

## Original Contribution

# Thermoradiotherapy for Recurrent Esophageal Carcinoma

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**Abstract:** Sixteen patients with recurrent esophageal carcinoma who underwent thermo-radiotherapy from 1994 to 2002 were retrospectively analyzed. A total radiation dose was  $55.1 \pm 9.2$  Gy for post-operative recurrence ( $n = 9$ ) and  $46.1 \pm 14.3$  Gy for post-radiotherapy recurrence ( $n = 7$ ). Hyperthermia was performed for  $42.5 \pm 8.0$  min immediately after irradiation with radiofrequency capacitive heating devices; number of the sessions was  $10.7 \pm 9.3$ . Average  $T_{max}$  in 6 cases was  $44.0 \pm 4.4^{\circ}\text{C}$ . The overall local control rate (CR + PR) was 87.5%, and the 5-year cause specific survival rate was 25.0%. Median survival durations were 73.4 months for CR group and 7.0 months for PR + NC group ( $p < 0.001$ ). Thermo-radiotherapy may improve local control in patients with recurrent esophageal carcinoma.

**Key word:** recurrent esophageal carcinoma, radiotherapy, hyperthermia

## Introduction

Most cases with esophageal carcinoma are discovered as advanced diseases, and have a poor prognosis. Recurrence rates after radical treatment with radiotherapy, surgery and / or chemotherapy were reported as high as 75.7-85 %<sup>1)2)</sup>. Although treatment outcome of chemo-radiotherapy for esophageal carcinoma has improved in recent years<sup>3-5)</sup>, frequency of local recurrence after chemo-radiotherapy, which has very poor prognosis and many limitations to treat, have increased. When recurrent diseases are localized in intra-thoracic region, it seems that the local control is an important factor for outcome. To enhance the effect of radiotherapy or chemotherapy in these cases, we have been focusing attention on local hyperthermia. To our knowledge, however, there is no report of thermo-radiotherapy for intra-thoracic recurrence of esophageal carcinoma. The purpose of this study is to evaluate the treatment outcome of the thermo-radiotherapy in the cases with intra-thoracic recurrence of esophageal carcinoma.

## Materials and methods

From 1994-2002, 16 patients with recurrent intra-thoracic esophageal carcinoma who underwent thermo-radiotherapy were retrospectively analyzed. Treatment preferences criteria were under 80 years and general condition of PS 1-2. Characteristics of patients are shown in Table I. All patients were men and had subcutaneous fatty layer of the chest wall less than 1.5cm. In seven cases of post-radiotherapy group, mean total radiation dose at initial radiotherapy was  $59.7 \pm 7.6$  Gy. In five cases, double cancer was recognized in past years.

Details of treatments are shown in Table II. A Thermotron RF-8 capacitive heating device utilizing 8 MHz (Yamamoto VINITA Co., Osaka, Japan) was used in hyperthermia. Hyperthermia was applied within 30 min after radiotherapy once or twice a week. A treatment posture of all cases was supine position. Upper and lower electrodes were 30 cm in diameter. For cooling of the skin surface, the

**Table I.** Characteristics of patients

|                    |                         |                  |
|--------------------|-------------------------|------------------|
| Sex                | Male                    | 16               |
|                    | Female                  | 0                |
| Age                |                         | $65.6 \pm 10.0$  |
| Performance status | 1                       | 6                |
|                    | 2                       | 10               |
| Initial treatment  | operation               | 9                |
|                    | radiotherapy            | 7                |
| Recurrent form     | intra-esophagus         | 3                |
|                    | mediastinal lymph node  | 13               |
| Tumor size         |                         | $4.4 \pm 1.3$ cm |
| Pathology          | squamous cell carcinoma | 15               |
|                    | adenocarcinoma          | 1                |

**Table II.** Detail of the treatments

|                      |  |
|----------------------|--|
| Hyperthermia         |  |
| Machine              | Thermotron RF-8                        |
| Timing               | just after radiotherapy                |
| Schedule             | 1 session / week                       |
| Total                | $10.7 \pm 9.3$ sessions                |
| Time                 | $42.5 \pm 8.0$ min.                    |
| RF-output            | $1031 \pm 415$ W                       |
| Electrode            | 30cm / 30cm                            |
| Patient position     | Supine position                        |
| Radiotherapy         |  |
| Linac 6 or 10MVX-ray |  |
| Fraction             | 1.6-2Gy / fraction                     |
| Total Dose           | Post-operation : $55.1 \pm 9.2$ Gy     |
|                      | Post-radiotherapy : $46.1 \pm 14.3$ Gy |
| Chemotherapy         |  |
| CDDP+5-FU            | 11 / 16                                |

