

## Result of Radiotherapy for Esophagus Cancer

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Among 165 patients of esophagus cancer treated by either radiation alone or postoperative radiation, median survival period was 6.6 months, 16% 3 years and 8% 5 years crude survival. In biphasic plotting of survival curve semilogarithmically all nonresponder died within one year regardless of treatments and in responder each 1, 2, 3 years survival rate was 80%, 70%, 60% in the group of postoperative radiation among 20 patients (54% of 37 patients) respectively and 62%, 38%, 23% each in the group of radiation alone among 61 patients (48% of 128 patients) respectively, better survival rate of postoperative radiation vs radiation alone in 3 year ( $P < 0.01$ ).

The most common cause of death was dysphagia 55%, and majority of patients died by failure to control the disease locally 62%, 88% of stricture were associated with persistence of cancer in esophagus. 50% of patients was found to have locoregional metastatic nodes. Preoperative diagnostic failure rate was for metastatic locoregional nodes was 54%, for grossly metastatic nodes 29.7%, for blood borne organ metastasis 13.5%, and for local extent of the disease 14%.

The residual cancer at surgical margin c. positive node was not effectively killed by either 5000 to 5500 cGy conventional radiation or 5290 to 5750 cGy with 115 cGy fraction in 2 times daily; hyperfractionated radiation. However hyperfractionation schedule decreased the both acute and late complications in this study.

**Key Words:** Esophagus cancer, Radiotherapy

### INTRODUCTION

In 1978 first linear accelerator was installed at Kosin medical center. Since then 260 patients of esophagus cancer have been treated by irradiation and postoperative irradiation. As reported by others<sup>3,4,13,21</sup> the result of our treatment is not promising. The purpose of this study is for analysis of our radiotherapy data in comparison with others for future pertinent treatment modality and technique to improve survival rate. The data analysis and the results of hyperfractionated irradiation is preliminary, however.

### MATERIALS AND METHODS

260 patients (255 male and 5 female) with the esophagus cancer were treated by radiotherapy between 1978 and 1985, however 165 patients of those were studied because valuable informations were available for analysis of survival data on basis of visiting hospital or replied questionnaire. The

other 95 patients were lost to follow up (36.5%).

#### 1. Age Distribution of Patients

35 of 260 patients were less than 49 years of age, 205 patients were between 50 and 69 year old and 20 patients were older than 70 years of age (Fig. 1).

#### 2. Site

The site of esophagus cancer was divided in 3 parts; the upper third was from the entrance of esophagus to the upper edge of the aortic arch, middle third from the latter to the lower edge of the pulmonary arteries and the lower third from the latter to the stomach cardia.

The esophagus cancer distributed in these three parts were 25 patients (20%), 82 patients (64%) and 21 patients (16%) respectively in radiation alone group (128 patients), and no patients (0%), 20 patients (54%) and 17 patients (46%) respectively in postoperative radiation group (37 patients). Among 128 patients of radiation alone group we divided into subgroups of regularly fractionated radiation (95 patients) and hyperfractionated radiation (33 patients). There were 22 patients (23%), 54 patients (57%) and 19 patients (22%) each in upper

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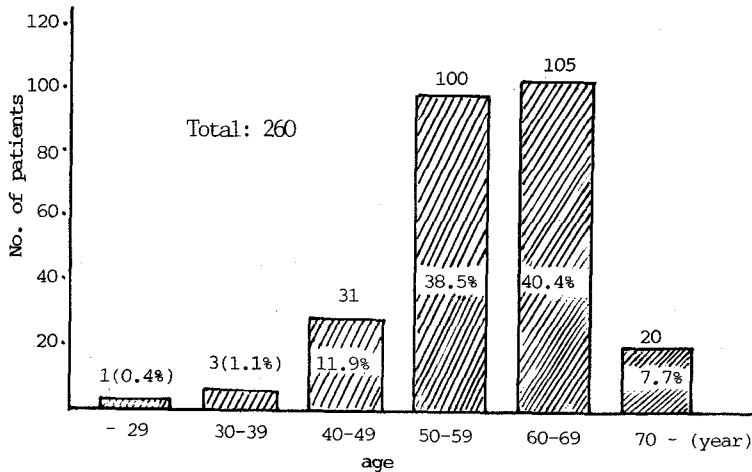


Fig. 1. Age distribution of patients of esophageal cancer.

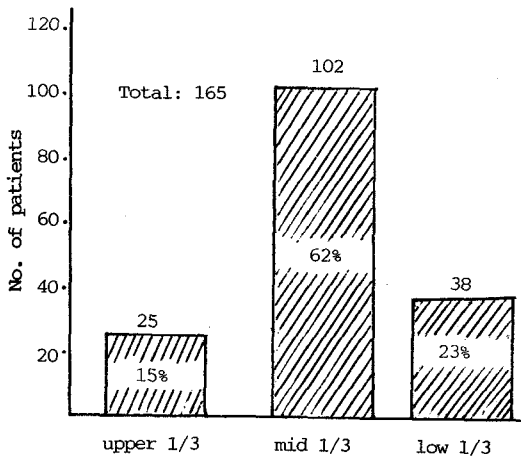


Fig. 2. Involved site of the esophagus cancer.

1/3, middle 1/3 and lower 1/3 of esophagus in the subgroup of regularly fractionated radiation and 3 patients (9%), 28 patients (85%) and 2 patients (6%) respectively each in upper 1/3, middle 1/3 and lower 1/3 of esophagus in the subgroup of hyperfractionated radiation (Fig. 2).

### 3. Staging

In 128 patients of radiation alone group, there were 10 patients (7.8%) in stage I, 38 patients (29.7%) in stage II, 78 patients (60.9%) in stage III, and 2 patients (1.6%) in stage IV, and in 37 patients of postoperative radiation group, there were 2 patients (5.4%) in stage I, 10 patients (27%) in stage II, 24 patients (64.9%) in stage III and 1 patient (2.7

%) in stage IV. (Fig. 3). In 95 patients of subgroup of regularly fractionated radiation, there were 9 patients (9.5%) in stage I, 30 patients (31.6%) in stage II, 55 patients (57.9%) in stage III and 1 patient (1%) in stage IV, and in 33 patients of subgroup of the hyperfractionated radiation, there were 1 patients (3%) in stage I, 8 patients (24.2%) in stage II, 23 patients (69.7%) in stage III, and 1 patient (3%) in stage IV.

### 4. Histopathologic Type

Out of 260 of all irradiated patients at our institution, 227 patients (87.3%) were well to moderately differentiated squamous cell carcinoma, that was the most frequent histologic type, 27 patients (10.4%) of next order was undifferentiated carcinomas and adenocarcinoma was found in only 6 patients (2.3%) (Table 1).

