Digestive and Liver Disease 51 (2019) 1610–1616

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

Different prognosis of patients with esophageal carcinoma with M1a and regional node involvement

Tae Ryong Chung[a,c], Jie-Hyun Kim[a,c,*], Ik Jae Lee[b,c,**], Yeona Cho[b,c], Jun Won Kim[b,c], Chang Geol Lee[b,d], Da Hyun Jung[a,c], Jae Jun Park[a,c], Young Hoon Youn[a,c], Hyojin Park[a,c]

[a] Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[b] Department of Radiation Oncology, Yonsei University College of Medicine, Seoul, Republic of Korea
[c] Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[d] Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 7 February 2019
Accepted 9 May 2019
Available online 4 June 2019

Keywords:
Definitive concurrent chemoradiotherapy
Esophageal squamous cell carcinoma
M1a node involvement

ABSTRACT

Background and purpose: Based on the 6th edition of the American Joint Commission on Cancer (AJCC) staging system for esophageal squamous cell carcinoma (ESCC), M1a node involvement was classified as regional node involvement in the revised 7th/8th edition. However, the clinical significance of M1a node involvement is unclear. Thus, we analyzed the prognostic value of M1a node involvement in patients with ESCC after definitive concurrent chemoradiotherapy (CCRT).

Materials and methods: In total, 188 patients with ESCC had M0 disease according to the 7th/8th edition AJCC. We reclassified 31 (16.5%) of these patients as having M1a disease according to the 6th edition. After definitive CCRT, we compared baseline characteristics between the two groups and analyzed the rates of responders and recurrence. Finally, we compared prognoses according to overall survival (OS), disease-specific OS, and disease-free survival (DFS).

Results: Among 31 patients reclassified to have M1a disease, 21 (67.7%) had supraclavicular lymph node metastasis and 10 (32.3%) had celiac lymph node metastasis. The number of responders was significantly lower for M1a disease based on univariate ($p = 0.004$) and multivariate ($p = 0.011$) analyses. Significantly lower survival rates were observed in individuals with M1a disease (median OS, 16.4 vs. 42.7 months; 5-year OS, 10.8% vs. 41.2%).

Conclusions: M1a node involvement should be differentiated from regional node involvement.

1. Introduction

The incidence of esophageal cancer varies worldwide but is highest in East Asia and South Africa [1–3]. Obvious differences were observed in the global distribution of different histologic subtypes. For example, adenocarcinoma is the most common histologic subtype in western countries, including those in Europe and the United States, whereas squamous cell carcinoma is the most common subtype in East Asia, including Korea [4], with 2420 new cases of esophageal cancer and 1531 recorded deaths in 2015 [1]. The age-standardized mortality rate was 2.3 per 100,000 population in men [1].

One of the standard treatments for locally advanced esophageal squamous cell carcinoma (ESCC) is definitive concurrent chemoradiotherapy (CCRT). In previous clinical trials, the survival rate with preserved esophagus after definitive CCRT was similar to that with neoadjuvant chemoradiotherapy followed by esophagectomy [5–8].

Lymph node involvement is the most important prognostic factor of esophageal cancer and is an accurate predictor of survival [9]. The 6th edition of the American Joint Commission on Cancer (AJCC) staging system for esophageal cancer defined lymph node metastasis as regional or non-regional distant metastasis depending on the location of the primary tumor. The AJCC developed the 7th edition of the staging system for esophageal cancer in 2010. In the new revised system, regional lymph nodes have been redefined to include any paraesophageal lymph nodes extending from the cervical nodes to the celiac nodes. The subtypes M1a and M1b were replaced with M1 for confirmed distant metastasis. This staging

* Corresponding author at: Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, 211, Eonju-ro, Gangnam-gu, Seoul 06273, Republic of Korea.
** Corresponding author at: Department of Radiation Oncology, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonjuro, Gangnam-gu, Seoul, 06273, Republic of Korea.
E-mail addresses: otilia94@yuhs.ac (J.-H. Kim), ikjae412@yuhs.ac (I.J. Lee).

https://doi.org/10.1016/j.dld.2019.05.014
1590-8658/

system is used in the revised 8th edition without any major changes [10,11]. However, it is based on data obtained from patients treated with surgery alone; whether this staging system is applicable to patients receiving CCRT for lymph node involvement and its related staging is extremely important regarding treatment response, and the prognosis after CCRT must be considered. Furthermore, because esophageal cancer has unique metastatic features, such as a bidirectional lymphatic spreading pattern, the location of the primary tumor should be considered when defining regional lymph nodes. However, the clinical significance of M1a node involvement based on the AJCC 6th edition staging system has not been well established.

This study aimed to analyze the impact of M1a node involvement based on AJCC 6th edition on treatment outcomes and recurrence and survival rates of patients with ESCC after definitive CCRT. Finally, we evaluated the prognostic value of M1a node involvement in patients with ESCC after definitive CCRT.

