

## External Beam Radiotherapy Alone in Advanced Esophageal Cancer

Sung Ja Ahn, M.D., Woong Ki Chung, M.D.  
Byung Sik Nah, M.D. and Taek Keun Nam, M.D.

Department of Radiation Oncology, Chonnam National University Medical School, Kwang-ju, Korea

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**Purpose :** We performed the retrospective analysis to find the outcome of external beam radiotherapy alone in advanced esophageal cancer patients.

**Methods and Materials :** One hundred and six patients treated with external beam radiotherapy alone between July 1990 and December 1996 were analyzed retrospectively. We limited the site of the lesions to the thoracic esophagus and cell type to the squamous cell carcinoma. Follow-up was completed in 100 patients (94%) and ranged from 1 month to 92 months (median; 6 months).

**Results :** The median age was 62 years old and male to female ratio was 104 : 2. Fifty-three percent was the middle thorax lesion and curative radiotherapy was performed in 83%. Mean tumor dose delivered with curative aim was 58.6 Gy (55 - 70.8 Gy) and median duration of the radiation therapy was 53 days. The median survival of all patients was 6 months and 1-year and 2-year overall survival rate was 27% and 12%, respectively. Improvement of dysphagia was obtained in most patients except for 7 patients who underwent feeding gastrostomy. The complete response rate immediately after radiation therapy was 32% (34/106). The median survival and 2-year survival rate of the complete responder was 14 months and 30% respectively, while those of the nonresponder was 4 months and 0% respectively ( $p=0.000$ ). The median survival and 2-year survival rate of the patients who could tolerate regular diet was 9 months and 16% while those of the patients who could not tolerate regular diet was 3 months and 0%, respectively ( $p=0.004$ ). The survival difference between the patients with 5 cm or less tumor length and those with more than 5 cm tumor length was marginally statistically significant ( $p=0.06$ ). However, the survival difference according to the periesophageal invasion or mediastinal lymphadenopathy in the chest CT imaging study was not statistically significant in this study. In a multivariate analysis, the statistically significant covariates to the survival were complete response to radiotherapy, tumor length, and initial degree of dysphagia in a decreasing order. The complication was observed in 10 patients (9%).

**Conclusion :** The survival outcome for advanced esophageal cancer patients treated by external beam radiotherapy alone was very poor. In the treatment of these patients, the brachytherapy and chemotherapy should be added to improve the treatment outcome.

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**Key Words :** External beam radiotherapy, Advanced esophageal cancer

### INTRODUCTION

Historically, most advanced esophageal cancers were treated with radiation therapy alone with disappointing results

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Reprint requested to : Sung Ja Ahn, M.D., Department of Radiation Oncology, Chonnam University Hospital  
Tel : 062)220-6858 Fax : 062)226-4443  
E-mail : ahsja@ppp.komet.net

that no more than 10% can expect to live beyond 5 years, and even operated patients, which usually form a better subgroup, could not expect more than 20% of 5-year survival.<sup>1-4)</sup> Untreated, it is invariably fatal because it extends directly into large vessels, the tracheobronchial trees, and lymphatics because there is no limiting serosa. Despite new strategies, the primary cause of failure is persistent or recurrent cancer in the primary tumor site of the esophagus.

Radiotherapy usually relieve the dysphagia at the time of completion of the radiotherapy, but the palliation duration lasts relatively in a short time. Nowadays, the trend in the

treatment of the advanced inoperable cancer patients of various primaries is the combination of the chemotherapeutic agents concomitantly to the radiotherapy and the results are very encouraging in terms of survival improvement as well as local tumor control. The current standard therapy for advanced non-resectable esophageal cancer should be the chemoradiation since radiotherapy alone might be the undertreatment modality. In our hospital the chemotherapy was introduced recently in the esophageal cancer management and the brachytherapy was also added in the regimen of radiotherapy expecting the improved treatment results.

