

## The Result of Radiotherapy in Esophageal Cancer

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During the period between March 1979 and August 1986, 177 patients with carcinoma of the esophagus were treated with radiotherapy in the Department of Therapeutic Radiology, SNUH. Among these, 25 patients who had incomplete treatment were excluded. So a retrospective analysis was undertaken of 152 patients who were treated by curative radiotherapy.

More than 80% showed response: Complete remission (22%), partial remission (63%) and no response (15%). The overall two-year and five-year actuarial survival rate were 22.9% and 13.3% respectively.

Prognostic factor was analyzed by its site, size, T stage, and tumor response.

Patients with the best five-year survival rate were those who had the tumor no more than 5 cm in length (17%) or confined to the upper third of the esophagus (26.6%).

Complete responders had 34.3% of 5-year actuarial survival, but no responders had 0% of survival.

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**Key Words:** Radiotherapy, Esophageal cancer, 5 year survival

### INTRODUCTION

In spite of recent advances in medical knowledge, diagnostic facilities, radiotherapy appliances and surgical techniques, esophageal cancer still remains among the tumors with a higher unfavorable prognosis and the overall five year survival rate has not changed essentially over the past three decades. Most series show five year survival rates ranging from 0~5% in unselected cases and from 9~20% in selected cases either with surgery, high dose megavoltage irradiation or a combination<sup>1)</sup>.

Progress in the development of thoracic surgery after World War II stimulated more vigorous operative therapy for esophageal cancer. However by the 1950s, the poor results obtained with surgical procedures and the development of radiotherapy units in the megavoltage range persuaded many clinicians to radiotherapy rather than surgery. We have carefully examined the treatments given to patients with carcinoma of the esophagus and have identified several factors that are of importance in the prognosis of patients.

### METHODS AND MATERIALS

During the period between March 1979 and August 1986, 177 patients with squamous cell car-

cinoma of the esophagus were treated with definitive radiotherapy in the Department of Therapeutic Radiology, SNUH. 25 patients who had incomplete treatment were excluded from this study (Table 1): 16 patients refused treatment, 4 patients developed T-E fistula during treatment and 5 patients had disease progression. So 152 patients who were treated by primary radiotherapy were entered in this study. Of these, 140 patients were male and 12 patients were female. Their ages ranged from 25 to 80 years, with a median age of 61 years (Table 2). All patients were followed for a minimum of 24 months or until death. All patients underwent endoscopic examination and had a biopsy proven squamous cell carcinoma. The patients were staged according to the TNM staging (Table 3).

But clinical tumor staging for the knowledge of tumor extension by AJC was only possible for T staging. 27 patients had T1 (18%), 82 patients T2 (54%) and 43 patients T3 (28%). The majority of cases were of advanced stage. Tumor sites were classified as upper, middle, and lower lesion by esophagographic findings. There were 20 patients with upper lesion, 100 patients with middle lesion and 32 patients with lower lesion. Supervoltage radiation therapy was delivered to the esophageal lesion with wide margins about the lesion. A tumor dose of 5000 to 6000 cGy was administered over 5 to 6 weeks at 180 to 200 cGy per fraction in most

**Table 1.** Patients received Radiation Therapy (1979-3-1986.8)

Radiation	No. of patients (%)
Complete RT	152 ( 86)
Incomplete RT	25 ( 14)
Minimum F/U	2 years
Total	177 (100)

**Table 2.** Patient Characteristics

Characteristics	No. of patients (%)
Sex	
Male	140 (92)
Female	12 ( 8)
Age (years)	
Range	25-80
Median	61
T-stage	
T1	27 (18)
T2	82 (54)
T3	43 (28)
Site	
Upper	20 (13)
Middle	100 (66)
Lower	32 (21)

cases. The treatment volume includes the lesion with at least 5 cm margins superiorly and inferiorly based on the esophagogram, endoscopic extent and the whole width of mediastinum.

The radiation dose to the tumor was gradually increased to 6000 cGy by using a combination of AP-PA parallel opposing portals initially up to 3600 cGy and then a 3 field technique, AP, RPO and LPO as shown in Fig. 1, 2.

Remission was decided by subjective symptoms and esophagogram at one month following the completion of treatment. Survival was calculated from the first day of treatment to the time of death or lost by Life-table method.

