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Results of External Irradiation and Low-Dose-Rate Intraluminal Brachytherapy for Esophageal Cancer

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The results of definitive radiotherapy to elucidate the optimal doses of external irradiation (ERT) and low-dose-rate intraluminal brachytherapy (ILBT) were analyzed. Between 1979 and 1998, 100 patients with esophageal cancer were treated with ERT and ILBT. ERT was given at a dose of 40–65 Gy/25–32 fractions and ILBT at 10–24.3 Gy/2–3 fractions. The 5-year actuarial survival rate for all cases was 13%, and that for patients with tumors of 5 cm or less in length was 22.6%, while for patients with tumors longer than 5 cm the rate was 5% ($p < 0.005$). In patients with tumors of 5 cm or less in length, the local control rate of those whose ILBT dose was 20 Gy or more was 83%, and for those with an ILBT dose of less than 20 Gy the control rate was 26.5% ($p = 0.014$). In patients with tumors of 5 cm or less in length, the results of treatment with 60 Gy ERT and 20 Gy ILBT were promising and did not cause severe late complications.

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In the treatment of esophageal cancer, it is important to obtain local control not only for the survival of patients but also for maintaining their quality of life. Further improvement of local control is therefore required.

Concurrent chemoradiotherapy has recently been used in the treatment of advanced esophageal cancer (1, 2). However, a considerable number of patients are not eligible for this treatment, because most patients with esophageal cancers are in poor general condition. Furthermore, there are reports demonstrating that adverse effects such as a severe or life-threatening esophageal ulcer or perforation can occur at higher rates in patients treated with concurrent chemoradiotherapy than with radiotherapy alone (1, 2).

These patients were treated with radiotherapy alone but the results with this method have been poor (3, 4). Thus intraluminal brachytherapy (ILBT) has been used in addition to external irradiation (ERT) and better results than those obtained with ERT alone have been reported (5, 6). However, the optimal doses of ERT and ILBT are still unclear.

We have been treating patients with esophageal cancer with a combination of ERT and low-dose rate ILBT (LDR-ILBT) for over 20 years. We analyzed the results of the definitive radiotherapy to elucidate the optimal doses of ERT and ILBT.

MATERIAL AND METHODS

Between September 1979 and July 1998, 381 patients with esophageal cancer were treated in the Department of Radiology, Hakodate National Hospital. Of these patients, 141 were treated with definitive radiotherapy with radical intent, 111 were treated with preoperative or postoperative radiotherapy and 129 patients were treated with palliative radiotherapy because of distant metastases at the initial diagnosis, or advanced disease (e.g. esophagotracheal fistura). Out of the 141 patients, 100 received ERT and ILBT, while the other 41 patients received ERT only because they were in poor general condition, or were unable to have ILBT owing to long tumor length, such as over 10 cm, or esophageal stenosis.

The remaining 100 patients without distant metastases, with the exception of metastasis to the supraclavicular lymph nodes, were available for this analysis.

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Patient characteristics

Patients' characteristics are listed in Table 1. Primary tumors were evaluated by the esophagographic and esophagoscopic findings and classified according to the classification of the Japanese Society for Esophageal Disease (7). Most cases (77%) were of the advanced type. Distant metastasis was evaluated by chest X-ray, liver scintigraphy and bone scintigraphy. After 1983, computerized tomography (CT) scans were also used. The regional lymph node could not be assessed because CT scans were not performed in all patients.

Treatment methods

The field of ERT included 3-cm safety margins both above and below the primary lesion and the width was usually 6 or 7 cm. Prophylactic irradiation of the supraclavicular lesion was not performed. Radiation treatment characteristics are listed in Table 2. ERT was initiated with parallel opposing anterior and posterior fields to doses of 35 to 45 Gy and was continued using a pair of anterior oblique fields to total doses of 40–65 Gy.

