Local Control may be the Key in Improving Treatment Outcomes of Esophageal Squamous Cell Carcinoma Undergoing Concurrent Chemoradiation

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ABSTRACT

Introduction: Little is known about the patterns of treatment failure following definitive chemoradiotherapy (CCRT), especially in esophageal squamous cell carcinoma (SCC). We evaluated definitive CCRT failure patterns and determined the predictive factors for treatment response in esophageal SCC.

Methods: We evaluated 136 consecutive patients with esophageal SCC treated with definitive CCRT. We evaluated the factors associated with complete remission (CR) after CCRT and analyzed the pattern of treatment failure of recurred patients and imcomplete remission patients. The failures were categorized as either within (locoregional failure) or outside the radiation field (out-field failure).

Results: Fifty-seven patients achieved CR after CCRT. Consolidation chemotherapy was significantly associated with CR. Only 4 (7.0%) patients had CR after CCRT in patients with M1a node (Celiac or subclavian lymph nodes involvement by 6th AJCC). During follow-up, 74 patients (54.4%) experienced locoregional failure, 26 (19.1%) out-field failure, and 35 (25.7%) no failure. Esophageal obstruction prior to CCRT, residual tumor according to the

first follow-up endoscopy, and poor follow-up computed tomography responses were significantly associated with locoregional failure.

Conclusion: Approximately 70% of treatment failures were local failures. Future therapeutic strategies need to focus on improving local control such as radiation dose modulation or surgical resection for residual tumors.

Key words: esophageal squamous cell carcinoma; concurrent chemoradiation; failure patterns; local control

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I. Introduction

Locally advanced esophageal squamous cell carcinoma (SCC) is a highly aggressive and fatal disease, which often persists or recurs after definitive concurrent chemoradiation (CCRT). In the past, surgery alone was the standard treatment for resectable esophageal cancer, but the prognosis remained poor with 5-year survival rates ranging from 20% to 27%.[1] The increased interest in multimodality approach for other solid tumors has resulted in active research in combined modality treatment for esophageal carcinoma.[2] According to the results of these recent studies, the current trimodality approach combining chemotherapy, radiotherapy, and surgical intervention confers significantly better prognoses and survival rates. Thomas et al. reported that 25% of patients assigned to multimodal therapy experienced a complete pathological response after resection and that 32% were alive after 3 years, whereas only 6% of patients treated with surgery alone lived for another 3 years.[3] The RTOG 8501[4] randomized controlled trial and an Eastern Cooperative Oncology Group (ECOG) trial [5] showed that chemoradiation therapy (CCRT) without additional surgery is a curative option for patients with locally advanced esophageal cancer. In RTOG 8501, the 5-year survival rate was significantly improved for patients treated with CCRT (26%) compared with those treated with radiation alone (0%). Other studies have shown that 17–51% of esophageal SCC patients achieve a complete response (CR) after CCRT;[5-7] however, 50% of these cases later develop cancer recurrence.

To date, few studies have investigated the failure patterns and associated prognostic factors

following CCRT in esophageal SCC,[8,9] and these studies were limited by small sample sizes and mixed patient populations of different histologic subtypes. Therefore, the aims of this study were to identify the factors predictive of CR in esophageal SCC and to analyze the patterns of treatment failure after definitive CCRT.

II. Patients and Methods

Patient population

We performed a retrospective analysis of 136 patients who were pathologically diagnosed of esophageal SCC and treated with definitive CCRT at Gangnam Severance and Severance hospital from January 2005 to December 2010. Pretreatment staging evaluations included a physical examination, esophagogastroscopy (EGD) with biopsy, endoscopic ultrasound (EUS), chest and abdominal computed tomography (CT) scans, and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) or PET-CT scans. The longitudinal and circumferential diameters, and T stage were evaluated using EGD and EUS, and the N and M stages were determined using EUS, chest CT, and PET-CT. The patients were categorized into three groups defined as intense, moderate, and no uptake, according to the degree of tumor FDG uptake measured by PET-CT. The clinical staging of SCC was classified by the 7th AJCC staging system[10]. Patients with distant metastasis at the time of diagnosis, those who received CCRT as a palliative or neoadjuvant treatment, those who underwent esophagectomy after CCRT or had other primary tumors were excluded from the study. All patients had M0 stage disease based on the 7th AJCC staging system. Among them, the patients who classified as M1a stage by the 6th AJCC edition were included in a subgroup analysis.