2. Materials and methods

2.1. Patient population

We retrospectively assessed 188 patients with ESCC histologically diagnosed at Gangnam Severance Hospital and Severance Hospital from July 1, 2006 to December 31, 2017. Clinical stage was determined via esophagogastroscopy with biopsy, endoscopic ultrasonography (EUS), chest and abdominal computed tomography (CT) scans, and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) or PET-CT scans.

The size of the ESCC was measured according to endoscopic longitudinal length; clinical TNM staging was performed according to the 7th/8th edition AJCC system. T stage was classified according to the size of the tumor on esophagogastroscopy and the depth of invasion of the tumor on EUS. However, it was classified as unevaluable if the lesion progressed and the endoscope could not pass through the esophagus. N and M stages were classified according to the number of regional lymph nodes and distant lymph nodes identified on EUS, CT, and PET-CT. Of the patients classified under the M0 group according to the 7th/8th edition AJCC staging system, we reclassified patients with metastatic lymph nodal lesions, such as in the supraclavicular area in upper esophageal cancer or celiac area in lower esophageal cancer, were reclassified under the M1a group according to the 6th edition AJCC staging system and performed a subgroup analysis.

2.2. Treatment and response assessment

All patients were treated with definitive CCRT after histologic confirmation of ESCC. In most patients, chemotherapy performed concurrently with radiotherapy (RT) consisted of cisplatin (75 mg/m^2; 4-h drip) on day 1 and 5-fluorouracil (1000 mg/m^2; continuous infusion) on days 1–4 every 4 weeks. Patients who received other chemotherapy regimens were also included. Patients with a good response to CCRT received 1–4 cycles of additional consolidation chemotherapy with the same regimen. RT was performed with three-dimensional conformal RT or intensity-modulated RT at the same time as the first day of chemotherapy. A conventional fraction schedule (5 days/week, 1.8–2.0 Gy/daily fraction) and the cone-down technique were used. Gross tumor volume (GTV) was defined as visible tumor and lymph node involvement on simulation CT or PET-CT images. Clinical target volume (CTV) was determined as GTV plus 3 cm craniocaudally, 1 cm laterally, and 3 cm into the gastric mucosa in case of gastroesophageal junction tumors. Planning target volume was then calculated using a uniform 0.5-cm expansion of the CTV borders. The treatment response was assessed on endoscopy and chest CT, abdominal pelvic CT, and PET-CT scans 3 months after the end of concurrent RT according to the Response Evaluation Criteria for Solid Tumors version 1.1. Complete response (CR) was defined as the absence of residual tumor confirmed on endoscopic biopsy via histologic examination and CT or PET. Patients who had a CR or partial response (PR) during the 3-month follow-up tumor assessment were defined as responders; patients with stable disease (SD) or progressive disease (PD) were defined as non-responders.

2.3. Patterns of treatment failure

We defined treatment failure as incomplete remission (PR, SD, and PD, i.e., those not achieving CR at 3 months after the definitive CCRT treatment) and recurrence during follow-up. Treatment failure was subdivided into locoregional failure (failure of treatment in the esophagus or regional lymph node in the radiation field) and outfield failure (failure of treatment in other areas). Additionally, we analyzed the statistical significance of locoregional failure and outfield failure in the M0 and M1a groups and the regions and organs that should be observed for outfield failure.

2.4. Statistical analysis

The chi-square and Fisher's exact tests were used to analyze statistical correlations between various categorical variables, and *t*-tests were used to analyze the statistical correlation between non-categorical variables. Overall survival (OS) was measured from the start date of the definitive CCRT to the date of death or the date of the last follow-up visit. Disease-free survival (DFS) was measured from the start date of the definitive CCRT to the date of progression or death. Survival curves were plotted using the Kaplan–Meier method. A p value <0.05 was considered statistically significant. The Statistical Package for the Social Sciences software version 22.0 (SPSS Inc., Chicago, IL) was used for statistical analyses.

3. Results

3.1. Characteristics of the patients

Table 1 shows the baseline characteristics of the patients in this study. We identified 188 patients with M0 disease according to the 7th/8th edition AJCC staging system and reclassified 31 of these patients (16.5%) as having M1a disease according to the definition in the 6th edition AJCC staging system. Of the 31 patients, 21 (67.7%) had metastatic supraclavicular lymph nodes, and 10 (32.3%) presented with metastatic celiac lymph nodes. Tumor size, which was measured using the longitudinal length of tumor infiltration, was significantly greater in M1a disease ($p = 0.046$). Most patients presented with clinical stage II or III disease. However, cases of clinical stage I disease were significantly higher in the M0 disease group than in M1a disease group ($p = 0.038$). Most patients received chemotherapy with the 5-fluorouracil plus cisplatin regimen, followed by consolidation chemotherapy. The median radiation dose was 58.1 Gy in M0 disease and 58.2 Gy in M1a disease.