### 5. Clinical Symptoms and Signs, and Duration of Symptoms

As seen in table 2 most frequent clinical problem was dysphagia in 96.5% of total 260 patients and associated weight loss in 92.3%. Next order was odynophagia in 25.8%, substernal pain 23.8%, and vomiting/ regurgitation and hoarseness was least frequent symptoms in 11.2% patients each. We found most of patients take 3 to 6 months to have final diagnosis as seen in Fig. 4.

### 6. Radiotherapy Technique

1) Curative regularly fractionated radiation (RFR); total doses of 6000 cGy in 6 to 7 weeks with

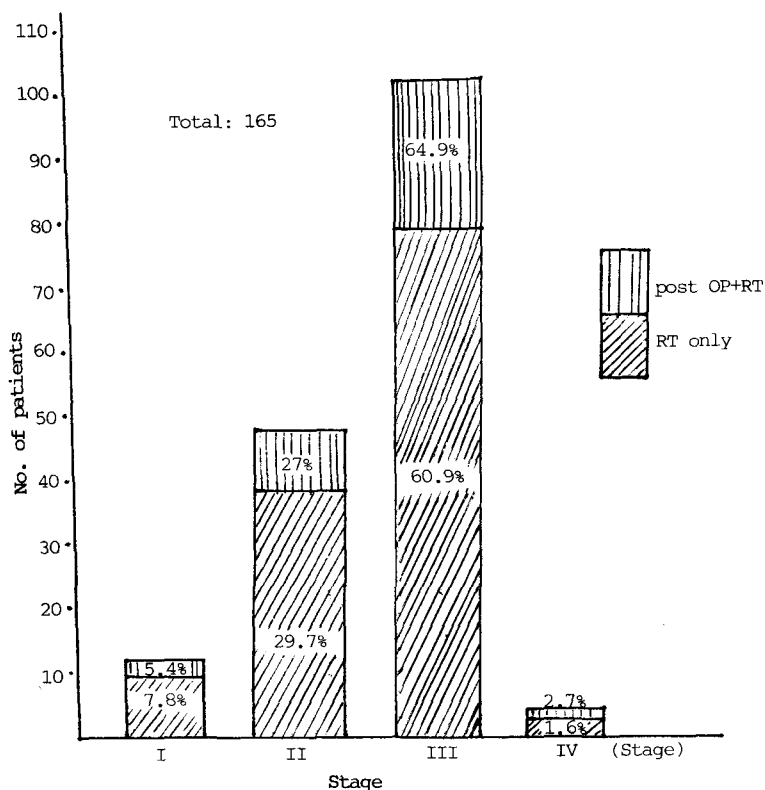


Fig. 3. Frequency of staging of esophagus cancer treated.

Table 1. Cell Type of Esophageal Carcinoma

Cell type	No. of patient	Rate (%)
Squamous cell carcinoma	227	87.3
Adenocarcinoma	6	2.3
Undifferentiated or poorly differentiated	27	10.4
Total	260	100

180 to 200 cGy fractional dose via 3 field technique were given. Radiation field encompassed longitudinally 6 cm and 3 cm laterally from the margin of gross tumor seen on esophagography and CT (computerized tomography). At total dose 4000 to 4500 cGy the field size was reduced to encompass the residual lesion by 90% isodose curve. Occasionally anterior and posterior parallel opposing portals were used for the lesions of lower 1/3 of esophagus and of low cervical esophagus.

2) Hyperfractionated radiation (HFR); total

Table 2. Main Symptoms at the Time First Seen

Symptoms	No. of patient	Rate (%)
Dysphagia	251	96.5
Weight loss (Mean loss of weight : 4.93 kg)	240	92.3
Odynophagia	67	25.8
Vomiting/Regurgitation	29	11.2
Substernal pain	62	23.8
Hoarseness	29	11.2
Others (Hematemesis, cough, dyspnea, aphagia, etc.)	34	13.1

doses of 6900 cGy in 6 weeks with 115 cGy fractional dose, 2 fractions per day in 4 to 6 hours interval, 5 treatment days per week were given. At total doses of 4600 cGy the radiation field was reduced. Others were same as those of curative RFR.

3) Postoperative radiotherapy; in postoperative RFR total doses of 5000 to 5500 cGy with 180 to 200

cGy fractional dose in 5 to 6 weeks were given and the others were same as curative RFR. In postoperative HFR total doses of 5290 to 5750 cGy in 5 weeks were given and others were same as those of HFR. Among 165 patients 128 patients (77.6%) were treated in curative attempt by radiation alone; 95 patients (74.2%) by RFR and 33 patients (25.8%) by HFR. 37 patients (22.4%) were treated by postoperative radiotherapy; 16 (43.2%) of them was treated by postoperative RFR and 21 (56.8%) by postoperative HFR.

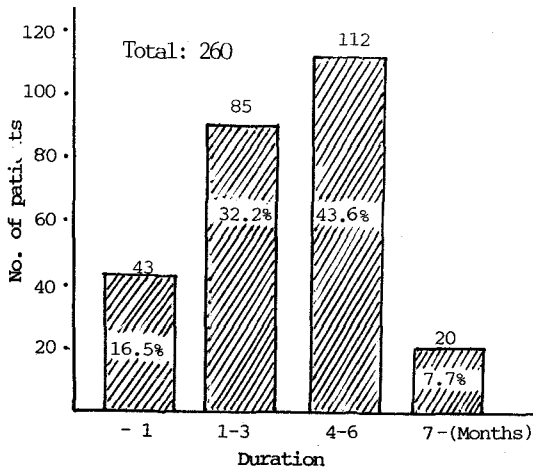


Fig. 4. Duration of chief complains of symptoms to diagnosis.

### 7. Operation

The operation was performed as the cancer was not to extend beyond adventitia into adjacent tissue and was found not to metastasize in mediastinum and other organs. The esophagus was resected at 5 cm above the margin of gross cancer with esophagectomy with esophagogastrostomy and the enlarged lymph nodes, if its were enlarged or suspicious to metastasis, were removed at the time of operation.

### 8. Data Analysis

Each 6 months interval of survival period from the end of radiation encountered in each patient for crude survival rate and duration of survivals were analyzed in regarding treatment parameters and nontreatment parameters. The numbers of patients alived in each 6 month period after radiation were plotted semilogarithmically belonging to each treatment parameter and nontreatment for figuring survival curve<sup>10</sup>. The analyzed data were compared in chi-square test.