Treatment and response evaluations

Gross tumor volume (GTV) was defined as visible tumor and involved lymph node(s) in simulation

CT or PET/CT images fused onto simulation CT images. Clinical target volume (CTV) was determined by expansion of GTV by 3 cm craniocaudally, 1 cm laterally, and 3 cm into the gastric mucosa in case of gastroesophageal junction tumors. Planning target volume (PTV) was then calculated by uniform 0.5-cm expansion of the CTV borders. Radiation therapy was started on day 1 of chemotherapy using 10-MV photon beams. A conventional fraction schedule (5 days per week, 1.8-2.0 Gy/daily fraction) and the cone-down technique were used in all patients. Cisplatin and 5-FU were administered in 97.1% of the patients, while the rest of the patients received carboplatin and 5-FU. Two cycles of chemotherapy were administered concurrently with radiotherapy. After CCRT, 66% of patients received 1-4 cycles of consolidation chemotherapy. The patients were restaged at about 3 months after completion of CCRT according to the results of the EGD, CT scans, and PET-CT. A CR was defined as no residual tumor, and a partial response was defined as the persistence of any residual tumor, as detected by EGD or imaging studies.

Patterns of treatment failure

Treatment failure was defined as disease recurrence after CR and incomplete remission after CCRT. The failures were categorized as either within (locoregional failure) or outside the radiation field (out-field failure). Based on the radiation treatment volume, locoregional failures were further classified as GTV failure or CTV failure which was determined by the attending radiation oncologist. The patterns and predictive factors of treatment failure were assessed.

Statistical analysis

The chi-square and Fisher's exact tests were used to evaluate the associations among various categorical variables, and the *t*-test was used for non-categorical variables. Survival time was measured from the date of diagnosis to the date of the most recent follow-up visit or date of death. Survival curves were plotted using the Kaplan–Meier method. Multivariate analysis was performed using the Cox proportional hazard model. A p-value < 0.05 was indicative of statistical significance.

All analyses were performed using the SPSS software (ver. 18.0; SPSS Inc., Chicago, IL).

III. Results

Patient characteristics

Table 1 shows the baseline characteristics of the 136 patients included in this study. The mean age was 65.6 years, and 130 (95.6%) of the patients were male. Most were diagnosed with clinical stage II (28.1%) or stage III (64.0%) cancer. All patients had M0 disease based on the 7th AJCC staging system. However, 21% among the patients had celiac or subclavian metastatic lymph nodes, defined as extended metastasis according to the previous staging system (the 6th AJCC). The mean tumor length and circumference were 5.38 (± 2.6cm) and 71.3 (±22.5, %), respectively. The median radiation dose was 54.0 (range, 45.0-77.0) Gy in 30 fractions of 1.8 Gy each, and the mean duration of radiotherapy was 46.4 (±8.9) days

Table 1. Baseline characteristics of the patients and lesions

Characteristics	Value (n, %)
Age (year, mean (range))	65.6 (31-81)
Gender	
Male	130 (95.6)
Tumor location	
Cervical	5 (3.7)
Upper thoracic	25 (18.4)
Mid thoracic	46 (33.8)
Lower thoracic	60 (44.1)
Gross appearance in endoscopy	
Mass forming (SMT[1]-like)	66 (48.5)
Ulcerative	70 (51.5)
Tumor category	

Characteristics	Value (n, %)
T1	15 (11.0)
T2	24 (17.6)
T3	77 (56.7)
T4	20 (14.7)
Lymph node category	
N0	28 (20.6)
N1	108 (79.4)
Metastasis category	
M0	136
M1a by the 6th AJCC[2]	21(15.4)
Clinical stage	
I	11 (7.9)
II	39 (28.1)
III	89 (64.0)
IV	0 (0)
Endoscopic stent insertion	13 (9.6)
Tumor histology	
SCC, WD[3]	18 (13.2)
SCC, MD[4]	86 (63.2)
SCC, PD[5]	32 (23.6)
Initial PET[6] uptake	120 (88.2)
Intense	85 (70.8)
Moderate	30 (25.0)
No uptake	5 (4.2)