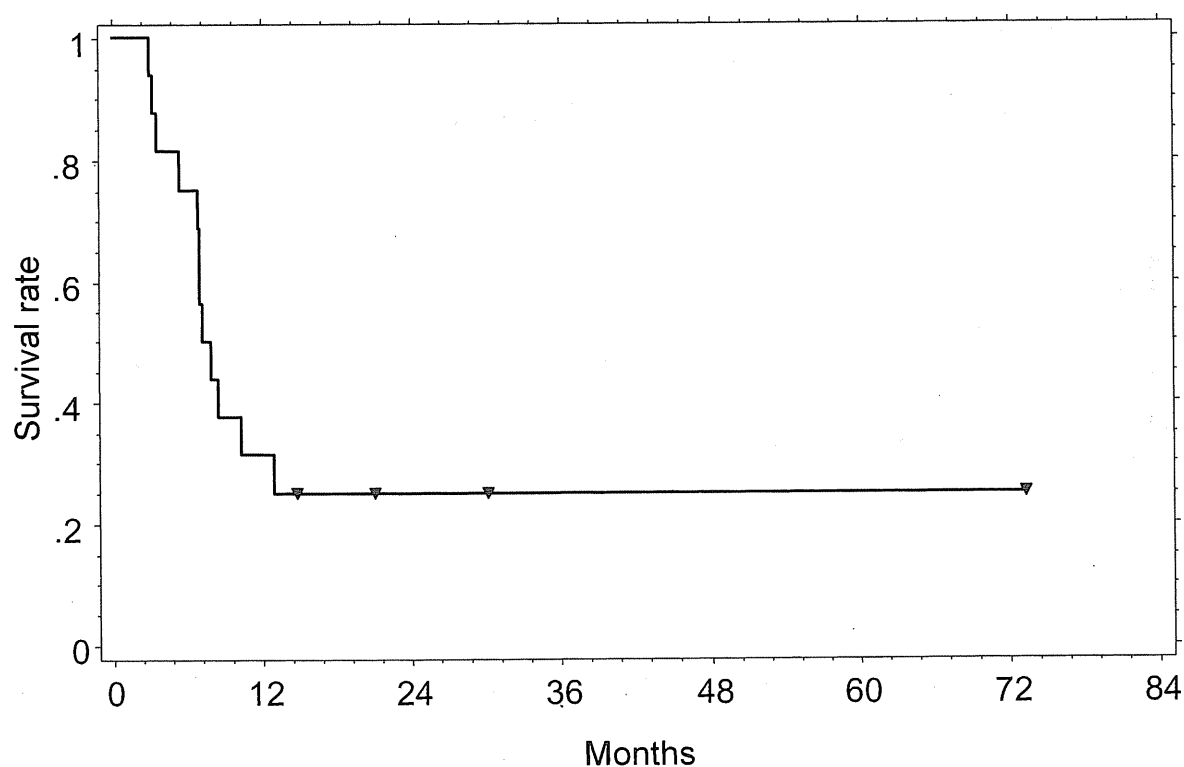
overlay-boluses were applied in addition to regular boluses attached in front of the metal electrodes. Circulating liquid of the overlay bolus was 0.5%NaCl saline water<sup>6)</sup>. Circulating liquid was cooled less than 5°C by using external cooling unit during treatment<sup>7)</sup>. Heating duration was  $42.5 \pm 8.0$  min. and sessions of treatments ranged from 2 to 34 times (mean  $10.7 \pm 9.3$ ). Hyperthermia alone was continued in some cases after the end of radiotherapy. The temperature was measured in six cases using a 4-point micro-thermocouple sensor, which was inserted into the esophagus through 12F catheter. In all cases, intra-esophageal temperature was calculated using our database of 72 cases intra-thoracic hyperthermia<sup>6)8)</sup>.

All patients were treated with external radiotherapy using a 6 or 10MV linear accelerator. A total dose of radiotherapy was  $55.1 \pm 9.2$  Gy for post-operative cases and  $46.1 \pm 14.3$  Gy for post-radiotherapy cases. The intra-esophageal  $^{60}\text{Co}$   $\gamma$ -ray irradiation was used together in one case. Combination chemotherapy with CDDP and 5FU was performed with 11 cases.