The clinical procedures for LDR-ILBT have already been reported (8). After local anesthesia was applied to the oral cavity, a flexible, gastric lavage catheter, 1 cm in diameter, was inserted as an outer tube via the mouth into the stomach under fluoroscopy and stabilized in situ.

Table 1

Patients characteristics

Sex	
Male	82
Female	18
Age (mean)	48–88 (69.5)
Site[1]	
Ce (cervical esophagus)	4
Ut (upper thoracic esophagus)	16
Mt (middle thoracic esophagus)	58
Lt (lower thoracic esophagus)	21
Ae (abdominal esophagus)	1
Tumor length	
≤ 5.0 cm	46
> 5.0 cm	54
Esophagographic and Esophagoscopic findings[1]	
Superficial type[2]	23
Advanced type[3]	77
Type 1 (protruding type)	5
2 (ulcerative and localized type)	17
3 (ulcerative and infiltrating type)	53
4 (diffusely infiltrating type)	2
Histology	
Squamous cell carcinoma	90
Adenocarcinoma	1
Adenosquamous carcinoma	1
Unknown	8

[1] According to the classification of the Japanese Society for Esophageal Disease (7).
[2] Superficial type is a tumor confined to submucosal muscle.
[3] Advanced type is a tumor invaded over submucosal muscle.

Table 2

Radiation treatment characteristics

	Mean (range)
External irradiation (ERT)	
Dose per fraction (Gy/fr)	2.2 (2.0–2.5)
Total dose (Gy)	54.1 (40–65)
NTD-2Gy (Gy)	57.1 (40–76.6)
Intraluminal brachytherapy (ILBT)	
Dose per fraction[1] (Gy/fr)	7.1 (6.5–8.0)
Total dose[1] (Gy)	16.4 (10–24.3)
Total dose (ERT+ILBT)	73.5 (60–97.6)
Overall treatment time (days)	69.9 (44–92)

[1] Doses were at the mucosal surface of the esophagus.

Subsequently, an inner tube containing dummy markers was first placed into the outer applicator tube and secured in the desired position under fluoroscopic observation. After the patient had been moved to the treatment room, the inner tube was replaced with a tube containing four or five cesium tubes of 2.22 GBq, arranged longitudinally (Fig. 1). The doses to the mucosal surface of the esophagus

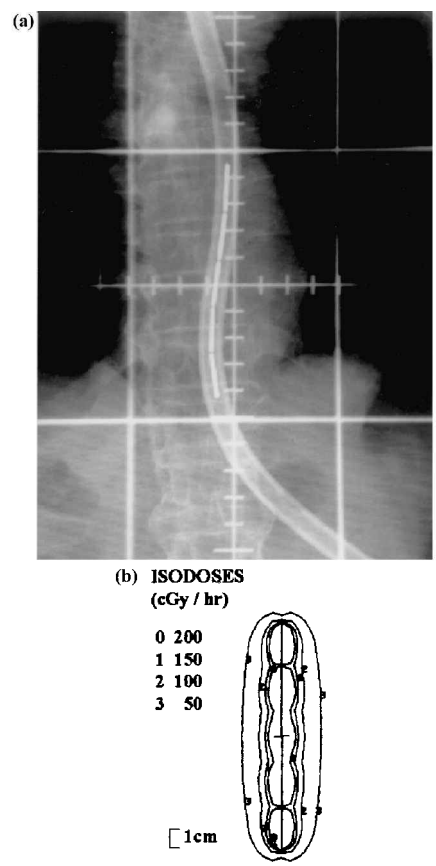

Fig. 1. (a) Simulation film and (b) dose distribution. An inner tube containing a dummy source was placed in the desired position under fluoroscopy.

were 10–24.3 Gy/2–3 fractions. LDR-ILBT was performed once a week after ERT. We did not have a definite policy for chemotherapy at the time of this study, therefore chemotherapy based on cisplatin and 5-fluorouracil was used. Five patients were treated with neoadjuvant chemotherapy and 2 patients with concurrent chemotherapy in order to potentiate the effects of radiotherapy. Because of their poor response to definitive radiotherapy, 14 patients were given adjuvant chemotherapy.

