

Results of Radiotherapy With and Without Chemotherapy for Esophageal Cancers

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This is a retrospective study of 62 patients with unresected squamous cell carcinoma of the esophagus treated by radiotherapy alone (25 patients) or combined chemotherapy and radiotherapy (37 patients). Of these, 14 of 25 patients treated by radiation therapy alone and 25 of 37 patients treated by combined chemotherapy and radiotherapy completed radiotherapy consisting of 55 to 60 Gy in 5 to 6 weeks and were analyzed for local control rate and survival rate. Follow up ranged from 6 days to 58 months. Three (8%) of 39 patients had a complete response, twenty-eight (72%) a partial response and eight (20%) minimal or no response. Overall median survival was 11 months for all stages. The 1 year and 2 year actuarial survival rates were 48.6% and 13% respectively. Age and stage had prognostic significances ($p < 0.05$, $p < 0.05$ respectively). The 1 year survival rate was 70.1% for stage I, 47.6% for stage II, and 28.4% for stage III. The median survival was 19 months for stage I, 11 months for stage II, 6 months for stage III, and 5.5 months for stage III with distant metastases. The 1 year survival rate of patients 55 years and above was 69.6%, 54 years and below was 0%. There was no significant difference in survival rate between treatment modalities, locations of tumor, and responses of tumor.

Key Words: Esophageal cancer, Radiotherapy, Chemotherapy

INTRODUCTION

Despite major efforts and advances in radiation therapy, chemotherapy and surgery, the treatment results of carcinoma of esophagus are poor. Various therapeutic approaches have been made, but the 1-year survival rate varied from 15% to 30% and 5-year survival rate does not exceed 5%, ranging 3-20%¹⁾. Major causes of this poor results include the difficulty in achieving local control, the high rate of lymph node metastases and distant metastasis^{2,3)}. Recently, in an attempt to improve local control and survival, a combined modality approaches have been described. Infusion of 5-FU was used alone or in combination with cisplatin or mitomycin-C or with the two agents. In 1976, Franklin et al⁴⁾ at Wayne state University treated carcinoma of esophagus by using preoperative 5-FU and mitomycin C with radiation. The median survival for the entire group was 18 months, showed marked improvement over historical group. Leichman et al⁴⁾ showed that median survival and 1 year survival of patients treated by a neoadjuvant program of chemotherapy (5-Fluorouracil and cisplatin) and radiation (3,000 cGy) was 22 months and 75% respectively, surpassed those of neoadjuvant surgical series (18 months and 57%). Multicentric trials

using concurrent radiotherapy and chemotherapy with or without surgery, such as SWOG and RTOG, confirmed this observations^{5,6)}. In this study, we analyzed the results of 39 patients treated with radiation therapy alone or combined chemotherapy and radiotherapy, examined prognostic factors.

MATERIALS AND METHODS

Between September 1985 and January 1991, 80 patients with esophageal cancer were treated at the Department of Radiation Oncology, Kyungpook National University Hospital. Of these, eighteen patients were excluded in this study, for the following reasons: nine received postoperative radiotherapy; nine had distant metastases. Patients with supraclavicular node metastases were included. Remaining 62 patients were treated with radical radiation therapy alone (25 patients) or combined chemotherapy and radiotherapy (37 patients). All had biopsy proven squamous cell carcinoma of esophagus, had been judged inoperable because of localized advanced tumor, medical contraindications, and patient's refusal. Patients with stage I or II were treated with curative intent, while other patients were treated palliatively. Follow up ranged from 6 days to 58 months. Patients characters of the 62 cases are shown in Table 1.

Table 1. Patient Characteristics

	RT alone	CT + RT
Number	25	37
Age		
Median	61	63
Range	42 – 73	43 – 75
Sex		
Male	25	35
Female	0	2
Performance		
0	8	19
1	15	16
2	2	2
Site		
cervical	5	3
thoracic		
upper 2/3	14	21
lower 1/3	6	13
Stage		
I	2	4
II	12	17
III	11	16