Characteristics	Value (n, %)
Chemotherapy	
Regimen	
5FU+ cisplatin	132 (97.1)
5FU +carboplatin	4 (2.9)
Consolidation chemotherapy	
Done	66 (64.1)
Radiotherapy	
Total dose (mean, Gy [range])	56.2 [4500-7700]
Duration (mean, day)	46. 4 ± 8.9

SMT[1], submucosal tumor;

M1a node[2], celiac or subclavian metastatic lymph nodes, defined as extended metastasis according to the 6th AJCC

WD[3], well differentiated; MD[4], moderately differentiated; PD[5], poorly differentiated

PET[6], positron emission tomography

Predictive factors for CR after CCRT

Fifty-seven patients (41.9%) achieved CR after definitive CCRT, and the mean follow-up duration was 20.3 (± 15.5) months. We analyzed predictive factors associated with CR after CCRT. The CR rate was higher for patients with tumors located at cervical lesions. Patients with inserted esophageal stents achieved a lower CR rate, as did those with "intense" initial FDG uptake in the main tumor mass, whereas all five patients with no FDG uptake achieved CR. Patients with stage M1a nodal involvement based on the 6th AJCC staging had lower CR rates than those with M0 disease. In addition, the patients that received consolidation chemotherapy after CCRT had significantly higher CR rates (Table 2). The mean RT dose was 56.7 Gy for the CR group and 55.7 Gy for the non-CR group, but this difference was not significant ($p = 0.352$).

Table 2. Predictive factors for complete remission after concurrent chemoradiation

Characteristics	CR (n=57) (n, %)	Non-CR (n=79) (n, %)	*p*-value
Age (yr, mean±SD)	66.4±8.6	64.9±8.5	0.328*
Location			**0.047**†
Cervical	5 (8.8)	0 (0)	
Upper thoracic	8 (14.0)	17 (21.5)	
Mid thoracic	19 (33.3)	28 (34.2)	
Lower thoracic	25 (43.9)	35 (44.3)	
Endoscopic stent insertion	1 (1.8)	12 (15.2)	**0.007**†
PET uptake of main mass			**0.007**†
Intense	30 (58.8)	55 (79.7)	
Moderate	16 (31.4)	14 (20.3)	
No uptake	5 (9.8)	0 (0)	
T stage (tumor depth)			0.056†
T1/2	21 (36.8)	18 (22.8)	
T 3/4	36 (63.2)	61 (77.2)	
N stage			0.053†
N0	16 (28.1)	12 (15.1)	
N1	41 (71.9)	67 (84.9)	
M stage (by the 6th AJCC)			**0.017**†
M0	53 (93.0)	62 (78.5)	
M1a	4 (7.0)	17 (21.5)	
Consolidation chemotherapy	44 (77.2)	50 (63.3)	**0.049**†
Radiotherapy			
Total dose (Gy, mean) (range)	56.7 (45.0-63.0)	55.7(45.0-77.0)	0.352*

* p value was obtained by t-test

† p value was obtained by Chi-square test

By multivariate analysis, M1a lymph node involvement base on the 6th AJCC staging was significantly associated with non-CR patients. The group treated with consolidation chemotherapy after the first cycle of CCRT achieved a higher CR rate (Table 3).

Table3. Multivariate analysis for complete remission after concurrent chemoradiation

Variables	Odds ratio*(95% CI†)	*p*-value
Location		0.780
Presence of stent		0.118
M1a node involvement[1]	0.199 (0.053-0.751)	**0.017**
Consolidation chemotherapy	0.403 (0.175-0.931)	0.033
PET uptake of main mass		0.950

Odd ratio* obtained by Chi-square test.

