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Concurrent Chemoradiotherapy in Locally Advanced Esophageal Cancer

Sang Jun Byun, M.D.*, Jin Hee Kim, M.D.*, Ok Bae Kim, M.D.* and Hong Suk Song, M.D.†

Departments of *Radiation Oncology and †Internal Medicine, Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Korea

Purpose: This study was designed to evaluate the results of local control, survival rate, prognostic factors, and failure pattern in locally advanced esophageal cancer.

Materials and Methods: We retrospectively studied 50 patients with locally advanced esophageal cancer treated with concurrent chemoradiotherapy at Keimyung University Dongsan Medical Center from June of 1999 to August of 2008. Seven patients with inappropriate data were excluded, and 43 patients were analyzed. There were 39 males and four female patients ranging in age from 43 to 78 years (median, 63 years). There were seven patients with stage IIA and 36 with stage III. Irradiation from 46 Gy to 63 Gy (median, 54 Gy) was carried out 5 days per week, 1.8 Gy once a day. There were eight patients with neo-adjuvant chemotherapy, and we mostly used 5-fluorouracil, cisplatin with 3 cycles for concurrent chemotherapy. The range of follow up periods was from 2 to 82 months (median, 15.5).

Results: There were nine patients that exhibited a complete response, 23 that exhibited a partial response, 9 that exhibited no response, and 2 that exhibited disease progression. The median survival time was 15 months. Two-year and 5-year survival rates were 36.5% and 17.3%, respectively. Two-year and 5-year disease-free survival rates were 32.4% and 16%, respectively. Treatment failure occurred in 22 patients (51.2%). Patterns of failure were categorized as local failure in 18 patients and distant metastasis in four patients. In a univariate analysis for prognostic factors related to overall survival and disease-free survival, the hemoglobin levels during chemoradiotherapy ($\geq$12 vs. <12, p=0.02/p=0.1) and the response to the treatments (CR/PR vs. NR/PD, p=0.002/p$<$0.0001) were statistically significant. In a multivariate analysis, only response to the treatments was revealed to be statistically significant. There was no statistical significance associated with patient age, gender, disease stage, T-stage, smoking history, tumor location, or neo-adjuvant chemotherapy.

Conclusion: Our survival rate was similar to those of other institutions. Local recurrence was the main reason for failure. It is suggested that further prospective studies should be performed to improve local control.

Key Words: Esophageal cancer, Concurrent chemoradiotherapy, Survival rate, Prognostic factor, Failure

Introduction

Squamous cell carcinoma in the esophagus is a lethal disease with poor prognosis. It is related to a lymphatic spreading pattern with defects in serosal lining, frequent direct extension into surrounding structures, and even metastasis.[1)]

In the past decades, surgery after diagnosis of the disease in a locally-advanced state was a standard therapeutic option and reported to have low curative rates. There were also several reports to demonstrate better outcomes with postoperative radiotherapy than those with surgery alone.[2~4)] DeMeester and Barlow[2)] suggested that improvement of survival rates might be expected because microscopic tumor after surgery could be eradicated by radiotherapy. The use of chemotherapy followed by surgery had proven to be not effective for preventing distant metastasis or local failure in esophageal cancer.[5)] There were also several trials assessing the effect of preoperative radiotherapy, but there was no clear benefit regarding survival in case of locally-advanced esophageal cancer.[6)]

Recently, concurrent chemoradiotherapy has been associated with more favorable outcomes for locally-advanced esophageal

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Reprint requests to Jin Hee Kim, M.D., Department of Radiation Oncology, Dongsan Medical Center, Keimyung University, 194 Dongsan-dong, Jung-gu, Daegu 700-712, Korea
Tel: 053)250-7665, Fax: 053)250-7984
E-mail: jhkim@dsmc.or.kr

cancer because it can improve local control and combat micrometastases simultaneously. Chemotherapeutic agents like cisplatin and 5-fluorouracil (5-FU) are typically used as radiosensitizers and impart anti-tumor effects.[7,8)]

A phase III trial in the United States, Radiation Therapy Oncology Group (RTOG) 85-01[9)] revealed that the addition of chemotherapy to radiation therapy is superior to radiation therapy alone. Furthermore, concurrent chemoradiotherapy has become a standard of treatment for locally-advanced esophageal cancer.