## RESULTS

### 1. Survival Rate

Median survival period was 6.6 months, and among total 165 patients 58 patients were alived for 1 year, 35 patients for 2 years, 26 patients for 3

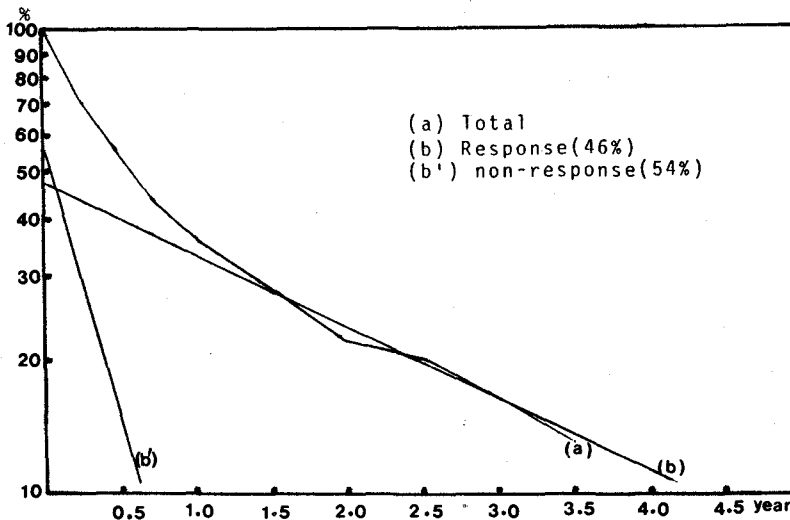


Fig. 5. Survival rate of total patients of esophageal cancer and analysis of two compartments with the response and the non-response to radiotherapy.

years, 22 patients for 3.5 years, and only 6 patients for more than 5 years. Thus, survival rate for 1, 2, 3 years and 5 years was 35%, 21%, 16% and 8%, each as seen Fig. 5. Only 6 patients were alive more than 5 years following radiation alone and 5 years survival rate by radiation alone was 9%.

The survival curve exhibited biphasic components when plotted semilogarithmically; the first steeper component interpreted as nonresponder was 54% and second slow regression component interpreted as responder was 46%<sup>10)</sup>. All patients of nonresponder died within one year and responders were alive 70% in one year, 47% in 2 years, 34% in 3 years and 29% in 3.5 years as seen in Fig. 6.

In comparison between the group of radiation alone and postoperative radiation, survival rate of 46% for one year, 38% for 2 year and 32% for 3 year in the group of postoperative radiation was superior to survival rate of 32% for one year, 18% for 2 years and 12% for 3 years in the group of radiation alone. However, survival rate in significant statistics was found in the group of postoperative radiation in 2 years follow up ( $P < 0.01$ ) (Fig. 7). As seen in Fig. 8, all nonresponder regardless of radiation alone (52%, 67 patients respectively) or postoperative radiation (46%, 17 patients respectively) died within one year. In responder each 1, 2, 3 year survival rate was 80%, 70%, 60% in the group of postoperative radiation among 20 patients (54%), respectively and 62%, 38%, 23% each in the group

of radiation alone among 61 patients (48%), respectively.

Table 3 shows survival rate of patients who were treated by postoperative radiation in correlation with the presence of residual disease at resection margin and/or locoregional metastatic lymph nodes postoperatively in review of surgical specimen. Positive nodes in paraesophageal or mediastinal nodes revealed worse in prognosis than if residual disease at surgical margin. Residual disease at surgical margin was 14% of 37 surgically resected patients and 4 of them died within 3 years, 21 of 37 patients had nodes positive, 57%, and 20 of them died within 3 years, 17 of 37 patients had either residual disease at surgical margin or positive nodes, 46%, and 13 of them died within 3 years. Its survival rate was 24% in 3 years. 4 patients (11%) were both positive and all of these were died within one year.

Each 11 patients of surgical margin negative or nodes negative were alive, more than 3 years, and 3 years survival rate was 34% and 69% each respectively. Best survival was found in 8 of 16 patients with both surgical margin and nodes negative, 50% survival rate. In comparison of survival between the group of RFR and HFR, no difference was found in early survival but long term survival after 3 years seemed to be better in the group of HFR as seen in Fig. 9.

However, there was no significance in statistics

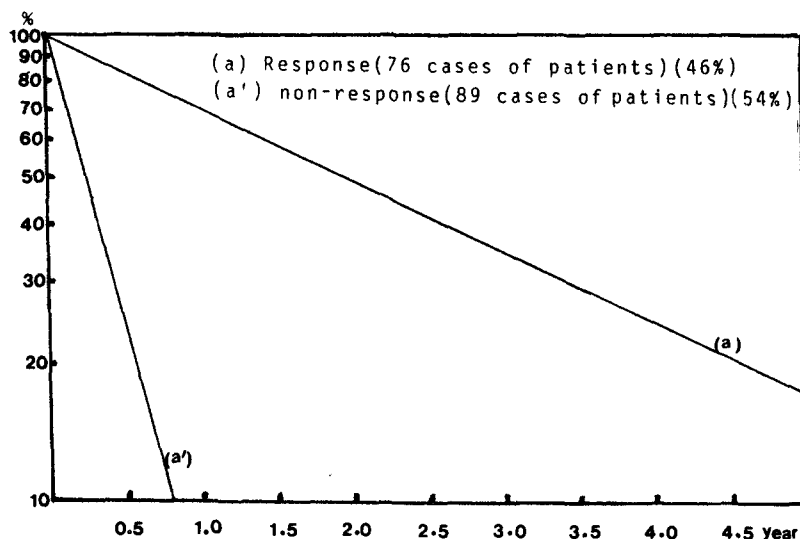


Fig. 6. Survival rate of patients of the esophageal cancer the response and the non-response to radiotherapy between July 1987 and Sep. 1985. ( ) : % of response to radiation.

