Clinical Results of Treatment of Advanced Esophageal Carcinoma With Hyperthermia in Combination With Chemoradiotherapy*

Takashi Sakamoto, MD; Hiroshi Katoh, MD; Tetsuro Shimizu, MD; Iwao Yamashita, MD; Shigeru Takemori, MD; Kenji Tazawa, MD; and Masao Fujimaki, MD

Chemoradiotherapy combined with hyperthermia was administered to 35 patients with advanced esophageal carcinoma who either required preoperative treatment or had nonresectable disease. As a rule, each patient received a total dose of 30 Gy in 15 daily fractions of 2 Gy, 5 d/wk. Bleomycin or cisplatin, in combination with fluorouracil, was employed as chemotherapy. Hyperthermia was applied by intraluminal heating twice a week for a total of six sessions using an apparatus (IH-500T; Japan Crescent Co Ltd; Tokyo, Japan) (radiofrequency, 13.56 MHz) with an intraesophageal applicator and two extracorporeal applicators placed on the chest and back. This treatment method obtained a response rate of 80%, consisting of a complete response rate of 22.9% and partial response of 57.1%. In 15 cases, the tumor became resectable (resectability rate, 42.9%) following treatment. The histologic study of the resected specimens revealed absence of viable tumor cells in five patients (33.3% of the resected cases) (markedly effective), and in six patients (40.0%), the combined therapy was considered to be moderately effective. No complications considered due to hyperthermia itself were recognized. The overall 5-year survival rate was 11.8%. In conclusion, chemoradiotherapy combined with hyperthermia was locally effective, yielding an overall response of 80.0%. However, the prognosis of the patients remains unfavorable. Advanced esophageal carcinoma requires treatment taking into account lymphatic and hematogenic metastasis at the beginning of treatment.

(*CHEST 1997; 112:1487-93)

Key words: clinicopathologic evaluation; esophageal carcinoma; high-temperature hyperthermia; multidisciplinary treatment; preoperative combined therapy

Abbreviations: CR=complete response; RF=radiofrequency

With recent developments and improvements in diagnostic technique, therapeutic approaches, and perioperative management, results of the treatment of esophageal carcinoma have gradually improved, but there are still many cases that are detected only at an advanced stage with invasion to surrounding organs or extensive lymph node metastasis. Owing to the extent of resection required for curative resection, there are many cases in which the surgeon is restricted in terms of operative approach. Consequently, the results of the surgical treatment of esophageal carcinoma are significantly poorer than those for other GI carcinomas. As a result, a multidisciplinary approach to advanced esophageal carcinoma is extremely important. However, despite the addition and combination of chemotherapy, immunotherapy, and radiotherapy to surgical treatment, at present and to our knowledge, there is no generally accepted therapeutic strategy for this disease entity.1-6

Recently, hyperthermia has been attracting attention as a therapeutic method with much potential. Much experimental work in vitro and in vivo has shown the antitumor effect of hyperthermia alone,7,8 and its synergistic effect in combination with radiotherapy and certain types of chemotherapy.9,10 Hyperthermia has therefore been recognized as one of the weapons in the anticancer arsenal. In experimental studies in our department, we employed three cell lines established from human esophageal carc-
noma, transplantable to nude mice, to examine changes in the proliferative ability of esophageal carcinoma cells under high-temperature conditions, and demonstrated the antitumor effect of hyperthermia.\textsuperscript{11,12}\ Furthermore, in 1983, using the intraluminal hyperthermia applicator developed by Sugimachi et al\textsuperscript{13} and the hyperthermia system devised in our department, we overcame the technical difficulties of delivering hyperthermia to lesions in the esophagus, which is located deep within the body and surrounded by vital organs such as the airway and aorta. Beginning in 1985, we included hyperthermia with radiotherapy and chemotherapy in the multidisciplinary treatment of advanced unresectable esophageal cancer.\textsuperscript{14,15}\ This report describes the clinicopathologic results in this series of cases.

\section*{Materials and Methods}

From November 1985 until December 1994, chemoradiotherapy combined with hyperthermia was administered to 35 patients (33 male and 2 female) with advanced esophageal carcinoma. Of these, 33 showed invasion to neighboring organs or distant metastasis at the time of diagnosis and had been evaluated as having unresectable disease. The other two patients were judged to have inoperable disease owing to their poor general condition. These patients were not included in any protocol study and represented the total number of patients with esophageal cancer who were judged to have inoperable disease and who were treated during that time at our institution. Patients ranged in age from 44 to 81 years (median, 65 years). The location of the main lesion was the intrathoracic esophagus in 32 patients, the cervical esophagus in 2, and the abdominal esophagus in 1. Tumor length ranged from 3 to 20 cm, with an average of 8.5±3.9 cm. Table 1 shows the radiologic, endoscopic, and histologic types.\textsuperscript{16,17}\ Patients were judged to have inoperable disease if they had T4 or N1 disease or if their general condition was extremely poor.