This study was designed to retrospectively evaluate the local control, survival rate, prognostic factors and failure patterns in locally-advanced esophageal cancer treated with concurrent chemoradiotherapy in our institution.

Materials and Methods

We retrospectively studied 50 patients with locally-advanced esophageal cancer treated with concurrent chemoradiotherapy at Keimyung University Dongsan Medical Center from June of 1999 to August of 2008. Patients underwent physical examination, complete blood cell count, chest X-ray, chest high resolution computed tomography, positron emission tomography computed tomography (PET-CT), and endoscopic biopsies to confirm the presence of disease and evaluate the clinical stage. PET-CT scan was performed since March of 2007 in our institution and only eight patients underwent PET-CT for clinical staging. The patients were grouped according to the AJCC TNM 6th edition staging method. The eligibility criteria for locally-advanced disease were stage T1N1M0 or T2-4, any N, M0. Periods for evaluating treatment outcomes were calculated from the first day of radiotherapy.

Two patients without regular follow-up after completion of concurrent chemoradiotherapy and five patients for whom we could not confirm treatment results due to the absence of appropriate follow-up examination were excluded from this study; in total, 43 patients were analyzed in our study. The patients' characteristics are presented in Table 1. There were 39 males and four female patients with a range of age from 43 to 78 years old (median, 63 years). There were seven patients with stage IIA and 36 with stage III. All patients were squamous cell carcinoma in pathology. The performance status before the treatments was Eastern Cooperative Oncology Group (ECOG). 0 in 22 patients and ECOG 1 in 21 patients.

Table 1. Patients Characteristics

Characteristics	Values
Age	43~78 (median 63)
Gender	
Male	39
Female	4
Pathology - Squamous cell carcinoma	
Well differentiated	4
Moderately differentiated	16
Poorly differentiated	5
Unknown	18
Stage	
IIA	7
III	36
Performance status	
ECOG* 0	22
ECOG 1	21
Radiation therapy dose (Gy)	
<54	6
≥ 54	37
T-stage	
T2	5
T3	17
T4	21
N-stage	
Nx	1
N0	10
N1	32
Tumor location	
Cervical	2
Upper thoracic	2
Middle thoracic	26
Lower thoracic	13

*Eastern Cooperative Oncology Group.

In radiation therapy planning, a margin of 5 cm above and below the GTV and 1.5-cm radial margin are usually applied to cover subclinical disease. The margin was reduced to 2 cm in above and below the GTV and 1 cm in radial margin after 45 Gy. Two-dimensional technique was applied for 28 patients until December of 2004 with anteroposterior (AP)-posteroanterior (PA) bilateral opposing fields up to 41.4 Gy and more than two fields to shield spinal cord for remaining dose. Three-dimensional conformal technique was used since Jan of 2005 for 15 patients. Forty-six Gy to 63 Gy of radiation was delivered with 6/10/15 MV photons (median, 54 Gy) for 5 days per week and 1.8 Gy once a day.

There were eight patients who underwent concurrent chemoradiotherapy 4 weeks after completion of neo-adjuvant chemotherapy. Six patients were treated with 5-FU/cisplatin

Table 2. Chemotherapeutic Regimens

Chemotherapy	No. (%)
Neo-adjuvant CTx* regimens	
5-FU†/cisplatin	6 (75.0)
Paclitaxel/cisplatin	2 (25.0)
Total	8 (100)
Concurrent CTx regimens	
5-FU/cisplatin	37 (86.0)
Docetaxel/cisplatin	3 (7.0)
Paclitaxel/cisplatin	2 (4.7)
5-FU only	1 (2.3)
Total	43 (100)

*chemotherapy, †5-fluorouracil.