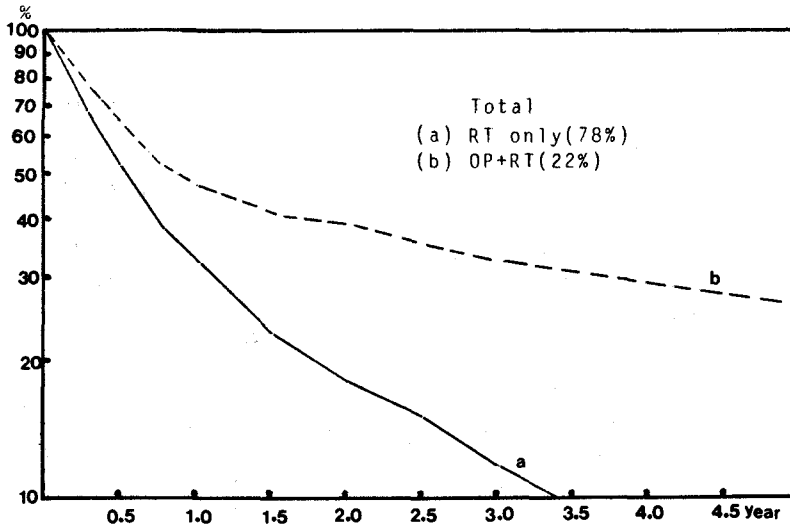
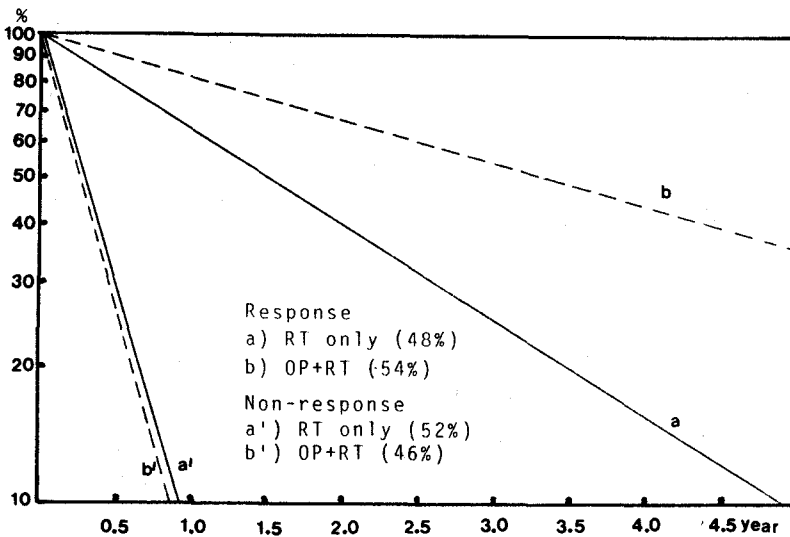


Fig. 7. Comparative survival rate between the radiotherapy and the postoperative radiotherapy.



Tit. 8. Comparative survival rate between the radiotherapy and the postoperative radiotherapy in the response and the non-response fraction to radiotherapy ( ) : % of response to radiation.

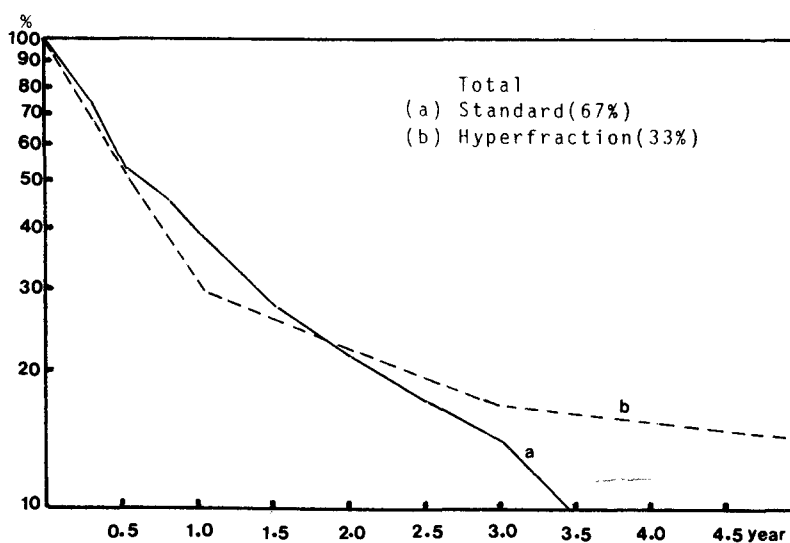
due to small number of patients. Fig. 10. shows two linear regression survival curve of RFR and HFR on plotting semilogarithmically. All patients of non-responder to radiation died within one year regardless of methods of treatment. The subgroup of RFR showed better % of response to radiation than those of HFR (48% vs 41%, 53 of 111 patients vs 22

of 54 patients). In responder the subgroup of HFR exhibited 78%, 55%, 41% and 36% in 1, 2, 3 and 3.5 year survival rate contrasted to 64%, 43%, 28% and 19% in 1, 2, 3 and 3.5 year survival rate of the subgroup of RFR as seen in Fig. 10. The statistically significant superiority was found in responders of HFR at 3 year survival ( $P < 0.05$ ). However, table 4

**Table 3.** Correlation of Survival and Residual Disease Postoperatively upto 3 Year Follow Up

		No. of patients	years of alive		
			1	2	3-
Surgical margin	positive	5 (14%)	3 (60%)	1 (20%)	1 (20%)
	negative	32 (87%)	15 (47%)	12 (38%)	11 (34%)
Postoperative lymph node metastasis	Positive	20 (54%)	6 (30%)	2 (10%)	1 (5%)
	negative	17 (46%)	12 (71%)	11 (64%)	11 (64%)
Surgical margin or lymph node positive		17 (46%)	7 (41%)	5 (29%)	4 (24%)
Both surgical margin and lymph node positive		4 (11%)	0		
Both surgical margin and lymph node negative		16 (43%)	10 (63%)	9 (56%)	8 (50%)

Total : 37

**Fig. 9.** Comparative survival rate between the standard radiotherapy and the hyperfractional radiotherapy.**Table 4.** Survival Comparison Between Regularly Fractionated and Hyperfractionated Radiation in Curative Radiation Attempt

Survival period (year)	0.25	0.5	0.75	1.0	1.5	2.0	2.5	3.0	3.5	4.0
Regularly fractionated RT 95 patients (74%)	72 (67)	54 (57)	47 (49)	39 (41)	27 (28)	20 (21)	16 (17)	12 (13)	7 (7)	6 (6)
Hyperfractionated RT 33 patients (25%)	18 (55)	11 (33)	2 (6)	2 (6)	2 (6)	1 (3)	1 (3)			

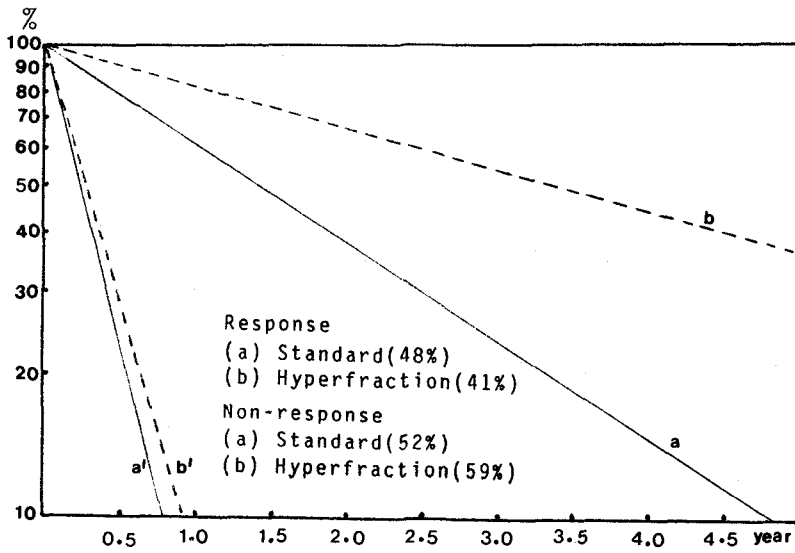


Fig. 10. Comparative survival rate between the standard radiotherapy and the hyperfractional radiotherapy with the response and the non-response fraction to radiotherapy ( ) : % of response to radiation.