Table 2. Presenting Symptoms

Symptom	Number (%)
Dysphagia	59 (95%)
Weight loss	23 (37%)
Substernal discomfort	12
Hoarseness	5
Odynophagia	4
Epigastric discomfort	3
Weakness	3
Throat discomfort	2
Epigastric fullness	1
Chest pain	1

there were only two females, ages ranged from 42 to 73 years, median age were 62 years. Presenting symptoms are shown in Table 2, 59 of 62 (95%) patients presented with dysphagia, 23 (37%) presented with weight loss. Diagnostic work up included a careful history and physical examination; complete blood count, liver function test; chest x-ray, a barium swallow, esophagoscopy with biopsy, computed tomography of chest and upper abdomen, and liver scan. Computed tomography

was used to identify possible metastases in mediastinal nodes, celiac node. According to the TNM system, stage I was in 6 cases (9%), stage II in 29 cases (46%), and stage III in 27 cases (42%). Tumor location in esophagus followed AJC divisions: 35 (56%) tumors were located in the upper-midthoracic esophagus, 19 (31%) in the lower one third of the thoracic esophagus, and 8 (13%) in the cervical esophagus. 14 patients had distant metastases at presentation (supraclavicular nodes in 12 patients, liver in 3, and lung in 1). Adequate hematologic and renal function (WBC \geq 4,000/uL, platelet count \geq 100,000/uL, BUN $<$ 25, creatinine $<$ 1.1) were required for treatment. Nutritional status was evaluated before treatment and appropriate treatment was given. Many patients, particularly those with lower third lesions, were given cimetidine or an oral sulcralfate solution to decrease esophageal and gastric mucosal irritation. 3 patients had a feeding gastrostomy due to poor oral intake. Survival was calculated using the Kaplan-Meier method from the day of treatment and statistical significance was evaluated by the log-rank testing method and the chi-square test.

Patients were treated with 6 or 10 megavoltage linear accelerator. Same dose and schedule of radiation therapy were used for radiotherapy alone or combined chemotherapy and radiotherapy. The treatment volume included the whole lesion, extended 5 cm above and below the lesion's margins, and surrounding nodes according to the location of primary tumor: for tumors of cervical esophagus, both supraclavicular nodes were included; for tumors of lower third, celiac nodes were included. The radiotherapy consisted of 180-200 cGy daily 5 days per weeks up to total of 5040 to 6000 cGy in 6 to 7 weeks. Initial treatment was given by anterior-posterior opposing fields with 180-200 cGy per day, 5 times per week. Both fields were treated on each day of treatment. To limit the spinal cord dose to 45 Gy, the plan changed to bilateral opposing fields or posterior oblique fields. Radiation therapy interrupted for WBC counts $<$ 2,000/uL and platelet count $<$ 100,000/uL.

Of 37 patients, 31 patients treated with regional radiotherapy concurrent with continuous 5-Fluorouracil (5-FU) venous infusion and bolus Mitomycin C injection, 3 received preoperative 5-FU and cisplatin, 1 received Mitomycin C and cisplatin, 1 received 5 cycles of 5-FU. For 31 patients, concurrent continuous 5-FU venous infusion (1000 mg/m²/d \times 4d, 20 mg per kg per 24 hr.) was given on days 1-4 and days 42-46; and a single

bolus injection of Mitomycin-C (10 mg/m²) was given on day 1. Patients were hospitalized during their first and fifth weeks of treatment for administration of the two 4-day infusions of 5-FU.

Patients were examined at least once weekly during treatment, and treatment morbidities were recorded. CBC was monitored weekly throughout the treatment course. Esophagogram were checked at field reduction, near the end of treatment, every 2 to 3 months during the first year following completion of radiation, and then at 4-6 month interval until last follow-up. Follow up ranged from 7 days to 58 months from the completion of radiotherapy. Of 39 patients, 4 lost to follow up in radiotherapy alone group, 3 in chemotherapy and radiotherapy group. Survival was measured from the time of initiation of treatment.

RESULTS

Eleven of 25 patients treated by radiotherapy alone could not complete the planned course due to complications (8), refusal (4). Remaining 39 patients were analyzed for local control, survival, and complications. 5-FU was not administered on day 29 in one patient due to leukopenia, 50% reduction in the dose of 5-FU was given in another one patient.

1. Response

The local response to treatment was evaluated by barium swallow and esophagoscopy. Complete response was achieved only in 3 patients (7%),

partial response was achieved in 28 patients (71%), the remaining 8 patients showed minimal or no response (Table 3). In stage III, ten patients (71%) achieved good palliation. Eight patients who could swallow at least liquids developed complete dysphagia, received a feeding gastrostomy during treatment. There was no statistically significant differences in local control according to treatment modalities and stage.