Regarding pretreatment clinical classification, in 27 patients, invasion to adjacent organs, consisting of the aorta, trachea, bronchus, and the pericardium, was found on preoperative submucosal esophagography.\textsuperscript{18}\ CT, endoscopic ultrasonography, or fiberoptic bronchoscopy (Table 2). Submucosal esophagography is a newly developed method by Saito\textsuperscript{19} in 1979 to determine the depth of esophageal cancer invasion prior to surgery. In this procedure, iodized oil fluid is injected into the submucosal layer through an endoscope and observation of the spread of the infused contrast medium facilitates the determination of the depth of esophageal cancer invasion to the adventitia. Among the eight cases in which invasion to neighboring organs was not recognized, distant metastasis to lymph nodes or other organs was recognized in six. The breakdown according to the TNM classification is shown in Table 2.\textsuperscript{19}\ When patients with dysphagia are defined as those who can take only liquids orally, it was observed in 16 patients. Hoarseness due to swelling of lymph nodes in the superior mediastinum was noted in three patients.

Treatments for patients showing invasion into adjacent organs or distant metastasis included chemoradiotherapy with hyperthermia, performed under a no surgery policy as described below.

As a rule, each patient received a total dose of 30 Gy in 15 daily 2-Gy fractions delivered from both anterior-posterior and posterior-anterior directions, over 3 weeks (Fig 1). In cases in which metastasis to cervical or abdominal lymph nodes was recognized, the radiation field was T-shaped to include the supraclavicular fossa and the root of the celiac artery. In other cases, a 6-cm-wide rectangular radiation field was selected to include the primary lesion and neighboring mediastinal organs. A total of 10 continuous 24-h subcutaneous injections of 7.5 mg of bleomycin was administered during the initial period of this study. Later, cisplatin in combination with fluorouracil was employed. Bleomycin alone was administered in 5 patients, both bleomycin and cisplatin in 9, cisplatin combined with fluorouracil in 12, and cisplatin alone in 5 patients.

Hyperthermia was performed by intraluminal heating twice a

\begin{table}[h]
\centering
\caption{Radiologic, Endoscopic, and Histologic Types*}
\begin{tabular}{ll}
\hline
Radiologic Types &  \\
Superficial & 0  \\
Tumorous & 3  \\
Serrated & 15  \\
Funneled & 5  \\
Spiral & 12  \\
Unclassified & 0  \\
Endoscopic &  \\
Superficial & 0  \\
Elevated & 8  \\
Depressed & 21  \\
Stenotic & 5  \\
Unclassified & 1  \\
Histologic &  \\
Squamous cell carcinoma &  \\
Well differentiated & 7  \\
Moderately differentiated & 19  \\
Poorly differentiated & 5  \\
Unknown & 1  \\
Small cell carcinoma & 3  \\
\hline
\end{tabular}
\begin{flushleft}
*See references 16 and 17.
\end{flushleft}
\end{table}

\begin{table}[h]
\centering
\caption{Pretreatment Clinical Classification (TNM)*}
\begin{tabular}{ll}
\hline
Classification & No. (\%)
\hline
T4 & 27 (77.1)  \\
Tumor invaded &  \\
Aorta & 13 (37.1)  \\
Bronchus & 8 (22.9)  \\
Trachea & 8 (22.9)  \\
Pericardium & 2 (5.7)  \\
Others & 2 (5.7)  \\
N1 & 16 (45.7)  \\
M1 & 16 (45.7)  \\
TNM stage &  \\
III &  \\
T3N1M0 & 2 (5.7)  \\
T4AnyNM0 & 17 (48.6)  \\
IV &  \\
M1 LYM & 14 (40.0)  \\
M1 HEP & 1 (2.9)  \\
M1 SKI+OSS+LYM & 1 (2.9)  \\
\hline
\end{tabular}
\begin{flushleft}
*TNM=TNM classification of the esophagus (fourth, fully revised edition/1987).\textsuperscript{19}\ The M1 categories are specified according to the following notation: LYM=lymph nodes; HEP=hepatic; SKI=skin; OSS=osseous.
\end{flushleft}
\end{table}
Radiotherapy (parallel opposing portals: 2 Gy/day)  total 30 Gy