This study reports the outcome of a retrospective analysis of the advanced esophageal cancer patients treated with external beam radiotherapy alone to be used as the control data comparing with those of chemoradiation group or combined with brachytherapy group in the future.

#### MATERIALS AND METHODS

The registered patients from Jul. 1990 to Dec. 1996 diagnosed as esophageal cancer to the Department of Radiation Oncology, Chonnam University Tumor Registry are presented in Table 1. Of those, cases referred from outside hospitals or diagnosed with histologically nonsquamous cell carcinoma were excluded. And cervical lesion sites other than thorax were also excluded in this analysis to reduce the variance. One hundred and six cases histologically confirmed squamous cell carcinoma limited to the thorax were analyzed retrospectively.

Pretreatment disease evaluation included the medical history and physical examination, complete blood count, and liver and renal function tests. Biopsy specimens were taken from any suspicious area seen on endoscopic studies. The

imaging study consisting of chest radiograph, esophagogram, and computerized axial tomography scans were performed. We determined the length of the esophageal cancer by the esophagogram and the periesophageal and regional lymph node involvement by chest CT scan. But the extent of the esophageal wall penetration could not be figured-out definitely and though we applied the TNM clinical staging system,<sup>5)</sup> we did not perform the stage grouping separately.

Radiotherapy (RT) was administered using a 6 MV (Mevatron, Siemens Co.) or 10 MV (Clinac 1800, Varian Co.) photon beams. Initial radiation ports included the involved esophagus and adjacent mediastinum. Treatment fields were usually 8 cm in width. Superior and inferior limits were at least 5 cm beyond the lesions seen on planning barium swallow films. The supraclavicular fossa was not included in the irradiation fields routinely except for the lesions in the upper thorax. An isocentric technique via a pair of parallel opposed anterior and posterior ports was used. A tumor dose of 3,960 or 4,000 cGy (180-200 cGy daily fractions 5 days per week) was prescribed at midplane and then, the total 6,000 to 7,020 cGy was intended to give to the central axis of the beam composed of three or four oblique ports sparing the spinal cord depending on the tumor size and surrounding critical normal tissue.

During treatment, patients had been examined at least once weekly to evaluate acute toxicity and nutritional condition. Follow-up consisted of clinical examination every month during the first six months and then every three months during 2 years. The local response to treatment was evaluated by esophagogram. Complete response was defined as negative findings in esophagogram. Smooth narrowing of esophageal lumen on esophagogram was regarded as complete response. Follow-up was completed in 100 patients (94%) and ranged from 1 month to 92 months (median; 6 months).

Survival rates were calculated using the actuarial methods and calculated from the first date of radiotherapy. Statistical analysis of the data was done using the SPSS software package. Comparison of prognostic variables were made using the Mantel Haenzel and Cox model for univariate and multivariate analysis.

#### RESULTS

Age ranged from 44 to 84 years old with the median 62

Table 1. Tumor Registry of Department of Radiation Oncology, Chonnam University Hospital : Esophageal Cancer

Treatment Modality	1990. 7. 1996. 12.
Radiotherapy (RT) Alone	187
Surgery + Postop. RT	61
Surgery + Postop. Chemoradiation	5
RT + Chemotherapy (CT)	14
Concomitant	5
Neoadjuvant CT	5
Preoperative	4
Incomplete therapy or No Therapy	16
Total	283

and male to female ratio was 104 : 2. The most common lesion site was the midthorax area (62%) and the distribution of upper and lower esophageal lesion was 20% and 18%, respectively. Curative radiotherapy was performed in 83% of all patients (88/106). The other patients characteristics are shown in Table 2. Mean tumor dose delivered with external

beam was 58.6 Gy (55 - 70.8 Gy) and median duration of the radiation therapy was 53 days.