2. Survival

Overall median survival was 11 months, the 1 and 2 year actuarial survival was 48.6% and 13% respectively (Fig. 1). Nine patients (23%) are alive with a follow up of 8 to 59 months after beginning of treatment. Survival was analyzed in terms of age, site of primary tumor, TNM stage, treatment modalities, and presence of weight loss (Table 4). Using a univariate analysis, stage and age were prognostically significant variables ($p < 0.05$ and $p <$

Table 3. Response

	RT	CT+RT	Stage			Total
			I	II	III	
CR	1	2	2	1	0	3
PR	10	18	4	14	10	28
MR	3	3	0	2	4	6
NR	0	2	0	2	0	2
Total	14	25	6	19	14	39

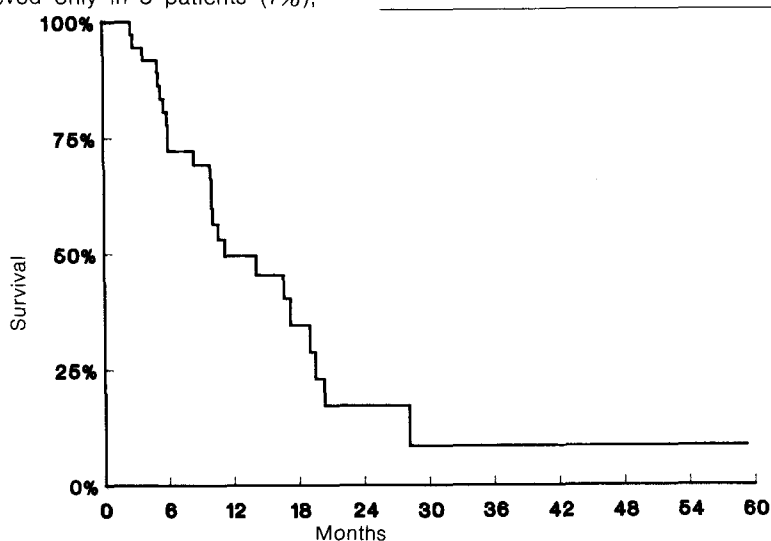


Fig. 1. Actuarial overall survival.

0.05, respectively).

Age: The median survival was 17 months for patients of age 55 years and above, 8 months for age 54 and below ($p < 0.05$) (Fig. 2). All 8 patients with age 54 and below died within 1 year, had comparable stage distribution to patients with age

Table 4. Actuarial Survival

	Number	Actuarial survival		
		Median (mo.)	1— year	2— year
Overall	39	11	48.6%	13.3%
Treatment				
RT	14	11	48.1%	25.9%
CT+RT	25	11	47.1%	8.5%
Location				
upper	4	6	18.6%	0%
middle	22	10	36.9%	14.3%
lower	13	16	60.7%	13.2%
Stage				
I	6	19	70.1%	27.7%
II	19	11	47.6%	13.4%
III	14	6	28.4%	0%
Weight loss				
(+)	17	13	52.8%	37.9%
(-)	22	10	42.6%	4%
Age				
< 55	8	8	0%	0%
> 55	31	17	60.8%	16.7%

55 years and above: four had stage 2, and four had stage 3.

Stage: The median survival times by TNM staging were 16 months in stage I and II, and 6 months in stage III (Fig. 3). The 1 year and 2 year survival rates were 56.8% and 22.9% in stage I-II, 28.4% and 0% in stage III ($p < 0.05$). Patients with distant metastases (M1) died within 1 year with median survival of 5.5 months.

There were no significant differences in survival as to the location of tumor, treatment modalities, presence of weight loss (Fig. 4).

3. Pattern of Failure

We couldn't evaluate pattern of local failure due to low complete remission rate and small number of patients. Of 39 patients, 6 (15%) patients had developed metastases, sites of metastases included lung (2), skip metastases (2), liver (1), bone (1), and supraclavicular node (1).

Table 5. Complications

Complication	Number
Esophagitis	23
Anorexia or nausea	10
Hematologic toxicities	7
Gastritis	3
Tracheoesophageal fistula	3
Herpes zoster	2
Esophageal stricture	1

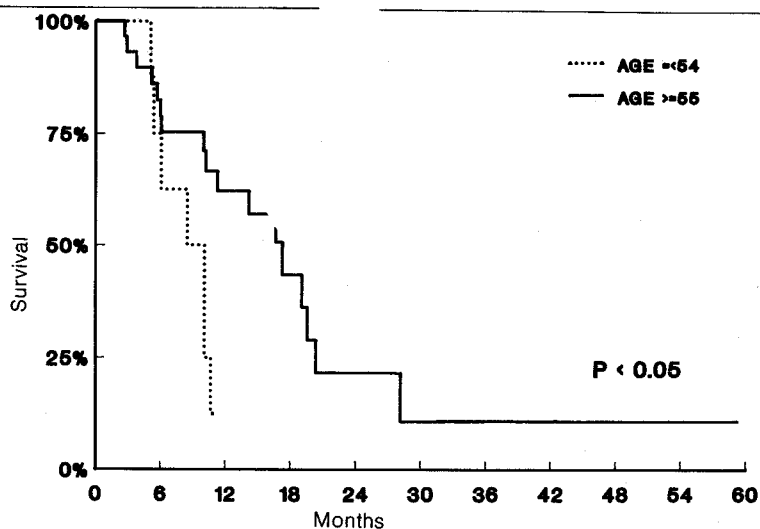


Fig. 2. Actuarial survival by age.