CI†, confidence interval

The patterns of treatment failure after CCRT

There were 22 patients (16.2%) who experienced cancer recurrence after CR and 79 patients who did not achieve CR after CCRT, one of which was lost to follow-up. Thus, 100 total patients classified as treatment failures were analyzed to identify the clinical factors associated with treatment failure patterns. Fig. 1 shows that 74 patients (54.4%) experienced locoregional failure, 26 (19.1%) out-field failure, and 35 (25.7%) no evidence of failure. Among the locoregional failures, there were 73 (98.6%) GTV failures and 1 (1.4%) CTV failure.

Table 4 shows the predictive factors related to locoregional failure after CCRT. In the patients with stents inserted at the time of diagnosis, the locoregional failure rate was higher than the out-field

failure rate. After CCRT, 62.9% of the patients with locoregional failure showed residual tumor mass during the first follow-up endoscopy. Those with good follow-up CT responses had a much higher out-field than locoregional failure rate (38.5% vs. 16.2%).

Table 4. Comparison of the predictive factors related to treatment failure patterns at locoregional failure *versus* outfield failure after concurrent chemoradiation

Characteristics	**Locoregional failure (N=74) (n, %)**	**Outfield failure (N=26) (n, %)**	***p*-value**
EGD finding			0.543*
Mass forming (SMT like)	36 (48.6)	13 (50.0)	
Ulcerative	38 (51.4)	13 (50.0)	
Location			
Cervical	1 (1.4)	1 (3.8)	0.876*
Upper thoracic	13 (17.6)	5 (19.2)	
Mid-thoracic	25 (33.8)	8 (30.8)	
Lower thoracic	35 (47.2)	12 (46.2)	
Endoscopic stent insertion	13 (17.6)	0 (0)	**0.015***
Radiotherapy			
Total dose (Gy, mean)	56.0	56.8	0.614†
After chemoradiation			
Follow up endoscopic finding			
No tumor	26 (37.1)	16 (61.5)	**0.028***
Residual tumor	44 (62.9)	10 (38.5)	
Endoscopic pathology			
Pathologic CR[1]	44 (62.9)	21 (80.8)	0.075*
Non pathologic CR	26 (37.1)	5 (19.2)	

Characteristics	Locoregional failure (N=74) (n, %)	Outfield failure (N=26) (n, %)	*p*-value
CT response‡			
CR	12 (16.2)	10 (38.5)	**0.021***
PR[2]/SD[3]/PD[4]	62 (83.8)	16 (61.5)	

CR[1] complete response; PR[2] partial response; SD[3]stable disease; PD[4]progressive disease

* p value was obtained by Chi-square test. † p value was obtained by t-test

‡ According to RECIST (Response Evaluation Criteria in Solid Tumours) criteria

Among the locoregional failure group, 71 patients had local recurrence in the esophagus and 10 had node recurrence. Distant metastatic lesions in the treatment failure patients occurred in the bone (4%), lung (13%), brain (1%) and liver (1%). Fig. 1 shows a flowchart for the clinical course after CCRT in this study.