## RESULTS

Among the 152 patients, 28 patients were lost during follow up. Their follow up period ranged from 1 to 24 months, with a median of 4 months. These patients were all included in this statistical analysis. More than 80% showed subjective and

**Table 3.** TNM Staging for Esophageal Cancer

Primary tumor (T)	
TO	No demonstrable tumor
TIS	Carcinoma in situ
T1	Tumor involves 5cm or less of esophageal length with no obstruction nor complete circumferential involvement nor extraesophageal spread
T2	Tumor involves more than 5cm of esophagus and produces obstruction with circumferential involvement of the esophagus but no extraesophageal spread
T3	Tumor with extension outside the esophagus involving mediastinal structures
Regional lymph nodes (N)	
Cervical esophagus (cervical and supraclavicular L/N)	
N0	No nodal involvement
N1	Unilateral involvement (movable)
N2	Bilateral involvement (movable)
N3	Fixed nodes
Thoracic esophagus (nodes in the thorax)	
N0	No nodal involvement
N1	Nodal involvement
Distant metastasis	
M0	No metastases
M1	Distant metastases. Cancer of thoracic esophagus with cervical, supraclavicular, or abdominal lymph node involvement is classified as M1

**Table 4.** Response Rate\*

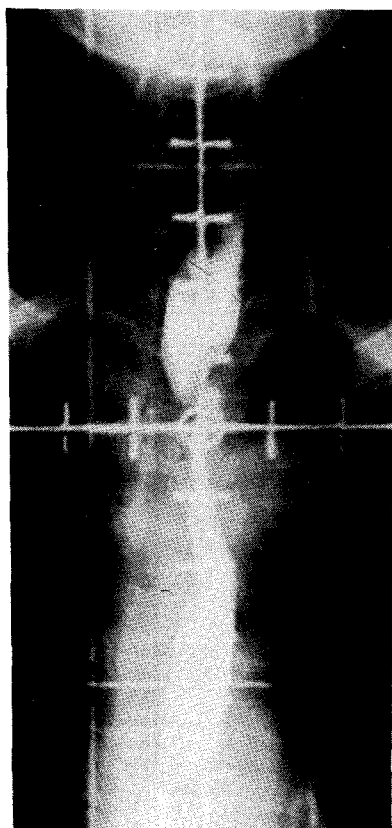
Response	No. of patients (%)
CR	33 (22)
PR	95 (63)
NR	24 (15)

\* at one month after completion of treatment.

**Table 5.** Response Rate by T-Stage (%)

	T1	T2	T3
CR	13/27 (48)	14/82 (17)	6/43 (14)
PR	13/27 (48)	57/82 (70)	25/43 (58)
NR	1/27 ( 4)	11/82 (13)	12/43 (28)

objective response: complete response (22%) partial response (62%) and no response (16%) (Table 4). Response rates by T stage were illustrated in table 5. The median survival was 7 months. The overall two-year and five-year actuarial survival



**Fig. 1.** Simulation film, anterior and posterior parallel opposing field.

rates were 22.9% and 13.3% respectively (Fig. 3).

The fourteen patients are still alive with the follow up period between 24 and 62 months. Five year actuarial survival rates by the size of the tumor in its largest dimension indicated that while tumors larger than 5 cm showed poor survival rates (7.8% with 5 to 10 cm and 16.7% with over 10 cm), those patients with lesions up to 5 cm showed a five-year survival rates of 17% ( $p < .05$ ) (Fig. 4). Five-year survival rates by T-stage were 14.3% with T1, 10.7% with T2 and 16.2% with T3 ( $p > .05$ ) (Fig. 5).

Evaluation of a five-year survival rate by the location of the tumor indicated that the lesion in the lower third showed the worst prognosis, while the lesion in the upper and middle third showed survival rates of 26.6% and 12.6% respectively ( $p > .05$ ) (Fig. 6). Five-year actuarial survival rate by the degree of response indicated that while no responders had 0% of survival, complete responders had 34.3% of survival ( $p < .05$ ) (Fig. 7).

**Table 6.** Survival in Carcinoma of Esophagus

Study and treatment technique	5 years survival	
	No of pts.	
Akakura et al. 1970		
Preoperative RT plus OP	29/117	24.8
OP only	31/229	13.6
Marks et al. 1976		
preoperative RT plus resection	14/101	13.9
preoperative RT plus		
OP (not resection)	0/ 0	0
preoperative RT without OP	6/195	3.1
OP only (curative)	2/ 33	6.1
Nakayama, 1964		
preoperative RT plus OP	3/ 8	37.5
OP only	4/ 21	19
Pearson, 1969		
RT only	20/ 99	20.2
OP only	41/363	11.2