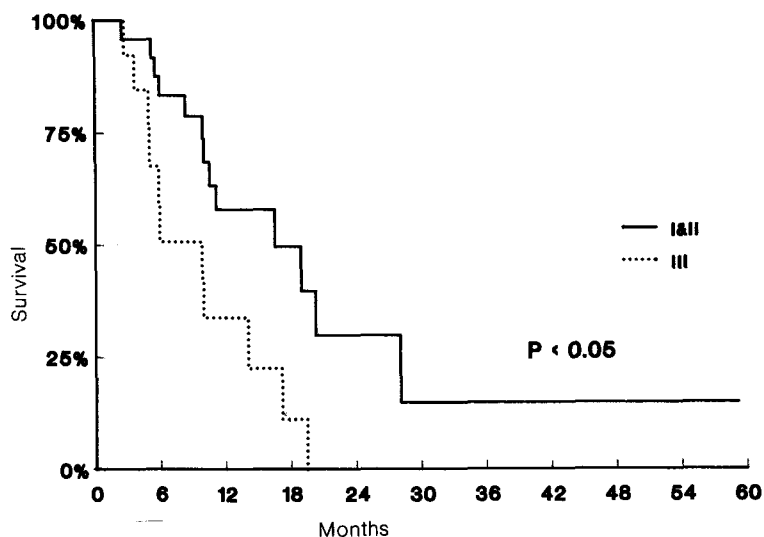


Fig. 3. Actuarial survival by stage.

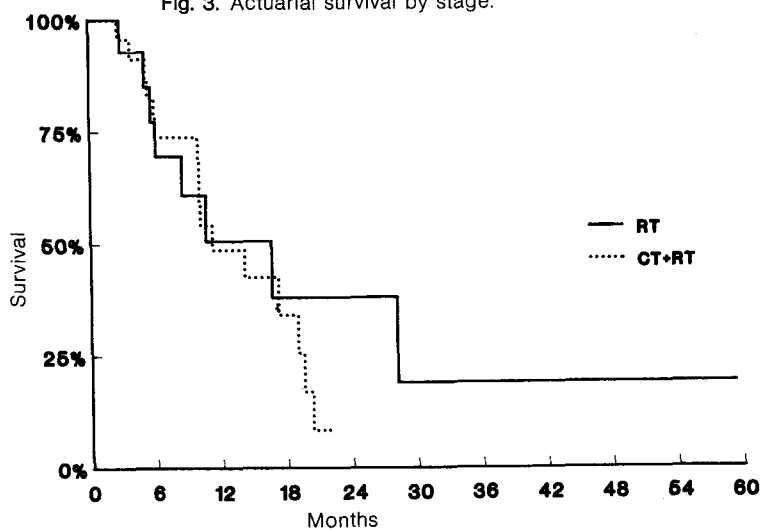


Fig. 4. Actuarial survival by treatment modality.

4. Morbidity

The observed morbidities are shown in table 5. Twenty-three (58%) patients developed a transient esophagitis. Esophagitis was usually moderate in severity and was controlled without hospitalization. Ten of twenty-five patients (40%) treated by chemo-radiotherapy developed mild degree of anorexia or nausea or vomiting. Three patients developed a tracheoesophageal fistula during treatment. Of 25 patients treated by chemo-radiotherapy, hematologic tolerance was satisfactory in 23 patients: one patient had the second course at half dose because of leukopenia, one could not receive a second course of 5-FU due to persistent leukopenia.