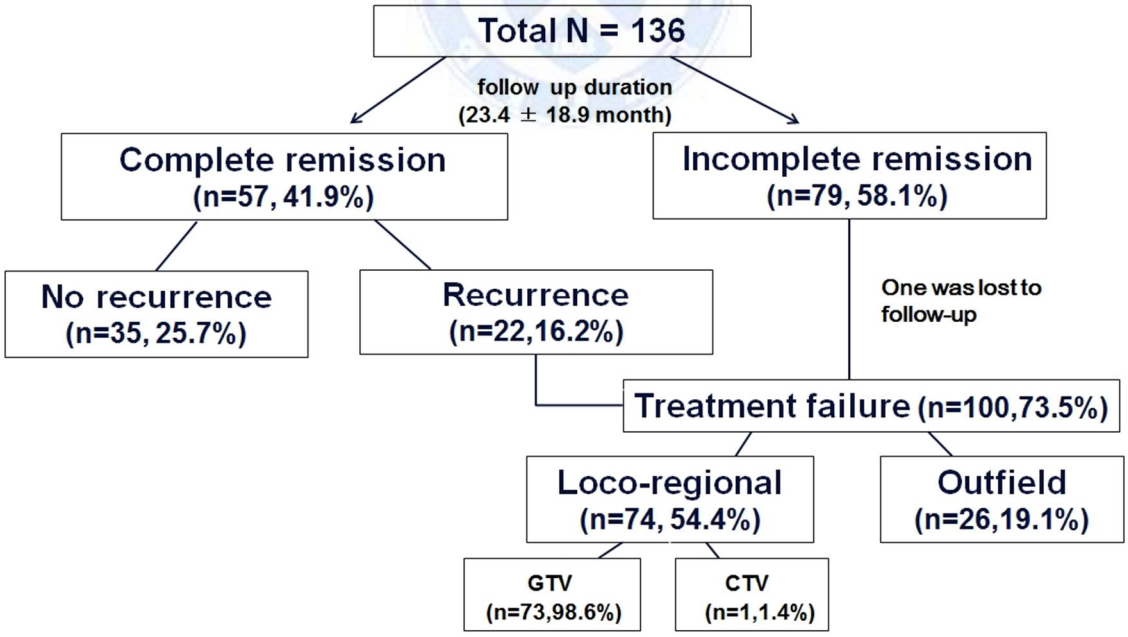

Fig.1. Flowchart depicting the clinical course after concurrent chemoradiation

GTV; gross tumor volume, CTV; clinical target volume.

Survival rate

The mean follow-up duration of total enrolled patients was 23.4 ± 18.9 (median: 19.0) months, and the median overall survival (OS) time for the entire cohort was 12.0 months. Fig. 2.a shows that the OS rate of the CR group was significantly better than that of the non-CR group (median OS: 26 months) (*$p<0.001$*). Fig. 2.b shows that the OS rate of the locoregional failure group was higher, albeit not statistically significantly so, than that of the out-field failure group (median OS: 30 vs. 25 months) *($p=0.725$)*