Table 3. Treatment Response

Response	No. (%)
Complete response	9 (20.9)
Partial response	23 (53.5)
No response	9 (20.9)
Progression of disease	2 (4.7)
Total	43 (100)

and two patients were given paclitaxel/cisplatin before concurrent chemoradiotherapy. Concurrent chemoradiotherapy was administered, mainly 5-FU/cisplatin-based regimens with continuous infusion. 5-FU 1,000 mg/m^2 with 5% dextrose in water 500 mL was delivered, starting on days 1 to 4 as a continuous intravenous infusion. Cisplatin 75 mg/m^2 with 0.9% normal saline 500 mL was delivered during 1 day with 3-week interval. Thirty-seven patients were treated with 5-FU/cisplatin and two of them were administered additional chemotherapy. One was given additional docetaxel/cisplatin, and another one patient was treated with paclitaxel/cisplatin. Three patients were treated with docetaxel/cisplatin and one of them received additional dose of 5-FU/cisplatin. Two patients were treated with paclitaxel/cisplatin and one of them received additional 5-FU/cisplatin treatment. The remaining 1 patient was administered only 5-FU (Table 2).

Follow-up chest CT scans or endoscopic examinations were performed at 1 to 3 months after completion of concurrent chemoradiotherapy. We used World Health Organization (WHO) criteria including complete response (CR), partial response (PR), no response (NR), and progression of disease (PD) for assessment after completion of concurrent chemoradiotherapy.[10] The range of follow-up periods was from 2 to 82 months with a median of 15.5 months. The time to local failure and distant metastases were analyzed from the starting day of any treatment modalities including neo-adjuvant chemotherapy and concurrent chemoradiotherapy after diagnosis.

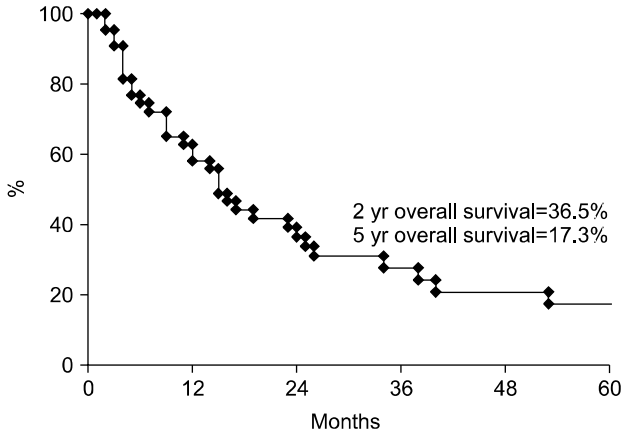

Fig. 1. Overall survival curve.

The Kaplan-Meier method was used to estimate overall survival rates (OS) and disease-free survival rates (DFS). Univariate analysis evaluating factors associated with OS was performed by a log-rank test. Factors found to influence survival on univariate analysis were then analyzed by Cox proportional hazard regression analysis. Statistical analyses were performed with SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA).

Results

1. Local control and survival

As shown in Table 3, there were nine patients showing complete response (20.9%), 23 presenting partial responses (53.5%), nine showing no response (20.9%), and two with disease (4.7%). Two-year and 5-year overall survival rates were 36.5% and 17.3%, respectively (Fig. 1). Two-year and 5-year disease-free survival rates were 32.4% and 16%, respectively (Fig. 2). The median survival of all patients was 15 months.

2. Prognostic factor

We analyzed several factors that may impact disease prognosis including patient age, gender, disease stage, smoking

history, total radiation dose, prior treatments before concurrent chemoradiotherapy, hemoglobin level at the time of chemoradiotherapy, tumor location in the esophagus, response to treatment and absence or presence of neo-adjuvant chemotherapy.