## DISCUSSION

In the present series the actuarial five year survival rates of 152 patients were 13.3%. Patient selection strongly influenced the results of any individual series: Nakayama et al (37.5%) and Pearson (20%) (Table 6)<sup>2-6</sup>. Curability of esophageal cancers is impaired by the special anatomic features of the organ. There is no fibrous serosa acting as a barrier to the spread of tumor beyond the confines of the esophageal wall. Rich lymphatic networks in the submucosa and muscularis facilitate the spread of tumor circumferentially, transversally, and longitudinally. Distant spread of tumor within the esophagus is relatively common. Surgery or radiotherapy can cure only localized esophageal cancer, although there are differences in the extent of tumor which can be encompassed by either method<sup>6</sup>. Neither of these two forms of therapy demonstrated clear cut superiority.

Combined modality therapy of esophageal carcinoma involving preoperative radiation has been employed by a number of investigators. Akakura et al. compared a group of 117 patients treated with preoperative radiation with a historical control group of 229 patients who underwent surgery alone<sup>7</sup>. The overall resection rate was increased from 40-82%, and the 5-year survival rate increased from 14-25%. However, operative mortality also increased from 13-21%. Although some centers have noted improved resection rates and survival compared to surgery alone, overall results

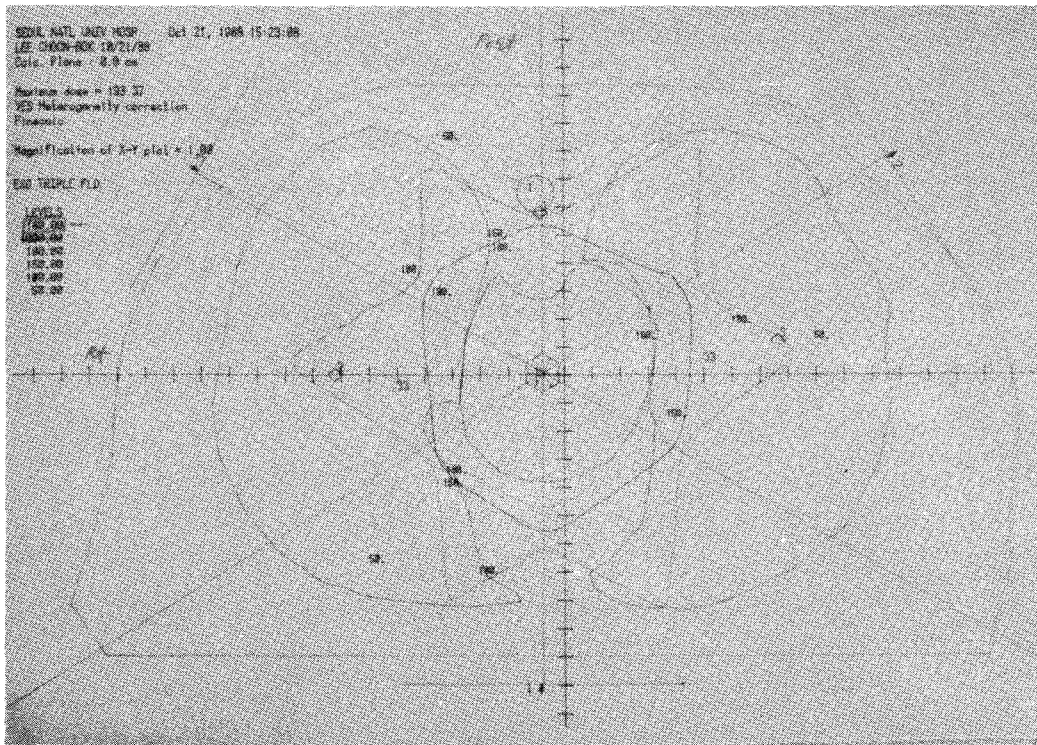


Fig. 2. A typical isodose distribution for the radiation treatment of esophageal cancer, three fields one anterior and two posterior oblique.

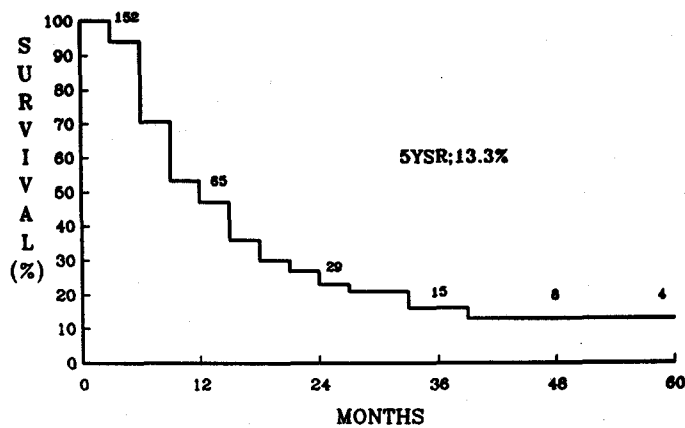


Fig. 3. Overall Actuarial Survival.

are still extremely poor, with 5-year survival rates of less than 20%<sup>7-10</sup>.