DISCUSSION

This study reports the treatment results of esophageal cancer. Radiation therapy has been used for many years as primary treatment in patients with inoperable or unresected esophageal squamous cell carcinoma. Recently, reports using combined radiotherapy and chemotherapy without surgery showed improvements in survival over radiation therapy alone^{7,8,9}. In a review of published series, the survival was quite variable possibly due to differences in patient selection¹⁰. In reported series, 1 and 2-year survival rate is 18-39% and 4.5 ~27% for radiation therapy alone, 47~64% and 28-41% for combined modality therapy

respectively¹¹). In our study, the overall median survival was 15 months, 1 and 2 year actuarial survival was 56.5% and 18% respectively. This results is comparable to that of radiation therapy alone group in reported series. We did not note any improvement in survival in combined modality group over radiotherapy alone group. Lawrence et al⁷ suggested a separation of potentially curable patients (stage I -II) from the incurable patients (stage III-IV). The median survival of stage I and II patients was nearly 2 years, compared with 8 months of stage III and IV patients⁷. In our study, median survival was 16 months for stage I and II months for stage II, and 6 months for stage III. Survival rate decreased with the advance of clinical stage, in younger age group. There have been few reports of a more favorable prognosis for older age group (age > 65 years)^{12,13}. In our study, 31 patients were 55 years and above had better survival ($p=0.05$), indicating that radiotherapy can be more useful in the older age group. In many report, it was showed that prognosis is more favorable for females^{12,13}, for cervical esophageal cancer compared with thoracic or abdominal sites, for patients with good general condition, and for patients without major weight loss and for shorter tumors. But we could not observe these prognostic factors. According to literature^{5,6}, N.E.D. (No Evidence of Disease) rate is related to radiation dose, 60-69 Gy can be taken as the routine radical dose, but we could not find any dose-response relationships due to few patients. Main causes of radiation therapy failure is recurrence and the uncontrolled tumors, and radical cure of tumor is very difficult in theory. In a study of autopsy findings, Mantravadi et al¹⁴ showed that 78% of cases treated with radiotherapy alone had residual primary tumor. Elkon et al¹⁵ showed that in patients treated with radiation alone 70% had local failure and 48% had distant failure. Yang et al¹⁶ showed that 40% of long term survivals treated by radiation died of local recurrences. In our study, CR rate was only 7% (3/39), most patients showed partial response, 71% (28/39).

According to these results, it is assumed that curative effects are low and tumor easily recur and can not be effectly controlled in the treatment of esophageal carcinoma only radiotherapy. Hence, local control must be improved to increase survival. A prospective clinical trial conducted by the Eastern Cooperative Oncology Group (ECOG) showed that patients treated by radiotherapy concurrent with one dose mitomycin-C and two

courses of 5-FU infusion had better median survival than patients treated by radiotherapy alone¹⁷. In our study, significant difference between treatment modalities were not observed. Most cancers are advanced at presentation. Thus early detection, development of effective drugs and methods of combination are essential for improving long term survival. We found that radiotherapy provide good palliation (71%) in patients with advanced disease, which is comparable to the results reported by Wara et al¹⁸. In a report of combined radiotherapy and chemotherapy, morbidities were in excess of those obtained with radiation alone because of hematologic and other chemotherapeutic complications¹⁹, but complication rate was less than all surgical series. The late radiation complication such as stricture were noted in 11% of patients¹⁹. In our study, the morbidity of the combined treatment regimen was not differ significantly from that of radiation alone except acute effects of chemotherapy such as anorexia, nausea, and mild hematologic toxicities.

We could not derive any conclusion except poor results of esophageal carcinoma treated by radiation or combined radiation and chemotherapy. In review of reported series^{17,19}, the combination of infusional 5-FU, mitomycin C, and radiation is an effective and relatively well tolerated regimen in the treatment of esophageal cancer, and is preferred alternative to esophagectomy or radiation therapy. Further studies are needed to clearly define the most adequate agent(s) and radiotherapy modalities.

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≡ 국문초록 ≡

식도암의 방사선치료 결과 고찰

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방사선치료 단독(25명) 또는 화학요법과 방사선 병용치료(37명)를 받은 62명의 식도암환자에 대한 후향성분석의 결과는 다음과 같다. 방사선 단독치료를 받은환자중 14명이, 병용치료를 받은환자중 25명이 계획된 치료를 끝내었다. 추적기간은 6일에서 50개월 이었다. 39명중 완전관해는 3명(8%)에서, 부분관해는 28명(72%)에서 보였다. 중앙 생존기간은 11개월이었고, 1년 및 2년 생존율은 각각 48.6%, 13%이었다. 나이와 병기가 예후에 유의한 영향을 미쳤다. 병기에 따른 1년 생존율은 1기에서 70.1%, 2에서 47.6%, 3기에서 28.4%이었고, 중앙생존기간은 1기에서 19개월, 2기에서 11개월, 3기에서 6개월 원격전이가 있는 3기에서는 5.5개월 이었다. 나이에 따른 1년 생존율은 55세 이상에서 69.6%, 54세 이하에서 0%이었다. 치료방법, 종양의 위치, 원발병소의 반응에 따른 생존률에는 유의한 차이가 없었다.