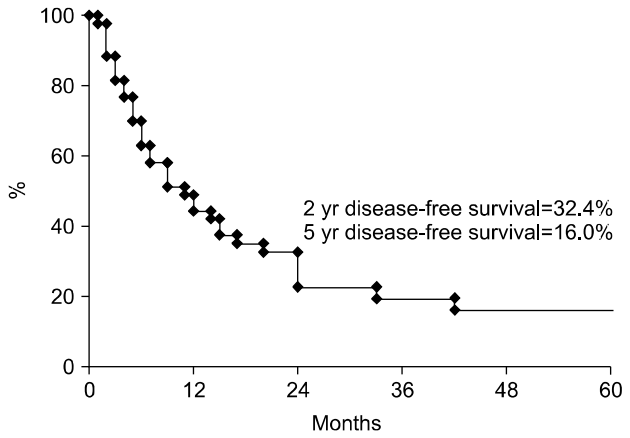

Fig. 2. Disease free survival curve.

As shown in Table 4, on univariate analysis for identifying potential prognostic factors related to overall survival, hemoglobin level at the time of chemoradiotherapy (<12 vs. ≥12, p=0.02) and response to treatments (CR/PR vs. NR/PD, p=0.002) were statistically significant (Fig. 3, 4) and the total dose of radiation therapy (<54 Gy vs. ≥54 Gy, p=0.06) was marginally significant. On multivariate analysis, response to treatments was only found to be statistically significant (95% confidence interval [CI], 1.289 to 7.595; hazard ratio [HR], 3.129; p=0.012).

On univariate analysis for identifying potential prognostic factors related to disease-free survival, response to treatments (CR/PR vs. NR/PD, p<0.0001) was statistically significant and hemoglobin level at the time of chemoradiotherapy (<12 vs. ≥12, p=0.1) was marginally significant. On multivariate analysis, response to treatments was also found to be

Table 4. Univariate Analysis of Prognostic Factors Related to Overall Survival

Values		No.	Overall survival		p-value	Disease-free survival		p-value
			2 yr	5 yr		2 yr	5 yr	
Age	≤62	19	36.8	12.6	0.814	24.1	16.1	0.172
	>62	24	36.5	21.9		41.5	41.5	
Gender	Male	39	35.6	18.2	0.602	35.8	29.8	0.585
	Female	4	50.0	0		0	0	
Stage	IIA	7	68.6	0	0.43	35.7	0	0.589
	III	36	30.1	22.6		33.5	33.5	
T-stage	T2	5	75.0	-	0.981	30.0	-	0.251
	T3	17	100	56.3		48.8	39.0	
	T4	21	85.7	57.1		18.9	18.9	
Smoking	(+)	37	37.6	19.3	0.671	35.1	29.2	0.686
	(−)	6	25.0	-		0	-	
Performance status (ECOG*)	0	27	56.2	32.4	0.196	38.0	38.0	0.502
	1	8	37.5	-		18.8	-	
	2	2	50.0	-		50.0	0	
	3	6	25.0	-		33.3	-	
Hemoglobin (g/dL)	<12	15	20.0	13.3	0.02	23.6	23.6	0.1
	≥12	28	45.1	17.4		38.1	28.6	
Neo-adjuvant chemotherapy	(+)	8	37.5	25.0	0.734	38.9	38.9	0.63
	(−)	35	36.1	14.6		33.2	24.9	
Chemotherapy regimen	5-FU†/cisplatin	37	47.9	22.0	0.853	35.9	28.7	0.906
	Taxol/cisplatin	5	53.3	26.7		26.7	26.7	
Tumor location	Cervical	2	50.0	-	0.548	0	-	0.274
	Upper thoracic	2	-	-		-	-	
	Middle thoracic	26	34.6	18.5		30.8	30.8	
	Lower thoracic	13	46.2	23.1		62.9	42.0	
Radiotherapy dose (Gy)	<54	6	16.7	-	0.06	20.0	-	0.417
	≥54	37	39.7	18.5		35.5	29.6	
Response	CR‡/PR§	32	59.6	30.0	0.002	42.8	35.7	<0.0001
	NR‖/PD¶	11	18.2	0		9.1	-	

*Eastern Cooperative Oncology Group, †fluorouracil, ‡complete response, §partial response, ‖no response, ¶progression of disease.