Postoperative irradiation also did not improve survival for patients with lymph node involvement but did improve local control<sup>11,12</sup>. In this study the

patients who had preoperative or postoperative RT were excluded. More than 80% of patients had relief of dysphagia in this series. Improvement of dysphagia with radiation therapy has been reported as 60-79%<sup>13</sup>.

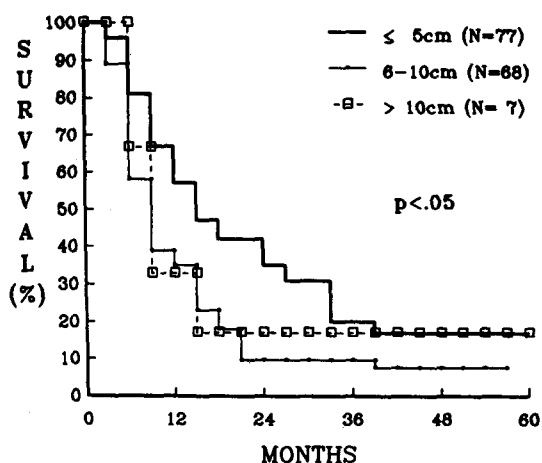


Fig. 4. Overall Survival by Size.

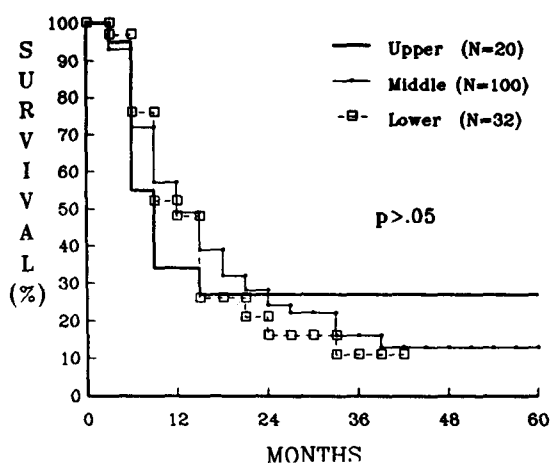


Fig. 6. Overall Survival by Site.

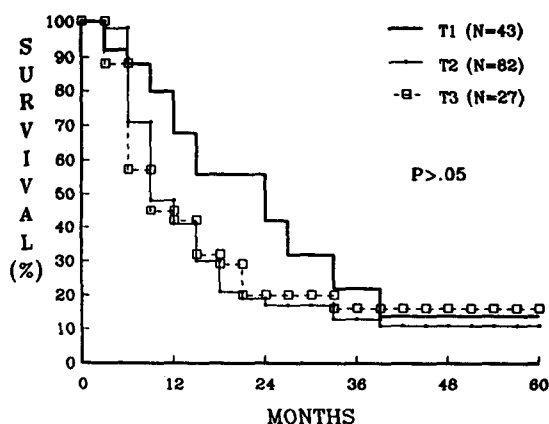


Fig. 5. Overall Survival by T-Stage.

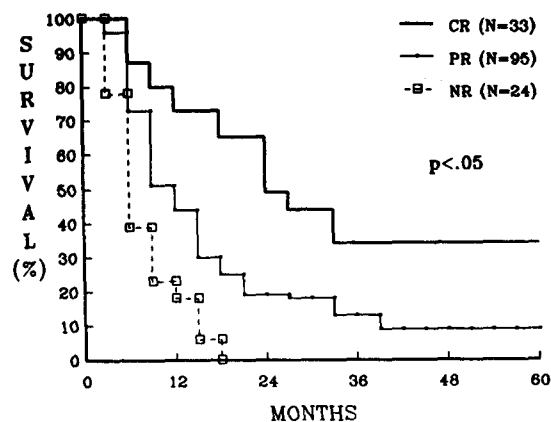


Fig. 7. Overall Survival by Response.