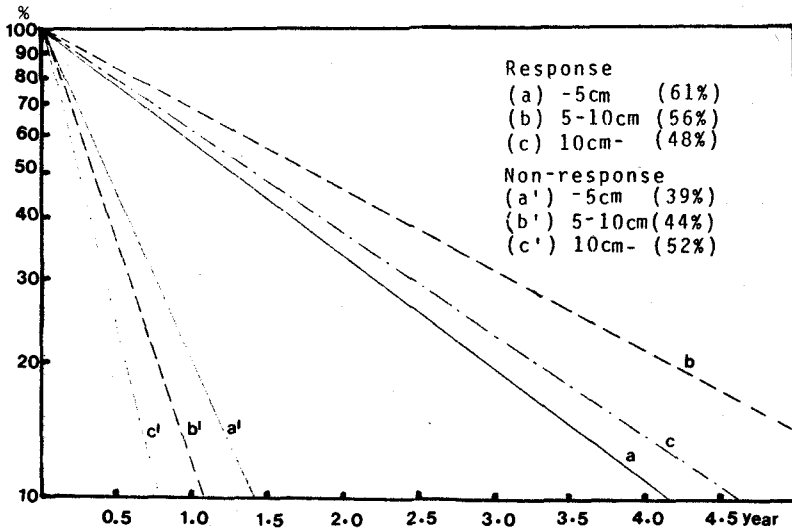


Fig. 11. Comparative survival rate depending on the length of involved segment of esophagus in the response and the non-response fraction to radiotherapy. ( ) : % of response to radiation.

demonstrates clear inferiority of the HFR in survival figure in radiation alone group. Thus, superiority of later survival rate in HFR was due to less late complications that could be attributed to improvement of survival rate because local control of esophagus cancer itself was done by surgical

resection before irradiation.

There was no difference of survival rate according to clinical staging as seen in Fig. 11. The Fig. 12. shows survival curve in different age group. The patient less than 49 years old tended to have better survival than the other older age group. Fig. 13.



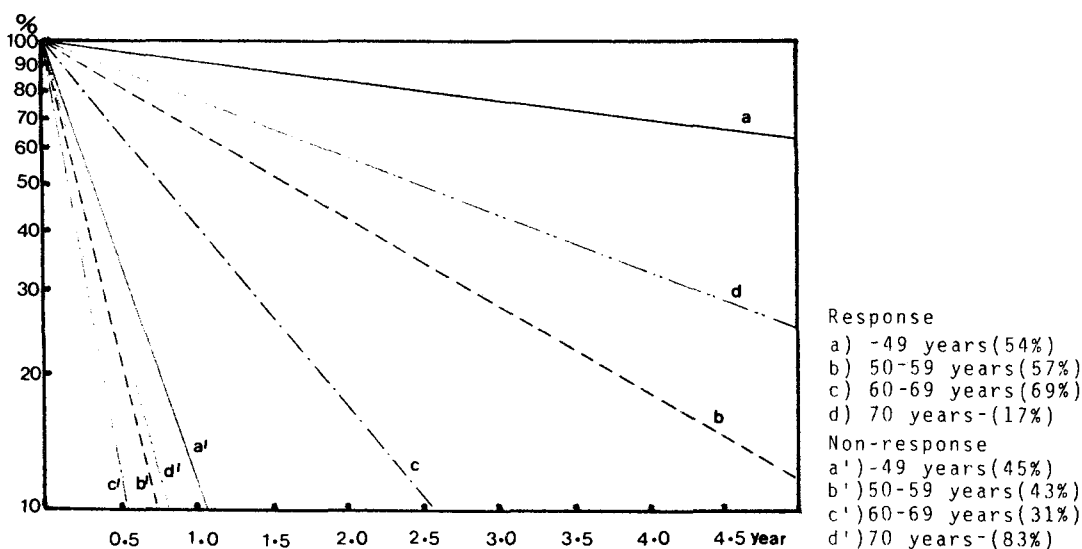


Fig. 12. Comparative survival rate of patient's age of esophageal cancer in the response and non-response fraction to radioterapy. ( ) : % of response to radiation.

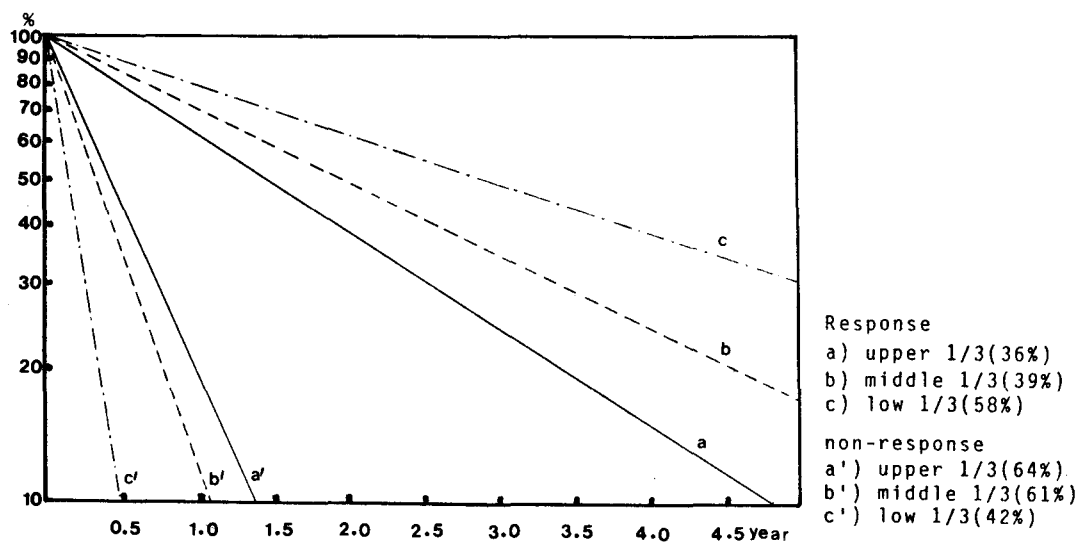


Fig. 13. Comparative survival rate of the involved site of the esophagus in the response and the non-response fraction to radiotherapy. ( ) : % of response to radiation.

exhibits superior survival figure of the cancer located at lower one third of esophagus, that was contributed by surgery.