The tumor response was evaluated by measuring the tumor size mainly with CT before and after the radiation therapy. Grading of tumor response was as follows: complete tumor regression was designated as complete response (CR),  $\geq 50\%$  regression in volume

**Table III.** Results of local control and intra-esophageal Tmax

|       |                 | calculated Tmax              |
|-------|-----------------|------------------------------|
| CR    | 5 / 16 (31.3%)  | $42.2 \pm 1.6^\circ\text{C}$ |
| PR    | 9 / 16 (56.3%)  | $41.6 \pm 2.4^\circ\text{C}$ |
| NC    | 2 / 16 (12.6%)  | $41.0 \pm 1.2^\circ\text{C}$ |
| CR+PR | 14 / 16 (87.5%) | $41.6 \pm 2.0^\circ\text{C}$ |



**Fig. 1.** Overall survival curves by Kaplan-Meier method in all cases.

as partial response (PR), <50% response or <25% increase as no change (NC). To identify prognostic factors for overall survival, univariate analyses were performed using age, performance status score, tumor size, radiation dose, sessions of hyperthermia and chemotherapy. The overall survival rate was calculated from the start of radiation by the *Kaplan-Meier* method. The statistical significance of the difference between the actuarial curves was assessed using the *log-rank* test. The follow-up periods were 4-73 (average 14) months.

## Results

Results of local control and calculated intra-esophageal Tmax are shown in Table III. The tumor response was CR in 5 cases, PR in 9, and NC in 2 (CR + PR: 87.5%). Measured intra-esophageal temperature of six cases was  $44.0 \pm 4.4^{\circ}\text{C}$  (calculated temperature:  $41.6 \pm 2.0^{\circ}\text{C}$ ). Tmax was  $44.4 \pm 7.8^{\circ}\text{C}$  for CR group (2 cases) and  $43.2 \pm 3.3^{\circ}\text{C}$  for PR (4 cases). Calculated intra-esophageal Tmax was highest in CR group followed by PR and NC groups, but not significant.

The 5-year overall survival rate with Kaplan-Meier method was 25% for all patients as shown in Fig. 1. Median survival duration was 8.0 month (3.1-73.4 month). CR group showed significantly better prognosis than PR + NC group ( $p < 0.001$ ) (Fig. 2).

Overall survival curves by the initial treatment are shown in Fig. 3. There was no significant difference of the survival between post-operation group and post-radiotherapy group, although long-term survival cases were recognized only in post-radiotherapy group.

Results from univariate analyses for survival are shown in Table IV. There were no significant