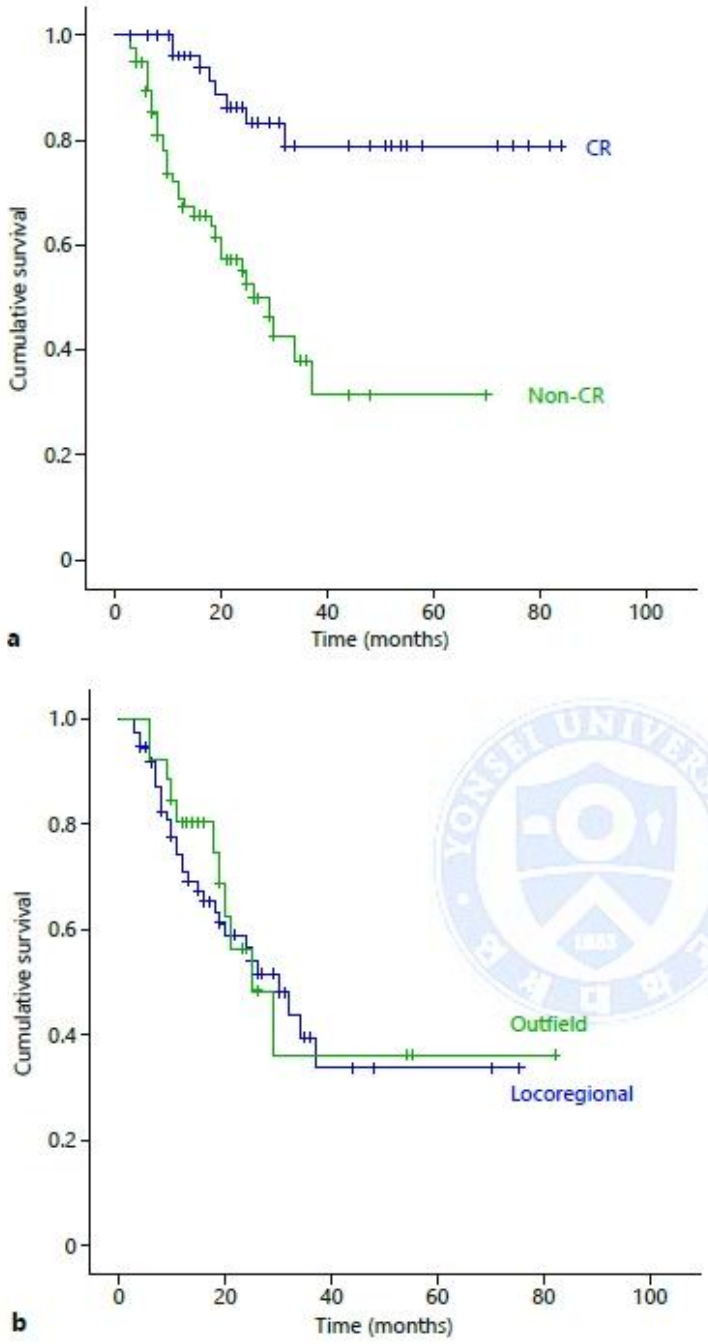

Fig. 2. a The overall survival rates of the complete response (CR) and non-CR groups. The CR group showed a significantly higher survival rate ($p < 0.001$). b. The overall survival rates of the locoregional failure and out-field failure groups (median OS: 30 versus 25 months, $p = 0.725$).

IV. Discussion

Both definitive and neoadjuvant CCRT followed by surgery are curative treatment options for locally advanced esophageal carcinoma.[3] Even though significant survival advantages have not been demonstrated for either therapeutic option, the patients in this study showed a positive response and favorable prognosis after CCRT. Previous studies that separately analyzed patients with SCC and esophageal adenocarcinoma determined different prognoses for these two groups following preoperative CCRT. In patients with esophageal adenocarcinoma, the achievement of node negative disease after CCRT is the best predictor of clinical outcome.[11] In SCC, conversely, CR of the primary tumor predicts a positive long-term outcome in patients with SCC.[12] However, studies about predictive factors for CR after CCRT focused on esophageal SCC have been rare. Notably, our study population consisted exclusively of patients with esophageal SCC, and we demonstrated that tumor location, FDG uptake, esophageal obstruction (stent insertion required), consolidation chemotherapy, and T, N staging and M1a node involvement based on the 6th AJCC edition, were all associated with CR after definitive CCRT. Using multivariate analysis, M1a node involvement base on the 6th AJCC edition and consolidation chemotherapy were confirmed to be predictive factors for CR after CCRT. According to the previous study, esophageal SCC might have higher metastatic potential than esophageal adenocarcinoma.[13] Therefore, the role of consolidation chemotherapy may be more important in esophageal SCC than esophageal adenocarcinoma although further study will be necessary. And, clinical significance of M1a node involvement base on the 6th AJCC edition should be reinvestigated although theses nodes are regarded as regional metastatic lymph nodes based on the 7th AJCC edition.

In previous studies, at least 40% of patients that underwent CCRT experienced locoregional failure, but not all of them developed distant metastases.[4,13] Welsh et al.[14] reported that most cases of local failure after definitive CCRT occur in the GTV, but their study group was composed of mainly adenocarcinoma patients. Our study shows that 74% of the esophageal SCC patients experienced

locoregional failure after CCRT and that the factors associated with locoregional failure included endoscopic stent insertion at the time of diagnosis, endoscopic findings, and CT response after the first CCRT cycle. Approximately two-thirds of the patients with treatment failure were locoregional failures, of which 73% occurred in the GTV; this is similar to a previous study[14]. However, there was no significant difference between locoregional and out-field failure in terms of the survival rate, suggesting that local control of esophageal SCC is important for improvement of survival rate as well as control of distant metastasis. However, further study should be necessary about predictive factors of loco-regional failure and the way to improve local control in esophageal SCC after CCRT.