## 2. Causes of Death and Treatment Failures

Causes of death are listed in Table 5. Dysphagia was the most frequent cause of death (26.5%), and

next order was dysphagia with dyspnea (22.9%), poor general state (17.5%), dyspnea with chest discomfortness (11.4%) and unknown (7.2%). The group of the RFR showed 62% of death and 38% in the group of HFR. The group of radiation alone shows 79.4% of total death in contrast to 20.6% of death in the group of postoperative radiation.

There were 62% failure in 89 of 143 patients to control the disease locally and 89% of strictures in 58 out of 66 patients were associated with persistence of malignancy in esophagus as seen in table 6. The 51 of 111 patients treated by RFR developed esophageal strictures (46%). The complications such as pneumonitis, mediastinitis with fibrosis and variceal bleeding were 18.9% of treatment failure. Approximately 17.5% of the patients treated by radiation alone and postoperative radiation died by mediastinitis and mediastinal fibrosis with/or myocarditis and pneumonitis.

**Table 5. Causes of Death**

Symptoms/signs	No. of sx/signs
Dysphagia with poor intake	44 (25.6%)
Dysphagia with dyspnea	38 (22.9%)
Dyspnea with chest discomfortness	19 (11.4%)
Hematemesis	7 ( 4.2%)
Hemoptysis	5 ( 3.0%)
Tracheoesophageal fistula	9 ( 5.4%)
Poor general state	29 (17.5%)
Sudden death	2 ( 1.2%)
High fever	1 ( 0.6%)
Unknown	12 ( 7.2%)
<b>Total</b>	<b>156 causes (100%) in 143 patients</b>

### 3. Locoregional Lymph Node Metastasis

Table 7 demonstrates the distribution of metastatic lymph nodes in 165 patients, numbers in parenthesis in the column of each different treatment are newly developed metastatic lymph nodes during follow up period. Total 82 of 165 patients (49.7%) was found to have metastatic lymph nodes in either mediastinum, or supraclavicular and neck, or abdominal nodes before radiotherapy or during follow up period. New development of metastasis in lymph nodes was 19% of all patients that was not effected by modality of treatment. In attention to metastasis in the postoperative radiation group 11

**Table 6. Causes of Treatment Failure**

Benign stricture	8 ( 5.6%)
Malignant stricture by persistent cancer	58 (40.6%)
Local recurrence	16 (11.2%)
Persistent cancer bleeding	5 ( 3.5%)
Metastasis	8 ( 4.6%)
Pneumonitis	7 ( 4.9%)
Mediastinitis or/with myocarditis and mediastinal fibrosis	18 (12.6%)
Variceal bleeding	2 ( 1.4%)
Tracheoesophageal fistula	9 (6.3%)
Unknown	12 ( 8.45%)
<b>Total</b>	<b>143</b>

**Table 7. Locoregional Lymph Node Metastases Found in Patients of the Esophagus Cancer**

Site of nodal metastasis	RT alone		Postoperative RT	total
	Regular fractionated RT	Hyperfractionated RT		
Neck nodes	4 (2)	2 (1)	1 (1)	7 (4)
Supraclavicular nodes	21 (6)	10 (4)	5 (2)	36 (12)
Mediastinal nodes	16 (7)	4 (1)	9 (3)	29 (11)
Abdominal nodes	3 (1)	2 (1)	5 (2)	10 (4)
Total nodal metastasis	44 (16)	18 (7)	20 (8)	82 (31)
Total No. of patient	95	33	37	165
New metastasis rate during follow up	16.8%	21.2%	21.6%	18.8%
total lymph node metastasis %	46.3%	54.5%	54%	49.7%

- \* Mean total lymph nodes metastasis in patients treated by RT alone : 50.4%
- ( ) : No. of new development of metastasis during follow up period
- failure rate of diagnosis before operation : 20/37 = 54%
- failure rate of diagnosis of grossly metastatic node before operation : 11/37 = 29.7%

of 37 cases (29.7%) revealed preoperative diagnostic failure rate for the detection of gross disease in lymph nodes by the computerized tomography (CT scan) that procedure was performed as routine at our institution. The diagnostic failure rate concerning microinvasive nodes was found higher 54%. The rate of newly developed lymph node metastasis was also slightly higher in the group of HFR.

#### 4. Analysis of Blood Borne Metastasis

26 of 165 patients (15.8%) was found to have metastasis either before radiation or during follow up period. There was no different prevalence of blood borne metastasis according to methods of the treatment. We learned 13.5% (5 of 37 patients) of the diagnostic failure to detect distant metastasis in organs preoperatively, approximately 9% of this failure rate was due to the occult metastasis or new metastasis after radiation (Table 8).

#### 5. Complications

Table 9 exhibits the list of acute radiation reaction during irradiation period. The most frequent one was esophagitis (84%), next order was chest discomfortness with dyspnea and coughing (55%), poor intake (14%), leukopenia (10%) and infection (6%). 3 patients were found to fistula; one of them was cancer fistula between esophagus and trachea, and the other two patients developed anastomotic leak with persistent cancer at the surgical resection margin postoperatively. All of these 3 patients died immediately after the discharge from the hospital. In the group of HFR acute radiation

reactions and complications developed in less frequency and less severity in degree of reaction. There was also less frequency of acute reactions by postoperative irradiation due to lower total dose. Chronic complications are listed on Table 10. Total complication rate was 19.4% and the most frequent one was stricture of esophagus (6.1%) and next order was fistula of esophagus (5.5%) on the radiographic examination. In comparison of each subgroup of treatment parameters HFR tended to be slightly higher late complication rate in curative radiation, however complications seemed to be associated with disease parameters. The low late complication rate of postoperative irradiation was attributed by low total radiation dose.