The survival curve of all 106 patients is illustrated in Fig. 1. The median survival of all patients was 6 months and 1-year and 2-year overall survival rate was 27% and 12% respectively (Table 3). Improvement of dysphagia was shown in most of treated patients except for 7 patients who underwent feeding gastrostomy during or after radiotherapy. The complete response rate immediately after radiation therapy was 32% (34/106) and the median survival and 2-year survival rate of the complete responder was 14 months and 30% respectively while those of the nonresponder was 4 months and 0% respectively with the statistical significance ( $p=0.000$ ).

Survival difference by the various parameters is shown in Table 4. In the analysis according to the degree of dysphagia, the median survival and 2-year survival rate of the patients who could tolerate regular diet was 9 months and 16% while those of the patients who could not tolerate regular diet was 3 months and 0% respectively with the statistical significance ( $p=0.004$ ). The survival difference between the patients with 5 cm or less tumor length and those with more than 5 cm tumor length was marginally statistically significant ( $p=0.06$ ). However, the survival difference with the statistical significance according to the periesophageal invasion or mediastinal lymphadenopathy in the chest CT imaging study was not shown in this study.

In a multivariate analysis of prognostic factors affecting

Table 2. Patients Characteristics (N=106)

Characteristics	No. of patients
Age (yrs)	
range	44 - 84
median	62
Sex	
male	104
female	2
Tumor Location	
upper	24 (23%)
mid	58 (54%)
lower	24 (23%)
Tumor Length (cm)	
≤ 5	42 (40%)
>5	64 (60%)
Stage	
a	74 (70%)
b	20 (19%)
b	12 (11%)
Aim of Radiotherapy	
curative	88 (83%)
palliative	18 (17%)
Radiation Dose (Gy)*	
range	55 - 70.8
mean	58.6

\*Curative Radiotherapy Dose

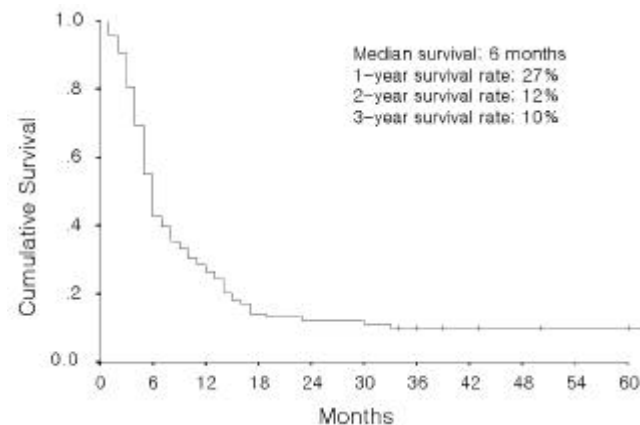


Fig. 1. The actuarial survival rate of all 106 advanced esophageal cancer patients treated with external beam radiotherapy alone.

Table 3. Summary of Therapeutic Results

	Radiotherapy alone (N=106)
Improvement of dysphagia (%)	93
Complete response (%)	32
Median Survival (months)	6
1- year survival (%)	27
2- year survival (%)	12
Pattern of Failure (No. of pts)	29
Local (esophagus) only	5
Distant Metastasis only	21
SCL only	5
Abdomen (LAP + ascites)	2
Brain + Bone	3
Pleura + Pericardium	4
Lung	4
Liver	3
Combined	3