Hypothermia (over 45°C for 30-40 min.)  total 6 sessions

Chemotherapy
- Bleomycin (7.5 mg)
- Cisplatin (70 mg m⁻²)
- 5-FU (500-1000 mg m⁻²)

Week

Figure 1. The protocol of chemoradiotherapy combined with hyperthermia for esophageal carcinoma. Bleomycin alone was administered in 8 patients, both bleomycin and cisplatin in 9, cisplatin combined with fluorouracil in 12, and cisplatin alone in 5 cases. 5-FU = 5-fluorouracil.

The protocol of chemoradiotherapy combined with hyperthermia for esophageal carcinoma. Bleomycin alone was administered in 8 patients, both bleomycin and cisplatin in 9, cisplatin combined with fluorouracil in 12, and cisplatin alone in 5 cases. 5-FU = 5-fluorouracil.

week for a total of six sessions using an apparatus (IH-500T; Japan Crescent Co Ltd; Tokyo, Japan; radiofrequency [RF], 13.56 MHz). Generally chemotherapy was initiated in the morning, followed by radiotherapy, then in the afternoon hyperthermia was added, within 2 h after radiotherapy. Subcutaneous injections of bleomycin were administered continuously for 24 h. Fluorouracil was also administered continuously for 24 h on days 1 to 5. The administration of cisplatin was started and ended simultaneously with hyperthermia. After one cycle of the above treatment, those patients showing regression of tumor worked up for resection while those patients who remained in the nonresectable category were given repeated treatment in the same manner, to the extent that they could tolerate it. For 20 patients with nonresectable carcinoma, additional combined therapy, consisting of radiation, chemotherapy, and hyperthermia was used whenever possible. Two of these 20 patients who had local recurrence received additional intraluminal hyperthermia (eight and four sessions, respectively). Eight received additional chemotherapy of cisplatin with an average dose of 161 mg and five received radiotherapy with an average dose of 50.1 Gy. No patient in the resectable group was retreated before the operation.

Figure 2 shows the schematic diagram of hyperthermia delivery. Intraluminal heating was applied with an intraesophageal applicator (The Second Department of Surgery, Toyama Medical and Pharmaceutical University Model, Toyama, Japan), the concept of which was based on the intraluminal antenna of Sugimachi et al for use in the esophageal lumen, inserted under pharyngeal anesthesia, and two extracorporeal applicators were placed on the chest and back. The tip of the intraluminal applicator was equipped with a rubber balloon, according to the length of the tumor. After insertion, 20 mL of water was instilled into the balloon to obtain good contact with the tumor surface, following which RF was generated between the intraluminal applicator and the two extracorporeal applicators. A thin electrode in the esophagus and two broad counter electrodes connected in parallel made it feasible to localize the electromagnetic field in the esophagus, and provide heat effectively to the tumor. Temperature measurement was performed with one or two thermocouples on the balloon surface (ie, on the tumor surface) at 1 min intervals. During hyperthermia, temperatures ranged from 42 to 44°C during the early study period in which nine patients were included. Since 1988, temperatures exceeding 45°C were sustained for >30 min. The duration of hyperthermia treatment in the initial study period was >30 min above that in the later period. We achieved the temperature goal in almost all cases both in the early and later study period. The average temperature at each session was 42.1 to 52.3°C. The average doses of combined therapy were 41.2±22.2 Gy radiation, 73.3±64.3 mg of bleomycin, 144.0±99.5 mg of cisplatin, and 4.110±2.521 mg of fluorouracil. The number of hyperthermia sessions ranged from 2 to 12 (mean, 5.1±2.3 sessions). Figure 3 shows the time course of temperature and RF output in one patient during hyperthermia. A temperature exceeding 45°C on the tumor surface could be obtained immediately after the beginning of the treatment using a low RF power under 100 W. Since heating could be obtained at low power, no water cooling system was necessary in most patients during the later study period and no skin damage was observed. The efficacy of treatment was determined by endoscopic or radiologic evaluation of the local and histologic effect at a median of 37 days (range, 22 to 96 days) after completion or discontinuation of treatment. Description of degrees of response was determined as follows. Complete response (CR) was disappearance of the lesion on esophagography and endoscopy. Partial response was a decrease of ≥50% in size as evaluated by the product of its two largest dimensions or a decrease of 30% in a single dimension. No change was neither a 50% bidimensional decrease lesion nor a 30% monodimensional decrease and the growth of the lesion was <25%. Progressive disease was an ≥25% increase in the size of the lesion. Since the definition of CR was based on the esophagography and endoscopic findings, biopsy to confirm CR evaluation.
was not performed. Histologic evaluation of therapeutic effectiveness was performed using resected specimens and the following classification based on the criteria of the Japanese Society of Esophageal Diseases was employed: ineffective (grade 0), no effect recognized cytologically or histologically; slightly effective (grade 1), some effects recognized but viable cancer cells consist of one-third or more of the total; moderately effective (grade 2), viable cancer cells constitute less than one-third of the total; and markedly effective (grade 3), absolutely no viable cancer cells recognized or only the cicatrix of the lesion recognized. A WBC count of \( \geq 2,900/\text{mm}^3 \) was taken to indicate leukocytopenia due to myelosuppression, a calcium level of \( \geq 11 \text{ mg/dL} \) indicated hypercalcemia, and a serum creatinine level of 2.0 mg/dL was taken to indicate renal dysfunction. Pulmonary fibrosis was diagnosed according to the physical examination findings, chest radiograph, and arterial blood analysis. The survival after the date of diagnosis in patients with nonresectable disease and after the operation in patients with resected disease was calculated according to the Kaplan-Meier method.