### DISCUSSION

The esophagus cancer is widespread disease though it is clinically well localized<sup>(15,16)</sup> and local treatment can never achieve cure<sup>(5,9,12,13)</sup> but there is no systemic treatment at present<sup>(1,17,23,23,28)</sup>. The survival rate of esophagus cancer therefore has been reported very poor regardless of the modality of treatment<sup>(3,5,9,11,12,13,17,21,23)</sup>. 9% of crude 5 year survival is same as others<sup>(3,11,21)</sup> utilization of bi-phasic survival curve when plotted semilogarithmically was arbitrary convenient to divide response group<sup>(11,13)</sup>, all nonresponse group died within one year regardless of modality of treatment and their survival curve was found identical to survival of the patient treated palliatively by other<sup>(10)</sup>. The second slow regressing component was for response

**Table 8.** Blood Borne Metastasis

Site	Regular fractionated RT	Hyperfractionated RT	Postoperative RT	Total
Lung	5 (4)	2 (1)	1 (0)	8 (5)
Liver	1 (0)	0	1 (1)	2 (1)
Bone	5 (2)	2 (1)	1 (1)	8 (4)
Brain	1 (1)	0	0	1 (1)
Others	3 (1)	2 (1)	2 (2)	7 (4)
<b>Total</b>	<b>15 (8)</b>	<b>6 (3)</b>	<b>5 (4)</b>	<b>26 (15)</b>
<b>Total No. of patient</b>	<b>95</b>	<b>33</b>	<b>37</b>	<b>165</b>
<b>New metastasis rate after RT</b>	<b>8.4%</b>	<b>9.1%</b>	<b>10.8%</b>	<b>9.1%</b>

- Total % blood borne metastasis = 26/165 = 15.8%
- Preoperative diagnosis failure rate = 5/37 = 13.5%
- ( ) : No. of new development of metastasis during follow up period.

group to radiation. The response is not synonymous with cure. The most important factor affecting survival was the treatment factor to control gross disease locally usually by surgery and to control simultaneously more area of microinvasive or occult regional disease. 3 year crude survival rate for postoperative radiation was 30%.

If both surgical margin and nodes were negative the survival rate was remarkably higher 50%. If lymph node was negative, survival had greatly improved<sup>8)</sup>. The node negative occasion might correspond to responder in biphasic survival curve and the occasion of node positive or grossly residual disease at surgical margin or both can be identical to first component, nonresponder. Radiation of conventional dose schedule is only effective for patients who do have negative nodes<sup>8)</sup>. The length of involved segment of esophagus was found not to be important in survival but staging concerning of mass size and nodal state is important factor affecting survival<sup>4,10,30)</sup>. Presence of residual disease is surgical margin beyond same above gross disease indicates submucosal or intramuscular lymphatic spread; the larger the tumor the greater the expected extent of local infiltration beyond visible margin, the more widespread lymph node metastasis the higher incidence of blood borne metastasis, therefore the less survival expected<sup>22)</sup>.

Blood borne metastasis in ours was 9%. The larger the tumor the more extensive ulceration, infection, patient debilitation, starvation, anemia, pain with each independently tending to limit volume and dose fraction. Extension of the tumor was greater than had been estimated in 14% of our resected patient versus 16% in autopsy finding reported A.M. Mandard<sup>8)</sup>. He found that higher than 5000 cGy in preoperative irradiation was 23% of sterilization of tumor versus 16% of sterilization of tumor by lower than 5000 cGy and only 39% of esophagus cancer had no local extension to adjacent trachea, bronchus, aorta, pericardium, pleura, mediastinum and stomach. We found 49.7% positive rate of locoregional nodes in neck, supraclavicular, mediastinum and abdomen before or during treatment and follow up period in our 165 patients. H.Akiyama<sup>15)</sup> reported 37.6% positive rate of nodes in mediastinum and abdomen but reported higher intraabdominal nodes 18.9%, than 13.7% in our surgical patients.

In our radiation alone group, incidence of abdominal nodes positive was very low 0.6% vs 13.7% incidence in our surgical patients, indicating presumably diagnostic procedure for abdominal

metastasis was not sufficient. Nodal metastasis above supraclavicular region was however high, 26%. Reason of high incidence would be delayed diagnosis from development of symptoms and high % of advanced stage and mid thoracic esophageal cancer as seen in fig 3,4. We learned that preoperative diagnostic failure rate was for metastatic locoregional node was 54%, for grossly metastatic node 29.7%, and for blood borne organ metastasis 13.5%. New metastasis in locoregional nodes was found in 19% of patients during follow up period, however, it is unclear it was new metastasis from other persistent disease or occult metastasis was initially harbored before treatment<sup>4,5)</sup>. Occult metastasis is fundamental dilemma for diagnosis<sup>5,8,15,16,22)</sup>.

The death of most of our patients was caused by dysphagia with or without dyspnea in 49% and next order by dyspnea with chest discomfortness as seen in Table 5. Dysphagia was caused by stricture in 46% of treatment failure. 88% of stricture was associated with persistent cancer and radiographic benign stricture 8 cases can not exclude associated malignancy in failure<sup>10)</sup>. 62% of treatment failure was associated with persistent malignancy and local recurrences<sup>3,4,5,10,11)</sup>. Late reaction complications encountered associated with or without persistent disease have caused death. Many of the patients who died mainly from local failure have occult distant metastasis which would ultimately have caused death. Acute and late reaction complications were less frequent and not serious in postoperative radiation and HFR in comparison with RFR as in Table 9 and 10, respectively due to low dose fraction in HFR. 5000 cGy with 250 cGy daily fractions in irradiated field of 140 cm<sup>2</sup> has been claimed as an optimum dose without compromising normal tissue tolerance, to control local tissue. Maximal survival with dose regimens whose median normal standard dose (NSD) based on Ellis' formula was 1679 rets<sup>10,26)</sup>.

This dose however may be inadequate for local control of majority of esophagus cancer and associated positive node in preoperative studies<sup>5,21)</sup>. C.Mercke et al<sup>14)</sup> looked at the response of skin metastasis from an esophagus cancer to various dosage regimens designed to give the same cumulative radiation effect as a standard 4000 cGy in 20 fractions over 4 weeks<sup>7,14)</sup>. Regimens varying from 17.8 Gy given in 2 fractions over three days to the standard course produced complete responses in all metastasis. Skin reaction was less pronounced with regimens using fewer, large fractions than with conventional fractionation. Na-

**Table 9.** Acute Radiation Reaction and Complication During Radiotherapy

Kinds	RT only		OP + RT	
	Regular fractionated	Hyperfractionated	Regular fractionated	Hyperfractionated
Eosphagitis	92 (97%)	25 (76%)	10 (63%)	11 (52%)
Chest discomfort dyspnea/coughing	61 (64%)	15 (45%)	7 (44%)	7 (33%)
Poor intake	10 (11%)	6 (18%)	4 (25%)	3 (14%)
Leukopenia	8 ( 8%)	3 ( 9%)	3 (19%)	3 (14%)
Fistula	1 ( 1%)		1 ( 6%)	1 ( 5%)
Esophagus varix	1 ( 1%)		1 ( 6%)	
Recurrent laryngeal nerve palsy	1 ( 1%)		1 ( 6%)	
Cardiopathy				1 ( 5%)
Viral		1 ( 3%)	1 ( 6%)	1 ( 5%)
Infection Bacterial	5 ( 5%)	1 ( 3%)		1 ( 5%)
Fungal				
No. of patients 165	95	33	16	21