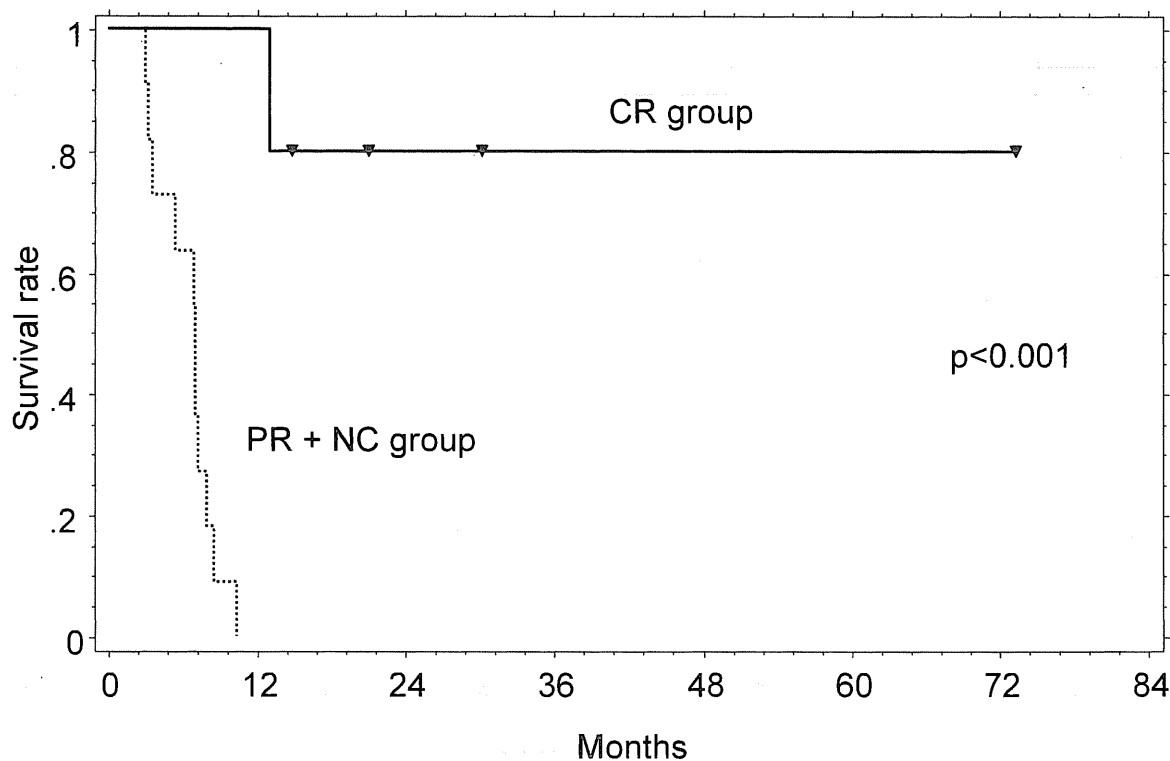


Fig. 2. Overall survival curves by Kaplan-Meier method according to the local effect.

factors affecting to the survival.

Acute toxicities over Grade 3 were not recognized during the treatment. Esophageal perforation after the treatment was recognized in one case.

## Discussion

Intra-thoracic recurrences of esophageal carcinoma after initial treatment are common, although there are some differences of recurrent form of esophageal carcinoma between operation and radiotherapy; local recurrence is more commonly observed after radiotherapy than after surgery. In post-operative recurrence, 12.1% were local recurrence and 18.2% were intra-thoracic lymph node metastases<sup>9)</sup>. In the report about recurrence after radiotherapy, local recurrence was as high as 78.4% but lymph node metastases including extra-thoracic regions were 33.3%<sup>2)3)</sup>.

According to the report of post-operative recurrence of esophageal carcinoma, re-operation was