The most important pretreatment factors in identifying patients who responded to treatment were the size of the primary lesion and the degree of obstruction<sup>3</sup>. Newaishy et al<sup>14</sup> reported the five-year survival rate was 12.6% for lesions up to 5 cm in length. Treatment volume, total tumor dose and fractionation are major determinants of response and cure in radiation therapy and are issues that remain unsettled in the management of patients with esophageal cancer<sup>3,6</sup>.

Many authors report the use of limited treatment volumes as advocated by Pearson<sup>15</sup>, in which the primary esophageal lesion is irradiated with approximately 5 cm of margin. In the Princess Margaret Hospital<sup>3</sup>, both large and small field areas were compared to survival and both showed

an optimum area of about 120 cm<sup>2</sup> but neither of these findings was statistically significant. Our study proves that 5 cm margin is sufficient.

The second radiation parameter examined was radiation dosage. Normally, one would expect to see an increasing survival with increasing dosage as more tumor cells were killed and an eventual decrease in survival as the incidence of fatal complications increased. In keeping with this principle we did note that patients without metastatic disease who were treated by a lower dose palliative course of radiotherapy had worse survival than if they had received radical doses of radiation and the last review of carcinoma of the esophagus from PMH by Rider and Mendoza in 1969 reported the incidence of pulmonary fibrosis to be as high as 80

% radiologically while the dosage of radiation used was 5000-7000 cGy. It thus appears that we have identified the optimum range of radiation (5000-6000) in which the survival was maximized and the complication rate was minimized.

The differences in survivorship after radiation therapy of lesions at different levels of the esophagus provides interesting material for speculation. There is no evidence that site, per se, is an important prognostic factor, but because of the cross-linkage between site, sex, age and method of treatment (because more patients with upper end tumors are female, younger, and irradiated) upper end tumors are associated with a better prognosis.

In our study, patients with the best five-year survival rate were the ones who had the tumor confined to the upper third of the esophagus. But it was not significant statistically ( $p > 0.05$ ). The degree of response was closely associated with the survival rate: Patients with complete response had 34.3% while partial response had 9.7% of five-year actuarial survival rate. The major late complication which occurred following radical radiotherapy were fibrous stricture formation, the development of fistulae and massive hemorrhage from the erosion of large intrathoracic blood vessels<sup>16</sup>. In order to improve outcome, several studies have investigated the role of chemotherapy<sup>12,17-20</sup>.

The Wayne State University experience suggests that combined chemotherapy and radiation can be used in most patients with localized esophageal cancer. The Wayne State experience, as well as that reported by Poplin et al<sup>19-21</sup> has a 10% multiyear survival rate which is approximately that of either surgery or radiation alone. Because there is a considerable probability for localized as well as distal failure, it is reasonable to intensify both radiation therapy and chemotherapy to try to improve tumor control (both local and distant). It is too early to know whether response to chemotherapy in cancer of the esophagus will lead to marked improvement in survival and/or a better cure rate.

Probably the best way to establish the value of chemotherapy in relation to its impact on overall survival is to carry out a prospective randomized trial.

## CONCLUSIONS

1. From March 1979 to August 1986 177 patients with esophageal cancer were treated: 152 patients were analyzed.
2. 84% of the patients showed relief of symp-

toms, and 16% showed no response.

3. Overall two-year and five-year survival rates were 22.9% and 13.3% respectively.
4. Patients with best five-year survival rate had tumor no more than 5 cm in length or confined to upper 1/3 of the esophagus.
5. Complete responders had 34.3% of five-year actuarial survival, but no responders had 0% of survival.

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== 국문초록 ==

### 식도암의 방사선치료 성적

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1979년 3월부터 1986년 8월까지 식도의 편평상피암으로 진단되어 서울대학교병원 치료방사선과에서 방사선치료를 받은 177명중 근치적 방사선 치료를 시행한 152명을 대상으로 후향성 분석을 시행하여 다음과 같은 결과를 얻었다. 80% 이상의 환자에서 관해를 보였으며, 이중 완전관해는 22%, 부분관해는 63% 이었다. 전체 환자의 2년, 5년 생존율은 각각 22.9%, 13.3%이었으며 식도암의 위치, 크기, 병기 그리고 관해 정도에 따라 생존율에 차이가 있었다. 식도 촬영상 5 cm 이하(17%) 또는 식도의 상부 1/3에 종양이 있는 경우(26.6%)에 가장 좋은 5년 생존율을 보였다.

관해 정도에 따른 생존율은 완전관해를 보인 경우의 5년 생존율이 34.3%인 반면 반응이 없던 경우는 0% 이었다