Further therapeutic strategies may be considered such as dose escalation radiotherapy or surgical resection of residual tumor to enhance local control following definitive CCRT. Although dose escalation radiotherapy was shown to improve local control and survival in patients with other types of solid tumors,[15,16] its efficacy has not been demonstrated in esophageal SCC.[17] For example, high-dose radiation therapy could substantially increase the risk of esophageal stricture and/ or perforation, a potentially life-threatening complication. In contrast, some studies presented that some patients were cured with salvage esophagectomy after CCRT, and long-term survival was not worse than expected.[18,19]

Although neither the RT dose nor the RT duration influenced the locoregional failure rate, subgroup analyses to determine the effective RT dose could be important. For example, patients with high tumor burden such as esophageal obstruction or M1a node involvement such as celiac or subclavian metastatic lymph nodes defined as extended metastasis according to the 6th AJCC could be candidates for potential subgroups, based on our findings. Especially, M1a node involvement according to the 6th AJCC may be good candidate of dose escalation radiotherapy with acceptable toxiticy or salvage operation after CCRT for local control.[20]

The sensitivity and specificity of FDG-PET are higher in esophageal carcinoma than other cancers,

such that accurate target volume delineation in radiotherapy might be possible using FDG-PET.[21] By means of target volume delineation using FDG-PET and advanced radiation therapy techniques, such as intensity modulated radiation therapy (IMRT), focal high-dose irradiation may improve the local control rate with acceptable toxicities in esophageal cancer.[22]

In this study, we excluded patients who received preoperative CCRT or had undergone salvage surgery. Prospective studies evaluating treatment responses and survival rates in treatment failure patients with additive surgery will be beneficial for improving treatment strategies in esophageal SCC.

V. Conclusion

The rate of local failure after CCRT was high in our study patients. Thus, local control is important for improving clinical outcomes and survival. Future therapeutic strategies to enhance local control for esophageal SCC should be investigated.

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ABSTRACT (IN KOREAN)

식도 편평 세포암의 근치적 동시항암화학방사선치료에서 국소 치료가 치료 결과를 개선하는 열쇠가 될 수 있다.

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식도의 편평세포암에서 근치적 동시항암화학방사선치료 이후에 발생하는 치료 실패의 양상에 대하여 아직까지 알려진 바가 별로 없다. 따라서 본 연구자들은 식도 편평 상피세포암에서 근치적 동시항암화학방사선치료 이후에 발생한 치료 실패 양상을 확인하고 치료반응의 예후 인자를 좀더 명확히 규명하고자 한다. 본 연구는 136명의 근치적 목적의 방사선 항암 병합요법을 시행한 식도 편평세포암 환자를 대상으로 후향적 연구로 진행하였다. 방사선 항암 병합요법 시행 후 완전 관해에 도달한 환자들의 연관된 임상요인을 분석하였고 재발환자와 불완전 관해에 이른 환자들을 대상으로 치료 실패의 양상에 대한 분석으로 진행하였다. 치료 실패의 양상은 국소 실패(locoreginal failure) 와 방사선 치료범위 외의 실패(out-field failure)로 구분하여 분석하였다.

57명의 환자가 근치적 동시항암화학방사선치료 후 완전 관해에 도달하였으며 항암공고요법은 완전 관해와 유의하게 연관된 임상 요인이었다. M1a 림프절 침범이 있는 환자 중 4명(7.0%)의 환자에서만 근치적 동시항암화학방사선치료 후 완전 관해에 도달하였다. 추적관찰 기간 동안 74명(54.4%) 환자가 국소 실패를 보였고 26명(19.1%) 환자는 방사선 치료범위 외의 실패를 보였으며, 35명(25.7%) 환자는 치료 실패가 없었다. 동시항암화학방사선치료 전에 식도 폐쇄 소견을 보였거나 첫 번째 추적관찰 내시경에서 병변이 남아있는 경우 추적 흉부 전산단층 촬영에서 나쁜 반응을 보인 경우는 국소 실패와 유의한 상관 관계를 보였다.

상기 결과를 통하여 치료 실패 양상의 약 70%가 국소 실패로 나타났으며 향후 근치적 동시항암화학방사선치료의 결과를 향상시키기 위하여 국소 치료의 중요성을 염두에 두고 치료 계획을 설정하는 것이 필요할 것으로 판단된다.

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