3.2. Treatment outcomes of patients with ESCC who received definitive CCRT (Fig. 1)

To analyze the treatment outcome after CCRT, we identified whether clinical CR was achieved 3 months after completing treatment. Three of the 31 patients with M1a disease and 41 of the 157

Table 1
Baseline characteristics of the patients with esophageal squamous cell carcinoma receiving definitive concurrent chemoradiotherapy.

Characteristics	Subgroup		*p* Value
	M0 stage based on the 7th/8th edition AJCC	M1a stage based on the 6th edition AJCC	
No. of patients (n, %)	157 (83.5)	31 (16.5)	
Age, years (mean ± SD)	67.3 ± 8.5	62.9 ± 10.0	**0.011**
Sex (n, %)			1.000
Male	148 (94.3)	30 (96.8)	
Female	9 (5.7)	1 (3.2)	
Tumor location (n, %)			**<0.001**
Cervical	18 (11.5)	0 (0)	
Upper thoracic	30 (19.1)	21 (67.7)	
Mid thoracic	54 (34.3)	0 (0)	
Lower thoracic	55 (35.1)	10 (32.3)	
Tumor size, cm (mean ± SD)			**0.046**
Length	4.8 ± 2.9	6.0 ± 3.9	
T stage (n, %)			**0.045**
T1	28 (17.8)	4 (12.9)	
T2	22 (14.0)	9 (29.0)	
T3	70 (44.6)	15 (48.4)	
T4	33 (21.0)	1 (3.2)	
Tx (unevaluable)[a]	4 (2.6)	2 (6.5)	
N stage (n, %)			**0.009**
N0	39 (24.8)	0 (0)	
N1	61 (38.9)	15 (48.4)	
N2	41 (26.1)	9 (29.0)	
N3	16 (10.2)	7 (22.6)	
Clinical stage (n, %)			**0.038**
I	21 (13.4)	0 (0)	
II	33 (21.0)	10 (32.3)	
III	99 (63.1)	19 (61.3)	
Unevaluable[a]	4 (2.5)	2 (6.4)	
Endoscopic procedures (n, %)			0.748
None	117 (74.5)	23 (74.2)	
Stent insertion (only)	27 (17.2)	5 (16.2)	
TTS balloon dilatation or bougination (only)	2 (1.3)	1 (3.2)	
Both procedures	11 (7.0)	2 (6.4)	
Tumor histology (n, %)			0.605
SCC, WD (G1)	26 (16.6)	2 (6.5)	
SCC, MD (G2)	87 (55.4)	20 (64.5)	
SCC, PD (G3)	23 (14.6)	4 (12.9)	
Undifferentiated (G4)	2 (1.3)	0 (0)	
N/A (uncertain invasiveness)	19 (12.1)	5 (16.1)	
Chemotherapy (n, %)			
Regimen			0.131
5-FU + cisplatin	144 (91.7)	31 (100.0)	
Others[b]	13 (8.3)	0 (0)	
Consolidation chemotherapy			0.237
Done	116 (73.9)	26 (83.9)	
None	41 (26.1)	5 (16.1)	
Radiotherapy			
Total dose, Gy (mean ± SD)	58.1 ± 6.8	58.2 ± 5.9	0.947

AJCC, American Joint Committee on Cancer; SCC, squamous cell carcinoma; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.
Bold value means statistical significance because *p* value is <0.05.
[a] Unevaluable was due to the fact that EUS cannot be performed because scope passing is limited.
[b] TS-1+cisplatin, xeloda + cisplatin, taxotere + cisplatin, 5-FU + leucovorin, cisplatin monotherapy.

patients with M0 disease achieved CR. The number of patients with M1a disease who achieved CR was lower than that of patients with M0 disease (Table 2a). Additionally, in three patients who achieved CR in the M1a disease group, two (66.7%) showed supraclavicular lymph node metastasis and one (33.3%) presented with celiac node metastasis. Next, we analyzed treatment outcomes in patients classified as responders or non-responders. Nineteen (61.3%) of 31 patients in the M1a disease group and 132 (84.1%) of 157 patients in the M0 disease group were considered responders. Multivariate analysis revealed that only M1a node involvement based on the 6th edition AJCC staging system was significantly associated with non-responders (Table 2b). In those with M1a disease, supraclavicular lymph node metastasis was found in 13 patients (68.4%) and celiac node metastasis was observed in six patients (31.6%). Three patients with M1a disease and 31 patients with M0 disease achieved CR. During follow-up, only seven patients with M0 disease experienced recurrence. The mean time to recurrence was 16 months. However, no statistically significant difference was observed between the two disease groups ($p = 1.000$).