**RESULTS**

Among the 16 patients in whom dysphagia had been observed before treatment, 15 of these 16 achieved improvement of oral intake and became able to take half a bowl of rice gruel or more. On evaluation of the local response, the response rate was 80.0%. Eight (22.9%) patients achieved CR, 20 (57.1%) achieved partial response, 6 (17.1%) achieved no change, and 1 (2.9%) achieved progressive disease. No pretreatment factor (tumor size, shape, patient age, sex, and histologic type) was found to correlate with response.

Following treatment, evaluation of the diagnostic imaging findings and the overall condition of the patients allowed reclassification as resectable in 16 cases, in 15 of which resection was performed (resectability: 42.9%). In one case, the operative findings indicated nonresectability; therefore, a gastric tube bypass using the greater curvature was performed. In the 19 nonresected cases, 3 patients had poor general condition, while the other 16 received nonsurgical treatment, because the evaluation of the primary lesion indicated the impossibility of radically curative surgery. Of the 15 surgically treated patients, 10 underwent intrathoracic esophagectomy with thoracotomy, 4 underwent blunt dissection, and 1 underwent pharyngolaryngoesophagectomy. The histologic study of the resected specimens revealed absence of viable tumor cells in five (33.3% for the resected cases and 14.3% for the total group studied) patients (markedly effective), while in six (40.0% for the resected cases and 17.1% for the total group studied) patients the combined therapy was considered moderately effective, based on the criteria of the Japanese Society for Esophageal Diseases.17

Concerning changes in TNM classification, no change was observed in either N or M classification, but a significant decrease in T4 lesions was obtained. Of 27 lesions classified before treatment as T4, a reduction to T3 or less was seen in 18 following treatment, although no effect was recognized in lesions involving the pericardium (Table 3). Among the 12 cases initially diagnosed as M1, operation was performed in 4 but in all 4 cases the postoperative classification was M1 LYM and the outcome was poor, with none surviving more than 12 months.

None of the patients showed any particular changes in general condition during hyperthermia. However, during the treatment period, leukocytopenia, which was the most frequent complication and was considered due to myelosuppression form chemotherapy, was seen in eight patients, pulmonary fibrosis in four patients, interstitial pneumonitis in two, hypercalcemia in three, transient renal dysfunction induced by combined cisplatin in three patients, esophagobronchial fistula that was considered due to progressive carcinoma, because it appeared 1 month after completion of treatment, in one, dysphagia due to radiation gastritis in one, and blindness due to fungal uveitis in one patient. All patients with pulmonary fibrosis had received bleomycin. The cause of hypercalcemia was unknown and there were no surgical complications directly related to the treatment. Leukocytopenia and renal dysfunction improved within 1 to 2 weeks of discontinuation of the treatment, but all four who developed pulmonary fibrosis died. Complications considered to be due to hyperthermia itself such as esophageal perforation, hemorrhage, or burn as a result of passing the