\* complete responder only

Table 4. Survival Outcome According to Prognostic Factors

Parameters	No. of Patients (%)	Median Survival (months)	2-year survival rate (%)	<i>p</i> value
Age (yrs)				
>60	56 (53)	7	13	0.0930
60	50 (47)	5	7	
Hemoglobin (g/ dl)				
>13	49 (54)	6	14	0.0777
13	41 (46)	6	5	
Dysphagia				
regular diet	26 (26)	9	16	0.0004
soft	33 (33)	7	18	
liquid	36 (35)	4	3	
no passage	6 ( 6)	3	0	
Site				
upper thorax	24 (23)	6	14	0.0261
midthorax	58 (54)	6	13	
lower thorax	24 (23)	4	0	
Tumor length (cm)				
5	42 (40)	7	14	0.0639
>5	64 (60)	5	8	
Periesophageal invasion*				
no	26 (25)	7	22	0.1373
yes	77 (75)	5	9	
Mediastinal LAP†				
no	33 (46)	7	16	0.3740
yes	38 (54)	6	11	
Stage				
I-III	74 (70)	6	13	0.1647
IVa	20 (19)	5	5	
IVb	12 (11)	4	8	
RT aim				
curative	88 (83)	6	13	0.0002
palliative	18 (17)	3	0	

\*Chest CT finding

† Stage IV patients were excluded.

the survival, the statistically significant covariates were tumor response to radiotherapy, tumor length, and initial degree of dysphagia in a decreasing order (Table 5).

The double primary cancer diagnosed in this analysis was shown in 3 patients (Table 6). The severe complication was observed in 10 patients (9%). Radiation dose and follow-up status of these patients are illustrated in Table 7.

### DISCUSSIONS

For patients with locally advanced non-resectable esophageal cancer radiotherapy has been the conventional treatment modality for many years and of which the local tumor control and 5-year survival rates have remained disappoint-

Table 5. Cox Proportional Hazard Regression Analysis

Variables	Significance	Relative Risk	95% CI	
Age	0.3485	0.9852	0.9549	1.0164
Site	0.3444	0.7768	0.4602	1.3112
Tumor Length	0.0086	1.1347	1.0327	1.2469
Initial Degree of Dysphagia	0.0272	1.4149	1.0399	1.9253
Aim of Radiotherapy	0.5770	1.2871	0.5302	3.1246
Hemoglobin level	0.7398	0.9697	0.8085	1.1629
Tumor Response to Radiotherapy	0.0000	5.4931	2.7976	10.7857

\*Statistically significant variables with the *p* value less than 0.05.

Table 6. Summary of Double Primary Cancer in Advanced Esophageal Cancer (N= 106)

Location of Esophageal Cancer	Survival Time (Mo.)	Site of Double Primary	Time of Diagnosis
Upper	2	supraglottic ca.	synchronous
Lower	2	tongue base	synchronous
Lower	39	tonsillar ca.	metachronous

Table 7. Illustration of Patients with Severe Complications

Side effect (No. of Patients)	Radiation Dose (cGy)	Radiotherapy Time (days)	Local Control	Survival Status
<b>Radiation</b>				
Pneumonitis (3)				
	6500	57	no	4 (D)
	6480	57	yes	12 (D)
	6660	67	?	Lost
Fistula (3)				
	6480	53	no	5 (D)
	6440	54	no	3 (D)
	6120	53	no	2 (D)
Esophageal Stricture (2)				
	6380	47	yes	80 (A)
	7080	62	yes	60 (A)
Laryngeal Edema (1)				
	6480	55	yes	6 (D)
Herpes Zoster (1)				
	7020	64	no	3 (D)

D : dead, A : alive without disease

ting.<sup>3, 4)</sup> Previously we reported the radiotherapy outcome of esophageal cancer treated between November 1985 and June 1990 in our Department of Radiation Oncology, Chonnam University Hospital with the poor results.<sup>3)</sup> Consecutively, in this analysis, the treatment outcome with external beam

radiotherapy alone was also very poor. In the treatment of cancers if one wants to achieve better disease-free and overall survivals, one has to improve the control rate over the locoregional disease.<sup>6)</sup> Our study showed that the complete responder at the time of completion of radiotherapy also showed the better median survival and 2-year survival rate than those of the nonresponder did.

