453-456.

Received : May 22, 1986
Accepted : February 3, 1987

Correspondence to :
Keiichi Fujiwara
Department of Obstetrics and Gynecology
Okayama University Medical School
2-5-1 Shikata-cho
Okayama 700, Japan