### Table 3—Clinical Classification (TNM) After Hyperthermia in Combination With Chemoradiotherapy for All the 35 Cases and Classification Before and After the Treatment for Operated-on Cases

<table>
<thead>
<tr>
<th>Classification</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>35</td>
</tr>
<tr>
<td>T4</td>
<td>9 (25.7)</td>
</tr>
<tr>
<td>Tumor invaded</td>
<td></td>
</tr>
<tr>
<td>Aorta</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Bronchus</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Trachea</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Pericardium</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>N1</td>
<td>16 (45.7)</td>
</tr>
<tr>
<td>M1</td>
<td>12 (34.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Operated-on patients</th>
<th>Before Treatment</th>
<th>After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td>13</td>
<td>2*</td>
</tr>
<tr>
<td>T&lt;4</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>N1</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>M1</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

*The lesion was not resected because of bypass operation in one patient.
applicator into the esophagus or heating at high
temperature exceeding 45°C were not recognized.

The Kaplan-Meier survival curves of the patients
are shown in Figure 4. The survival rate at 5 years
was 11.8% in all patients, 26.7% in resected cases,
and 0% in nonresectable cases. The longest current
postoperative survival period is 8 years and 7 months.

**DISCUSSION**

The results of esophageal carcinoma treatment
have improved to some extent due to developments
and improvements in surgical technique, diagnostic
capabilities, anesthesia, and perioperative manage¬
ment. However, many esophageal carcinomas are
already advanced at the time of detection, and many
of these are not candidates for curative resection,
resulting in poorer prognosis than carcinomas of
other sites in the GI tract. In our department, the
policy has been to first operate on all patients judged
to be candidates for curative resection. In cases in
which extensive invasion to other organs or distant
metastasis was recognized, we perform preoperative
treatment in order to maximize resectability. The concept of preoperative treatment in esophageal
carcinoma, initiated by the report on radiotherapy
from Clifton et al in the 1950s concerning radio¬
therapy, has been taken up by many other institu¬
tions. Chemotherapy is generally not given alone
as a single preoperative modality and is more com¬
monly employed in combination with radiotherapy. Combined treatment, based primarily on ra¬
diotherapy, was shown to obtain pathologically
recognizable response in 59.6% of cases by Fujimaki
et al and 55.7% by Iizuka et al.

Concerning hyperthermia, in addition to many
reports on the antitumor effect of this modality alone, it has also become clear that it has
synergistic effects with radiotherapy and chemother¬
apy. The authors previously reported on the
effectiveness of this approach in preclinical experi¬
ments using transplantable human esophageal carci¬
noma cell lines in nude mice. With the develop¬
ment of the intraluminal hyperthermia applicator
and the hyperthermia system developed in our de¬
partment, it was possible to overcome the problems
posed by the location of the esophagus deep in the
body, surrounded by vital organs such as the respira¬
atory tract and the aorta.

Based on the above work, we began to employ
hyperthermia in combination with radiotherapy and
chemotherapy in the multidisciplinary treatment of
those esophageal cancers, judged at the time of
initial diagnosis to be noncuratively resectable cases,
and we obtained pathologically recognizable effect in
73.3% (markedly effective + moderately effective) in
the resected cases and 31.4% overall, with total
disappearance of cancer cells in 33.3% for the
resected cases and 14.3% for the total group studied.
In other words, addition of hyperthermia to the
conventional approach based mainly on radiotherapy
obtained increased local antitumor effects, com¬
pared to the reports of Fujimaki et al and Iizuka et al
providing a theoretical indication of the poten¬
tial of combined hyperthermia. The purpose of
preoperative treatment includes obtaining a
decrease in tumor burden, increase in resectability,
and prevention of dissemination during intraoperative
manipulations. Sugimachi et al reported on the
histopathologic effects of preoperative treatment
based on examination of resected specimens. In their
study, cases judged as markedly effective had a
significantly better outcome than those in which the
results of the treatment were judged to be only
moderately effective or ineffective. The small num¬
ber of cases in the present series makes it difficult to
perform statistically significant comparisons, but
the improvement in local effects caused by hyperthermia
is thought to suggest to improvement in prognosis.