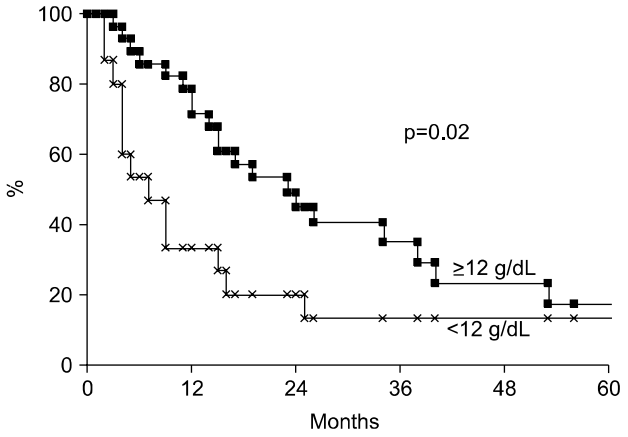

Fig. 3. Overall survival curves according to hemoglobin level.

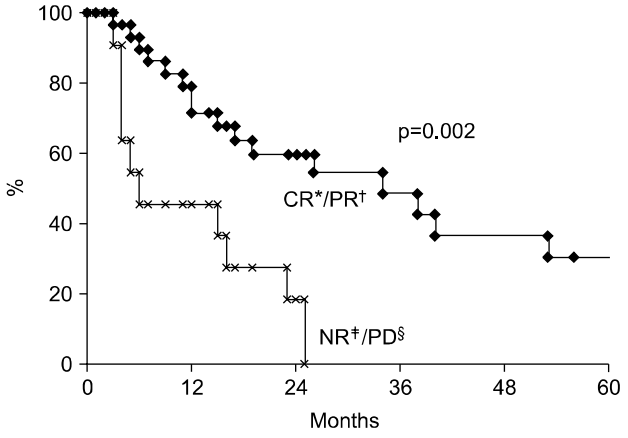

Fig. 4. Overall survival curves according to response after treatments. *complete response, †partial response, ‡no response, §progression of disease.

statistically significant (95% CI, 1.836 to 9.841; HR, 4.251; p=0.001). There was no statistical significance associated with patient age, gender, disease stage, T-stage, smoking history, tumor location, or neo-adjuvant chemotherapy.

3. Patterns of treatment failure

There were 22 patients with recurring disease (51.2%) and the patterns of the recurrence were separated to local failure in one patient among nine with complete response (2.3%), local progression in 17 patients (39.5%), and distant metastasis in four individuals (9.3%), as shown in Table 5. Disease recurrence in the one patient with a complete response occurred 42 months after completion of concurrent chemoradiotherapy. There was no patient who had both local treatment failure and distant metastasis.

Table 5. Patterns of Failure

Type of failure	No. (%)
Recurrence after complete response	1 (2.3)
Local progression	17 (39.5)
Distant metastasis	4 (9.3)
Total	22 (51.2*)

*percentage in all patients.

Table 6. Complications

Complication		No. (%)
Acute complication	Esophagitis	5/43 (11.6)
	Ulceration	1/43 (2.3)
Late complication	Stricture/obstruction	12/43 (27.9)

4. Complications

Endoscopic examination was performed 1 to 3 months after completion of concurrent chemoradiotherapy and five patients (11.6%) developed esophagitis. Three patients were diagnosed at 2 months and two patients at 1 month following chemoradiotherapy. The one patient (2.3%) with esophagitis after 1 month also suffered from ulcers.

Esophageal strictures and obstructions occurred in 12 patients (27.9%) with dysphagia. Six patients were found to have strictures 2 months after treatment and two patients developed dysphagia after 1 month. Dysphagia was found in the four patients at 5, 6, 7, and 22 months following treatment by follow-up endoscopic examination (Table 6).