Since 41 patients were not treated with a fraction size of 2 Gy or 5 times a week, we calculated the normalized total dose at 2 Gy (NTD-2Gy) as 2 Gy/fraction 5 times a week using the LQ + time model (9).

$$\text{NTD-2Gy} = \text{SRE} \cdot \text{D},$$

$$\text{SRE} = (1 + \text{d}/\delta - \gamma t'/\alpha\text{d})/(1 + 2/\delta - 0.7\gamma/\alpha)$$

$$\Delta = \alpha/\beta, \ \gamma = \ln 2/\text{Tpot}$$

where, SRE is the 'the standard relative effectiveness', D is the total dose, d is the fraction size, and t' is an average interfraction interval (the total treatment time divided by the number of fractions).

In this study, we defined $\alpha/\beta = 10$ Gy ($\alpha = 0.2$ Gy-1, $\beta = 0.02$ Gy-2), and potential doubling time (Tpot) = 4 days. Radiation treatment characteristics are presented in Table 2.

Evaluation of tumor response

The response of the primary tumor to irradiation was assessed by serial esophagography, endoscopy and biopsies. Esophagography and/or endoscopy was performed every 3–4 months for asymptomatic patients, and any clinically suspected tumor recurrence required biopsy and histopathological proof. CT scans were obtained at 3- to 6-month intervals for most recent patients, and those were used for evaluation of any recurrence of primary tumors and regional lymph nodes. Local control was defined as no evidence of clinical or pathological primary tumor recurrence.

The median follow-up to last contact or death was 26.9 months, ranging from 3 to 132 months. The cut-off for analysis was October 1999.

Analysis of the treatment outcomes

Survival plots were made using the Kaplan–Meier method and statistical analysis was carried out using the log-rank test. The survival curves were calculated from the start of radiotherapy. Fisher's exact probability test was used for testing among prognostic factors. Multivariate analysis was performed using Cox's proportional hazards model.

RESULTS

Survival

Thirteen patients were still alive and 87 patients had died at the cut-off date. Of the 13 surviving patients, 8 were disease free and 5 were alive with disease. Of the 87 patients who died, 51 died of locoregional recurrence, 12 died of distant metastases, and 22 patients died of other diseases. Of the 22 patients who succumbed to other diseases, 7 died of pneumonia, 4 of cardiac disease, 3 of other cancers (ureter, hypopharynx, gastric leiomyosarcoma), 2 of cerebrovascular disorders, 1 patient of renal insufficiency, 1 patient committed suicide, and the other 4 patients died of unknown causes. Autopsies were not performed in all cases. In addition, there were two treatment-related deaths, one due to radiation pneumonitis and the other due to complications of a salvage operation.

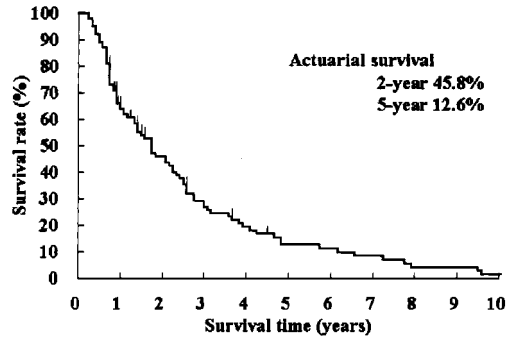

Fig. 2. Actuarial survival rates of all patients.

The 2-year and 5-year actuarial survival rates of all cases were 45.8% and 12.6%, respectively (Fig. 2).

According to tumor length, the 2-year and 5-year actuarial survival rates of patients whose tumor lengths were 5 cm or less were 59.5% and 22.6%, respectively, and for those longer than 5 cm they were 33.8% and 4.5%, respectively (Fig. 3). A significant difference was found between the two groups using the log-rank test ($p < 0.005$).