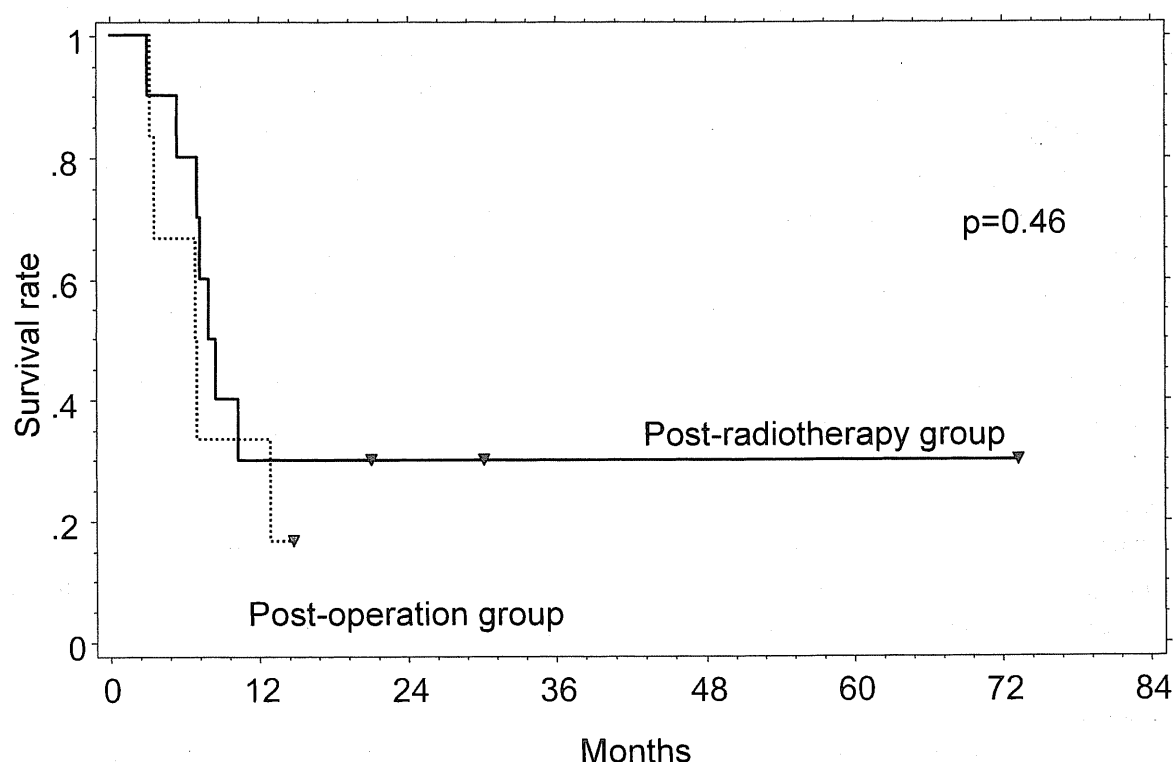


Fig. 3. Overall survival curves by Kaplan-Meier method according to the initial treatment.

Table IV. Results of univariate analyses for survival

|                                |                      |       |
|--------------------------------|----------------------|-------|
| Age                            | <70 vs $\geq$ 70     | 0.091 |
| Performance status             | 1 vs 2               | 0.917 |
| Tumor size                     | <5cm vs $\geq$ 5cm   | 0.408 |
| Total dose                     | <60Gy vs $\geq$ 60Gy | 0.441 |
| Total sessions of hyperthermia | <10 vs $\geq$ 10     | 0.123 |
| Chemotherapy                   | yes vs no            | 0.895 |

possible for 17.8% and significantly extended the survival periods<sup>10)</sup>. In the post-operative recurrence, chemo-radiotherapy is also useful and 3-year overall survival rate of 25% has been reported<sup>11)</sup>. Regarding the recurrence after a chemo-radiation, 25-26.1% of the 5-year overall survival rates were obtained by re-operation<sup>12)13)</sup>, but the re-operation was possible in only 8% cases<sup>14)</sup>. Therefore, role of the chemo-radiation therapy seems important, especially for the inoperable cases with intra-thoracic recurrence of esophageal carcinoma.

We have introduced the local hyperthermia to enhance the local effect of chemo-radiation. In spite of relatively low radiation dosage in our series, high CR rate of 31.3% was obtained, which is thought the effect by the local hyperthermia. CR group also showed significantly better prognosis than PR + NC group. The hyperthermia may be especially effective for the recurrence after radiotherapy, since less radiation dosage must be administered.

We developed the database of intra-esophageal temperature with RF heating device, also reporting that high intra-thoracic temperatures could be easily obtained<sup>6)8)</sup>. Calculated intra-esophageal temperature using this database was nearly the same as direct measurement in six cases of this series. Though significant difference of intra-esophageal Tmax was not observed among CR, PR and NC, relatively higher temperature in the CR group might lead to better local response.

Although several authors have reported good treatment outcome using intra-cavity hyperthermia of the esophagus for primary esophageal carcinoma<sup>15)16)</sup>, there has been no report of hyperthermia for the esophagus using capacitive heating device. In comparison with intra-cavity hyperthermia, capacitive heating device can heat wide area including mediastinal lymph node and treat the patient with esophageal stenosis.

Any factors in the univariate analyses did not show significant differences in survival. Small number of cases of this study may affect the results, and further study including more cases is necessary.

## Conclusion

Thermo-radiotherapy may improve local control in patients with recurrent esophageal carcinoma by enhancing the local effect of chemo-radiation. In particular, hyperthermia may be effective for the recurrence after radiotherapy, in which radiation dosage is limited to less than 50 Gy.

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## 再発食道癌に対する温熱放射線治療

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**要 旨:** 1994 年から 2002 年まで、温熱放射線治療を施行した食道癌再発 16 例の治療成績の検討。再発形式は術後再発 9 名、放射線治療後再発 7 名。放射線治療の総線量は、術後再発群で  $55.1 \pm 9.2\text{Gy}$ 、放射線治療後再発群で  $46.1 \pm 14.3\text{Gy}$  であった。温熱療法は、Thermotron RF-8 を使用し、平均時間  $42.5 \pm 8.0$  分、平均総回数  $10.7 \pm 9.3$  回であった。平均 Tmax は  $44.0 \pm 4.4^\circ\text{C}$  であった。局所制御率 (PR + CR) は 87.5% であった。全例の 5 年生存率は 25.0% であった。CR, PR+NC 群の中間生存期間は、73.4 ヶ月、7.0 ヶ月であった ( $p < 0.001$ )。温熱放射線治療は、食道癌再発に対する局所制御向上に有効であった。