Discussion and Conclusion

Although there have been several trials conducted with the goal of improving survival of locally-advanced esophageal cancer, it is still challenging to expect better outcomes in these patients. Herskovic et al.[11] reported a 50% 1-year overall survival rate and 38% 2-year overall survival rate, with a median survival period of 12.5 months in 121 locally-advanced esophageal cancer patients who received concurrent chemoradiotherapy. Smith et al.[12] also reported a 27% 2-year overall survival among 119 patients with stage I and II after concurrent chemoradiotherapy with a median survival period of 14.8 months. They also found improved overall survival in

patients with locally-advanced esophageal cancer compared to those who received radiation therapy alone. Two-year and 5-year overall survival rates were 27% and 9%, respectively, in chemoradiotherapy group, and 12% and 7%, respectively, in the group that only received radiation.

RTOG 85-01 showed that treatment with concurrent chemoradiotherapy resulted in significantly increased overall survival rates compared to radiotherapy alone in cases of locally-advanced esophageal cancer (T1-3 N0-1 M0). The overall survival rate for the concurrent chemoradiotherapy group at 5 years was 26% and 0% for the group that only received radiotherapy.[9] In our study, the overall survival rates at 2 years and 5 years were 36.5% and 17.3%, respectively, with a median survival periods of 15 months, similar to outcomes of other trials. However, the distribution of patients according to disease stage was relatively uneven, seven patients were stage IIA and 36 were stage III. More reliable results would be obtained if the study had been conducted with a more uniform patients group.

There are several factors related to prognosis in esophageal cancer patients including disease stage, tumor location, tumor size, histologic type, gender, ethnicity, patient age, and response to treatment. Generally, tumor oxygenation is also considered to be of prognostic value and effect local control of tumors in locally-advanced cancers.[13~17] Many investigators also have reported that hemoglobin level before treatment is a valuable prognostic factor.[18~21] In our study, the pre-treatment hemoglobin level higher than 12 g/dL is a significant prognostic factor in survival. Neuhof et al.[21] have reported that patients with hemoglobin concentrations >13.4 g/dL had significantly better overall survival rates than ones with lower hemoglobin concentrations. Rades et al.[20] also reported that the best overall survival rate was achieved when the hemoglobin concentration level was between 12.1 and 14.0 g/dL followed by levels >14.1 g/dL and <12 g/dL suggesting the existence of an optimal range of hemoglobin concentrations. Therefore, assessment of hemoglobin level before concurrent chemoradiotherapy and regular follow-up during the treatments are proposed to enhance the effect on patient prognosis.

Response to treatments has been also reported to be a prognostic factor related to survival rates.[22,23] Stahl et al.[22] reported that patients with tumors responding to treatment had a better probability of surviving, whereas the outcomes of non-responders was generally poor. We divided patients in our study into two response groups: patients with complete responses or partial responses and patients with no response or disease progression. Given the results of our study, patient prognosis in patients may be predicted according to the response to treatment.

Stage is one of the most meaningful prognostic factors in estimating survival rates including depth of tumor invasion, nodal involvement, and distant metastases. Results related to staging in our institution did not show any significance to expect the prognosis for esophageal cancer patients. However, the number of patients in our study was relatively small compared to other institutional studies. Furthermore, the TNM classification with 6th edition is simply assorted compared with recent staging system.

Esophageal cancers in men tend to have a more aggressive nature with poorer outcomes.[1] Result in our study did not show any statistical significance according to gender. However, the relatively small number of female patients in our study causes a little significance for expecting prognosis.

Herskovic et al.[11] reported a 39% rate of local recurrence after concurrent chemoradiotherapy, 7% were distant metastasis only and 5% were local recurrences with distant metastasis. In our study, local recurrence rate after complete response to treatment was 2.3%, local progression was found in 39.5% of the patients, and distant metastases were reported in 9.3% of the patients. There were no patients with local recurrence and distant metastasis at the same time. The patterns of treatment failure in our study are similar with other institutional studies.