In advanced cases of esophageal carcinoma with
invasion to other organs or distant metastasis, there
are two reasons to perform multidisciplinary treat¬
ment. The first reason is that mentioned above, ie,
improvement in postoperative prognosis, while the
second purpose is to enable oral intake of food by
decreasing the size of the tumor, thereby improving
the quality of life. Combination of hyperthermia with
chemoradiotherapy obtained a high overall rate of
effectiveness of 80.0%, and almost all patients with
nonresectable disease were relieved of dysphagia.
Palliative therapy for esophageal carcinoma has in-

---

**Figure 4.** The Kaplan-Meier survival curves of the patients treated with chemoradiotherapy combined with hyperthermia. Broken line, all cases (n=35); solid line, resected cases (n=15); gray line, unresectable cases (n=20).
cluded dilatation, intubation,26 external radiation, and more recently laser photoablation27 and brachytherapy.28 We believe that decrease of the esophageal tumor should lead to improvement of oral intake and our multidisciplinary treatment approach, including hyperthermia, might achieve a degree of palliation at least comparable to these methods. While some neoadjuvant studies have obtained response rates of 20 to 30%, these have generally included cases that were not extremely advanced. The initial advanced inoperable condition of all the patients in the present series underlines the importance of the results.

The antitumor effects of hyperthermia are considered to increase with higher temperatures.7,20-31 Using conventional RF hyperthermia with an esophageal intraluminal applicator, the depth of penetration of heat is considered to be 1 to 2 cm.32 In order for the effects of hyperthermia to reach the deepest parts of tumor, especially in surrounding organs, it is essential to warm the surface of the tumor even more. For this reason, we employed the high-temperature hyperthermia method which maintains the surface of the tumor at ≥45°C. Using an improved intraluminal applicator and two extracorporeal coiled applicators, the system that we developed does not require a cooling irrigation system, and since it uses ≤100 W power, it is safe and relatively easy to apply.

The main technical problem in hyperthermia is temperature measurement. With the technology available today, it is impossible to measure noninvasively the temperature in the deepest layers of tumor or surrounding organs or even in different parts of the tumor. Therefore, the approach we employed was to monitor the surface temperature of the tumor. It is hoped that a noninvasive method of temperature measurement will be developed to allow accurate assessment of antitumor effects of hyperthermia.

The second problem is the question of depth of penetration of heat. There are various methods of delivering hyperthermia, such as RF hyperthermia, without an intraluminal applicator, microwave hyperthermia,33 and the annular phased-array system. With these, however, it is difficult to make heat to reach the deepest part of the tumor, and heat distribution is not uniform. We believe that our intraluminal RF method and Sugimachi’s may be the best available methods13,32 at present for hyperthermia for esophageal carcinoma.

Complications in the present series included pulmonary fibrosis, mycotic uveitis, and radiation gastritis, but no complications considered to be due directly to hyperthermia itself such as esophageal perforation, hemorrhage, or burn as a result of passing the applicator into the esophagus or heating at a high surface temperature exceeding 45°C were observed. Since there was a fatality due to pulmonary fibrosis in the second half of our study bleomycin was substituted by cisplatin and fluorouracil. A clinical trial using this chemotherapeutic regimen is being performed by the Japanese Esophageal Oncology Group.34 Cisplatin has been reported to have synergistic effects with hyperthermia.9 To prevent the appearance of various side effects, it is necessary to give further consideration to aspects of combined regimens. Furthermore, since the value of preoperative radiation has been called into question by recent reports, it appears essential to evaluate combined therapeutic methods that involve zero or minimal levels of radiotherapy. Further studies concerning different chemotherapeutic agents, granulocyte colony stimulating factor, etc, should also be performed.

The effectiveness of hyperthermia combined with chemoradiotherapy was demonstrated by Sugimachi et al35 by a prospective randomized trial. The present study has shown hyperthermia to be effective, even in cases of advanced esophageal carcinoma evaluated as inoperable at the time of initial diagnosis. However, the prognosis of patients remains poor. Among two of the patients in whom the resected specimen revealed no viable cancer cells whatsoever, death occurred due to distant metastasis; therefore, further steps must be taken for the treatment of lymphatic or hematogenous metastases.

**CONCLUSION**

Hyperthermia combined with chemoradiotherapy yields local effects in patients with advanced cases of esophageal carcinoma evaluated as inoperable at the time of diagnosis. The present study showed an overall response in 80.0% of cases and most patients became able to ingest food orally. However, despite good local effects, there were several serious complications associated with the combined treatment. This suggests the necessity of improvement in hyperthermia technique and the revision of the combined regimen, in addition to prevention of complications.

**ACKNOWLEDGMENT:** The authors are indebted to Prof. J. Patrick Barroo of the International Medical Communications Center of Tokyo Medical College for his review of the article.

**REFERENCES**