In an attempt to improve the local control by radiotherapy, many studies have been carried out including altered fractionation, the use of proton and neutrons, and chemical modifiers as radiosensitizers. In a unique experience, at the University of Southern California, Herskovic et al.<sup>7)</sup> reviewed patients treated with a large field, split-course plan. The treatment volume, which extended from the supraclavicular area to the celiac axis, received 24 Gy midplane dose in 15 treatments in 3 weeks. This were repeated for a total of 72 Gy with field reduction. Only 1 patient of about 100 was alive, apparently with no evidence of disease (NED) several years after this treatment.<sup>7)</sup> Therefore, increasing radiation does and volume was not the solution to improve the outcome of esophageal cancer treatment. Nishimura et al.<sup>8)</sup> studied the effect of total treatment time and fractionation on the local control and survival of the esophageal cancer patients treated with radiotherapy alone and reported that accelerated hyperfractionation was the most important treatment-related variable and total treatment time might have a significant impact on the treatment outcome for esophageal cancer.

In an attempt to improve the poor results of single-modality therapy, a therapeutic approach has been changed. In the last few years interesting results have been obtained by chemoradiation for the treatment of squamous cell carcinoma of the esophagus. Recent reports have been shown encouraging results with 5-fluorouracil (5-FU), cisplatin (CDDP), and radiotherapy in patients with esophageal carcinoma. There is now evidence that combined modality treatment is superior to radiation alone and concomitant treatment with radiotherapy and chemotherapy improves survival and local control compared to radiotherapy alone.<sup>7, 9-11)</sup> One of the most interesting studies is that of Herskovic et al.,<sup>11)</sup> which showed such a significant advantage both in the reduction of local and distant failure and in median survival and overall survival rates in favor of the combined arms (survival of 50% at 12 months and 38% at 24 months vs. 33% and 10% for radiotherapy alone) when randomized

that the trial has to be stopped. Radiation with concomitant chemotherapy is now the standard treatment for non-resectable esophageal cancer. But, several questions remain unanswered regarding the optimal combined treatment in terms of optimal chemotherapy regimen and radiation dose. The cisplatin (CDDP), 5-fluorouracil (5-FU) and mitomycin C (MMC) are known as the most effective drugs for esophageal cancer; moreover, CDDP and 5-FU are well established as radiation sensitizers, and MMC is selectively toxic against hypoxic cells. When patients are treated with radiotherapy alone median survival is highly correlated to radiotherapy dose, justifying studies addressing the contribution of higher radiation dose combined with chemotherapy. Some studies reported the feasibility of giving 60 or 65 Gy with concomitant chemotherapy.<sup>12)</sup> Whether radiation dose escalation will result in improved outcomes is the purpose of ongoing study of Radiation Therapy Oncology Group (RTOG) trial comparing chemotherapy plus 64 Gy versus 50 Gy. High dose rate brachytherapy is effective for palliative treatment, and when it is used as a boost, some studies suggest that it could enhance local control rate. Local control rate was 62.8% and 19.6% respectively with and without high dose rate brachytherapy boost.<sup>13, 14)</sup>

From 1990 to 1996, the treatment method of advanced esophageal cancer was not changed in a great extent in our department. Since 1996, after then, concurrent chemoradiation regimen and high-dose rate Ir-197 intraluminal brachytherapy was introduced and we are expecting to have the better treatment outcomes as shown in many other published articles using combined regimen. We performed this retrospective study to obtain the baseline control clinical data comparing them with the results of current combined treatment regimen in the future.

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		1990 7		1996 12	
		106			
6 MV	10 MV X	55 Gy	70.8 Gy	가	
100 (94%)		1	92 ( ; 6 )		
		62		104 : 2	가
	83%	가			54%
		53			58.6 Gy (55 70.8 Gy)
		6	, 1, 2	27, 12%	7
					32% (34/106)
(14 )	2	(30%)		(4 ) 2	(0%)
			2		(p= 0.000).
9	16%			3	0% (p=0.004).
		가 가			가 가
				10	(9%).

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