According to esophagographic type, the 2-year and 5-year actuarial survival rates of patients with the superficial type were 76.6% and 20.4%, and those of advanced type were 36.5% and 10.6%, respectively (Fig. 4). A significant

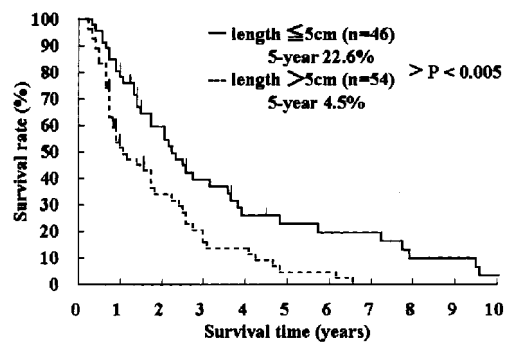

Fig. 3. Actuarial survival according to tumor length.

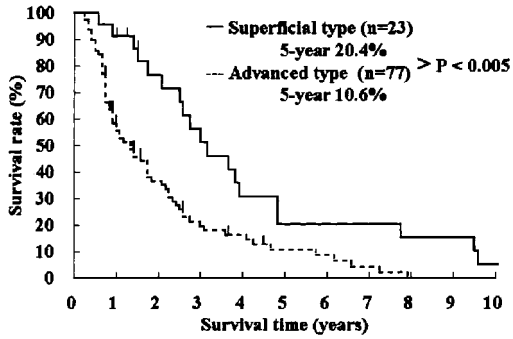

Fig. 4. Actuarial survival according to esophagographic findings.

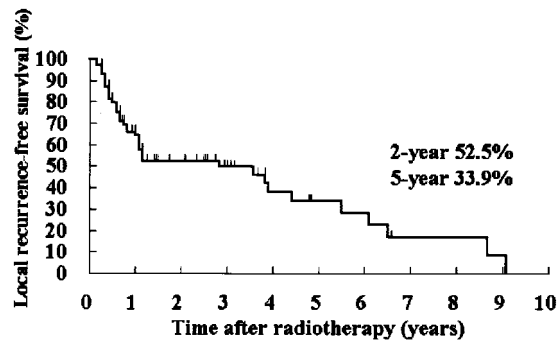

Fig. 5. Local recurrence-free survival in 70 cases with complete response (CR). 'Time after radiotherapy' is the interval from the completion of radiotherapy to the last follow-up date, or the date on which local recurrence had taken place.

difference was found between the two groups using the log-rank test ($p < 0.005$).

Response to radiotherapy (Table 3)

A complete response (CR) was obtained in 70 patients, a partial response (PR) in 25, no change (NC) in 3, and progressive disease (PD) in 2. The CR rate was 70.0%.

The CR rate of patients with tumor lengths of 5 cm or less was 78.3% (36/46), and that of patients with tumors longer than 5 cm was 59.3% (32/54). There was a significant difference between these CR rates ($p = 0.034$).

The CR rate for the superficial type was 100% (23/23), and that of advanced type was 61.0% (47/77). There was a significant difference between these CR rates ($p = 0.001$).

Local recurrence (Fig. 5)

Forty-one out of 70 patients who obtained CR had local recurrence. The 2-year and 5-year local recurrence-free survival rates were 52.5% and 33.9%, respectively; 10 out of 41 local recurrences (24%) occurred more than 2 years after radiotherapy. Eight recurrences were within the radiation field and two were outside the field. Even more than 5 years after radiotherapy, 4 patients had local recurrence within the radiation field.