**Table 10.** Chronic Complication after Radiotherapy

	Total No.	RT only		OP + RT	
		Regular fractionated	Hyperfractionated	Regular fractionated	Hyperfractionated
Fistula	9 (5.5%)	4 (4.2%)	3 ( 9.1%)	1 (6.3%)	1 (4.8%)
Stricture	10 (6.1%)	5 (5.3%)	4 (12.1%)		1 (4.6%)
Pneumonitis	4 (2.4%)	2 (2.1%)		1 (6.3%)	1 (4.8%)
Spinal cord myelitis	2 (1.2%)	1 (1.1%)			1 (4.8%)
Cardiomyopathy	1 (0.6%)	1 (1.1%)			
Infection	4 (2.4%)	2 (2.1%)	2 ( 6.1%)	1 (6.3%)	1 (4.8%)
Fibrosis of neck	2 (1.2%)	1 (1.1%)		1 (6.3%)	
Total	32/165 (19.4%)	16/95 (16.8%)	9/33 (27.3%)	4/16 (25%)	5/21 (23.8%)

kayama et al<sup>2)</sup> based concentrated preoperative irradiation of 2000 to 2500 cGy in 4 or 5 days upon observations of greater effect for large fractions in a model tumor system in mice. Dvivedi and Pradhan compared 670 cGy fraction given once weekly for 6 weeks with 6000 cGy given in standard, 200 CGy fraction five times per week for 6 weeks for patients with advanced esophageal, head and neck, cervix and breast tumors.

Mucosal reactions were less, and overall patient condition and tolerance were better when patients were treated once per week. Local control and survival were felt to be equivalent<sup>32)</sup>. 400 cGy daily

to 4400 cGy in 2 to 3 weeks was compared with standard 200 cGy fraction to 6600 cGy over 6 to 7 weeks and tumor control, palliation, and disease free survival rates were equivalent, as were the degree and severity of acute skin and mucosal reactions and chronic tissue injury on randomized trial of high fractional dose irradiation<sup>33)</sup>. This approach is attractive for the palliative patient in whom minimizing time and discomfort is important with regard to essential elements. Alternately use of multiple daily fractions of conventional size of dose or of hyperfractionation using a large number of daily fractions of less than conventional dose has

been attempted to make use of differences in cellular-repair mechanisms that exist between normal and tumorous tissue.

Rapid fraction may enhance the difference between actively proliferating tumor tissues and normal mucous gland that react acutely to radiation injury and slowly proliferating normal tissue that are more involved in chronic radiation injury<sup>6,18,19,20,26</sup>. 160 cGy fractional dose, 2 or 3 fractions daily upto 4800 cGy followed by additional 2200 cGy 3 to 4 weeks later produced significant mucositis though reactions resolved more rapidly. There were several suggestion of fractional dose of 160 and 120 cGy and 115 cGy but increasing higher total dose have been suggested when lower fractional dose used<sup>20</sup>. The other approach successfully has been widely used with relatively better result by preoperative conventional dose radiation and subsequent aggressive surgical resection of primary disease and simultaneous removal of lymph nodes<sup>2,5,8,25</sup>. Further combination of chemotherapy using 2 cycles of mitomycin or Cis-platin and 3000 cGy followed by resection have been reported to be partially success with 31% of free of tumor cell on resected specimen<sup>17,23</sup> and local recurrence decreased to 13% followed chemotherapy and 5000 cGy<sup>28</sup>.

### CONCLUSION

Radiotherapy has been extensively used in manage of the patient with cancer of esophagus. The nature of the disease is very much widespread as initially seen at the time of diagnosis, however main cause of death is apparently local and regional failure as seen in this study. Postoperative radiation represented better survival by removal of primary disease but at the time of surgery many of the patients had widespread metastasis in locoregional lymph nodes and conventional optimum dose schedule 5000 cGy with 250 cGy fractional dose or 6000 cGy with 200 cGy fractional dose was not sufficient to control local gross disease or associated positive lymph node but effective only to microinvasive or occult disease. HFR with smaller dose 115 cGy fractional dose, 2 fractions per day upto total 6900 cGy is felt to be too small fractional dose for esophagus cancer. Early detection and fewer larger fraction per week in large field including cardiac nodes in reducing field technique at tolerable dose followed by aggressive surgery is felt to be interesting in regarding advanced nature of disease.

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= 국문초록 =

### 식도암의 방사선 치료 결과

부산 고신의료원 치료방사선과  
정태식 · 문창우 · 염하용 · 양칠용

방사선 단독 치료나 수술후 방사선 치료를 받았던 165명의 식도암 환자중에서 평균 생존율은 6.6개월이었으며 3,5년 생존율은 16%, 8%였다. 생존율을 semilogarithmical하게 나타낸 biphasic plotting에서 보면 non-responder group은 치료에도 불구하고 1년내 모두 사망하였고 responder gorup 중에서는 수술후 방사선 치료를 받았던 환자 20명 (54%)은 1,2,3년 생존율이 각각 80%, 70%, 60%였으며, 방사선 치료만 받은 환자 61명 (48%)의 생존율은 각각 62%, 38%, 23%였다. 즉, 3년간의 생존율의 비교는 수술후 방사선 치료가 방사선 단독치료 보다는 좋았다( $p < 0.01$ ).

가장 많은 사망의 원인으로는 연하곤란(55%)이었으며 환자의 대다수는 국소적인 치료실패에 의해 사망하였으며(62%) 협착의 88%는 지속적인 암의 존재와 관련이 있었다. 환자의 50%는 국소적인 임파절 전이가 발견되었다. 수술전의 진단 실패율은 54%가 국소임파절 전이때문에, 29.7%가 육안적인 임파절 전이 때문에, 13.5%가 혈행성 전이 때문에 그리고 14%가 국소적인 직접 침범 때문이었다.

Conventional radiation (6000 cGy/30 fraction in 6 weeks)이나 hyperfractionation radiation (upto 6900 cGy, 115 cGy/fraction)이거나 관계없이 gross disease는 충분히 죽일수 없었다. 그러나 hyperfractionation 테크닉에 의해서 급성 방사선 염증이 감소되어서 환자의 고통을 덜어줄 수 있었으며 그후의 만성 부작용으로서의 방사선 합병증이 현저히 감소 되었다.