Generally, it has been found that acute complications in patients undergoing chemoradiotherapy are more severe than those of patients receiving radiation alone. These complications include esophagitis along with other common problems like nausea, vomiting, epidermitis, fatigue, and ulceration. Khurana et al.[24] reported a 6% rate of ulceration and 21% rate of esophageal stricture among 68 patients with esophageal cancer after concurrent chemoradiotherapy. Our results showed 11.6% of esophagitis with 2.3% of ulceration and 27.9% of esophageal stricture and obstruction. In our study, small number of patients and irregular follow-up periods might effect on the difference in the results compared with other

trials. Future studies need to examine at appropriate time with many patients group to get more reliable result.

In conclusion, the survival rates of patients with locally-advanced esophageal cancer treated with concurrent chemoradiotherapy in our study were similar to those of other institutions. Local recurrence was a main cause of treatment failure. It is suggested that further prospective studies need to be performed to improve local control.

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국문초록

국소적으로 진행된 식도암에서 동시항암화학방사선치료의 결과

계명대학교 의과대학 동산의료원 방사선종양학교실*, 내과학교실†

변상준*・김진희*・김옥배*・송홍석†

목 적: 국소적으로 진행된 식도암에서 동시항암화학요법 후 국소제어, 생존율, 예후인자 및 실패양상에 대해 알아보고자 하였다.

대상 및 방법: 1999년 6월부터 2008년 8월까지 계명대학교 동산의료원에서 국소적으로 진행된 식도암으로 진단받은 후, 근치적 목적의 동시항암화학방사선치료를 시행 받은 50명 중 추적검사가 이루어지지 않은 2명과 적절한 추적검사가 이루어지지 않아 치료의 효과를 판정할 수 없는 5명은 제외한 43명을 대상으로 하였다. 성별 구성은 남성 39명, 여성 4명이었고 연령분포는 43세에서 78세(중앙값, 63세), TNM 병기는 IIA기 7명(16.3%), III기 36명(83.7%)이었다. 방사선치료는 1.8 Gy씩 1일 1회, 주 5회로 방사선을 46～63 Gy (평균, 54 Gy)의 외부방사선을 조사하였다. 선행항암화학요법을 시행 받은 환자는 8명이었고 동시항암화학치료는 주로 5-fluorouracil, cisplatin을 3회 사용하였다. 추적관찰 기간은 2개월에서 82개월로 중앙값이 15.5개월이었다.

결 과: 전체환자 43명 중에서 완전 관해는 9명(20.9%), 부분 관해는 23명(53.5%), 무반응 9명(20.9%), 진행이 2명(4.7%)이었다. 전체 환자의 중앙생존기간은 15개월이었고, 2년 및 5년 전체생존율은 36.5%, 17.3%이었으며, 2년 및 5년 무병생존율은 각각 32.4%, 16%였다. 43명의 환자 중에서 22명(51.2%)에서 치료 실패를 보였고, 치료 실패 양상으로는 국소 재발 및 진행이 18명(41.9%), 원격전이가 4명(9.3%)이었다. 전체생존율 및 무병생존율에 영향을 미치는 인자에 대한 단변량분석상 항암화학방사선치료 시의 혈색소 수치(≥12 vs. <12, p=0.02/p=0.1)와 치료에 대한 반응 여부(완전관해 및 부분관해 vs. 무반응 및 병의 진행, p=0.002/p<0.0001)가 통계적으로 유의한 인자였다. 다변량분석에서는 치료에 대한 반응 여부만이 통계적으로 유의한 것으로 나타났다. 환자의 나이, 성별, 병기, 흡연의 과거력, 식도 내 종양의 위치 및 선행항암화학요법의 유무에 따른 유의한 차이는 관찰되지 않았다.

결 론: 국소적으로 진행된 식도암의 동시 항암화학방사선치료 후 생존율은 다른 연구들과 유사한 수준이며 주된 재발 양상은 국소 재발이었다. 그러므로, 국소제어율을 향상시키기 위한 추가적인 연구가 향후 필요할 것으로 생각된다.

핵심용어: 식도암, 동시항암화학방사선치료, 생존율, 예후 인자, 실패양상