Table 3

CR rate according to esophagographic findings after the initial radiotherapy

CR rate	
All cases	70.0% (70/100)
Tumor length	
≤5.0 cm	78.3% (36/46)[1]
> 5.0 cm	59.3% (32/54)
Esophagographic findings	
Superficial type	100% (23/23)[2]
Advanced type	61% (47/77)
Type 1 (protruding type)	80% (4/5)
2 (ulcerative and localized type)	64.7% (11/17)
3 (ulcerative and infiltrating type)	60.4% (32/53)
4 (diffusely infiltrating type)	0% (0/2)

[1] Significant differece between ≤5.0 cm and > 5.0 cm $p = 0.034$.
[2] Significant difference between the superficial type and advanced type ($p < 0.001$).

Prognostic factors using multivariate analysis

Age, sex, tumor length, esophagographic type, total radiation dose (doses of ERT normalized by NTD-2Gy + doses of ILBT) and overall treatment time were analyzed by multivariate analysis for prognostic significance for disease-specific survival in all cases (Table 4). Males had significantly higher hazards ratios than females ($p = 0.043$). Esophagographic type 2 (ulcerative and localized type) and type 3 (ulcerative and infiltrating type) had significantly higher hazards ratios than the superficial type ($p = 0.020$ and $p = 0.001$, respectively).

The relationship between local control and radiation doses of ILBT (Table 5)

Thirteen patients who obtained local control but whose follow-up periods were less than 2 years were excluded from this analysis. In patients with tumors of 5 cm or less in length, the local control rate of those treated with more than 20 Gy ILBT was 83% (5/6), and 26.5% (9/34) for those whose dose of ILBT was less than 20 Gy. There was a significant difference between them ($p = 0.014$). However, in patients with tumors of more than 5 cm in length, an even larger ILBT dose than 20 Gy did not improve the local control rate.

Adverse effects

One patient died of radiation pneumonitis. No severe radiation ulcer or perforation of the esophagus occurred. Esophageal stricture developed in 2 patients, but they were able to eat after endoscopical bougienage.

Table 4

Multivariate analysis of prognostic factors for disease-specific survival in all cases

Variable	Hazard ratio	95% CI	p-value	Better prognosis
Age	0.973	0.939–1.008	0.132	
Sex				
Male	2.160	1.026–4.549	0.043	Female
Female	1			
Tumor length (cm)	1.102	0.995–1.272	0.184	
Esophagographic findings				
Superficial type	1			Superficial type
Advanced type				
Type 1	1.903	0.411–8.809	0.410	
Type 2	3.619	1.221–10.726	0.020	
Type 3	5.673	2.016–15.962	0.001	
Total radiation dose (Gy) (ERT + ILBT)	1.015	0.978–1.053	0.441	
Overall treatment time (days)	1.007	0.990–1.024	0.428	

CI = confidence interval.

Salvage operation

Salvage operations were performed in 10 patients who had local recurrences and in one patient who could not obtain local control after radiotherapy. One patient died of complications of the salvage operation. The mean survival time after the salvage operation of 10 patients was 40.8 months (range, 3–117 months).

Double cancer

Double cancers were seen in 17 patients (17%). Of these, 7 were synchronous (hypopharynx 2, tongue 1, ureter 1, stomach 1, colon 1, prostate 1), and 10 were metachronous (hypopharynx 2, oropharynx 1, floor of mouth 1, stomach 4, thyroid 1, lung 1).

DISCUSSION

The 5-year survival rate is about 10% in patients with locally advanced esophageal cancer when they are treated with doses of 50–70 Gy ERT (4, 6, 10). However, doses of more than 70 Gy ERT are difficult to administer because of the danger of severe complications. In our study, by adding ILRT after ERT, we could obtain 5-year actuarial survival rates: 12.6% for all patients, and 10.6% for advanced type tumors, although there may have been a selection bias because the patients whose esophageal stenosis was too severe to insert an applicator tube after ERT were excluded.

Tumor length was a significant prognostic factor in patients with esophageal carcinoma treated with ERT alone (5, 8). In our study, patients whose tumor length was 5 cm or less had significantly better CR and survival rates than those with tumors of more than 5 cm in length. Other institutions that use ERT and ILRT have reported similar results (5, 8) in accordance with our results, indicating that it is difficult to cure esophageal tumors longer than 5 cm, even with ERT and ILRT.

The CR rate for tumors of the superficial type was 100% and that for the advanced type was 61%. There was a significant difference between them ($p < 0.001$). The disease-specific survival rates of patients with the superficial type were also significantly better than those for the advanced type. Thus, the existence of invasion over the submucosal muscle is an important prognostic factor for local control with radiotherapy. There have been similar reports of treatment with radiotherapy alone. Okawa et al. reported a 7.2% 5-year survival rate for the advanced type of esophageal cancer treated with ERT alone (10), while they recently reported a 45% 5-year survival rate for the superficial type of esophageal cancer treated by ERT alone (11). In advanced type cancer, there was a difference in CR

Table 5

The relationship between local control and dose of ILBT

Tumor length	Dose of ILBT at mucosal surface	No. of patients	No. of patients with recurrence	Local control rate
<5 cm	<20 Gy	34	25	26.5%
	≥20 Gy	6	1	83.3%[1]
≥5 cm	<20 Gy	31	23	25.8%
	≥20 Gy	16	12	25.0%

'Local control' defined as patients who could obtain local control for 2 years.

[1] Significant difference between the two groups ($p = 0.014$).

rates among types (Table 3). Type 3 (ulcerative and infiltrating type) had a poorer disease-specific survival than Type 2 (ulcerative and localized type) as assessed by multivariate analysis, indicating the radioresistance of tumors with strong invasive characteristics.

In our study, using LDR-ILBT, severe late complications were not seen, even though some patients were irradiated with 65 Gy ERT and 20 Gy/3 fractions of LDR-ILBT. Several papers have reported that late complications such as esophageal stricture or perforation occurred in patients treated with high-dose-rate ILBT (HDR-ILBT) (12–15). Hishikawa et al. reported that 15 out of 148 patients (10%) had esophageal stricture and 6 patients (4%) had esophageal fistulas after 60 Gy ERT and 12 Gy/2 fractions at 5 mm beyond the surface of the esophagus of HDR-ILBT (12). Yorozu et al. mentioned that 10 out of 58 patients (17.1%) had esophageal stricture after 40–60 Gy ERT and 16–24 Gy/4 fractions at 5 mm beyond the surface of the esophagus of HDR-ILBT (13). The incidence of late complications for our method was much lower than that for HDR-ILBT.

In this series, out of 11 patients who underwent salvage surgery, one patient died as a result of the complications of the operation in 1980. There have been no complications in recent cases. In the case of surgery alone, operative mortality is usually 10% or less (16, 17). The addition of preoperative radiotherapy and chemotherapy increases complications (18). However, in our experience, the addition of LDR-ILBT did not increase mortality of salvage surgery.

In patients with tumors of 5 cm or less in length, 35% (14/40) of local control was obtained. Those treated with 20 Gy ILBT or more had better local control than those treated with less than 20 Gy. In patients with tumors longer than 5 cm, 20 Gy LDR-ILBT or more could not improve the local control, indicating that it was difficult to obtain local control of advanced tumors measuring 5 cm or more, despite treatment with ILBT. However, irrespective of the dose of ILBT, local control was obtained in some tumors of 5 cm or more in length. These tumors might have been radiosensitive for various reasons. Our current recommendation for radiotherapy for esophageal carcinoma is 60 Gy/30 fractions by ERT and 20 Gy at the surface/3 fractions, once a week by LDR-ILBT.

In conclusion, we obtained an 83% local control rate in patients with tumors of 5 cm or less in length with ERT doses of 60 Gy and ILBT doses of 20 or 22 Gy. We think that LDR-ILBT is a promising boost therapy after ERT, since this treatment can be appropriate for patients whose general condition is not sufficient to tolerate concurrent chemoradiotherapy. The addition of LDR-ILBT did not cause severe late complications.

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