3.3. Patterns of treatment failure after definitive CCRT

We analyzed the treatment failure patterns of 148 patients (78.7%). In 99 patients (66.9%), esophageal and periesophageal regional lymph node metastasis was identified as locoregional failure, and outfield failure was found in 49 patients (33.1%). No statistically significant difference was observed in the percentage of locoregional and outfield failures between those with M1a and M0 disease. The treatment failure pattern in patients experiencing outfield failure was classified according to the distant organ or lymph node in which the metastasis occurred. The most common solid organs with outfield failure were the lung and pleura, accounting for seven patients (26.9%) with M1a disease and 22 patients (18.0%) with M0 disease (Table 3).

Table 2
Treatment outcomes classified according to clinical treatment response status 3 months after definitive concurrent chemoradiotherapy.

(a) Univariate analysis for complete response (CR)

	M1a disease (n = 31, 16.5%)	M0 disease (n = 157, 83.5%)	*p* Value
CR / Non-CR (n, %)			**0.048**
Complete response (CR)	3 (9.7)	41 (26.1)	
Incomplete remission (PR + SD + PD)	28 (90.3)	116 (73.9)	

(b) Univariate and Multivariate analysis for responders

	Responders	Non-responders	*p* Value	Odds ratio (95% CI)	*p* Value
T stage (n, %)			0.262		0.961
T1	28 (18.5)	4 (10.8)		1	
T2/T3/T4	123 (81.5)	33 (89.2)		0.967 (0.257–3.644)	
N stage (n, %)			**0.034**		0.262
N0	36 (23.8)	3 (8.1)		1	
N1/N2/N3	115 (76.2)	34 (91.9)		0.544 (0.132–2.233)	
Size (n, %)			0.081		0.365
<5 cm	60 (39.7)	9 (24.3)		1	
≥5 cm	91 (60.3)	28 (75.7)		0.672 (0.284–1.589)	
Clinical stage (n, %)			0.060		0.454
I	27 (17.9)	2 (5.4)		1	
II/III/Unevaluable	124 (82.1)	35 (94.6)		0.502 (0.083–3.045)	
M stage (n, %)			**0.004**		**0.011**
M0	132 (87.4)	25 (67.6)		1	
M1a	19 (12.6)	12 (32.4)		0.327 (0.139–0.771)	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
CI, Conference interval.
Bold value means statistical significance because *p* value is <0.05.

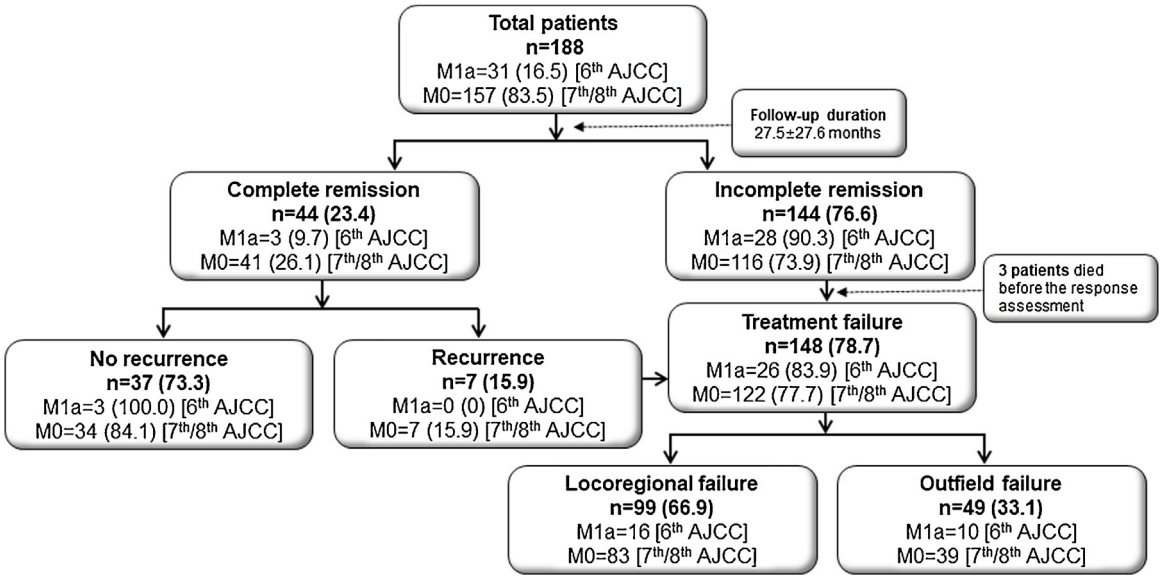

Fig. 1. Flow chart of treatment outcomes according to clinical course.

3.4. Survival rate

The median follow-up duration of all patients was 18.3 months. We analyzed 188 patients using the Kaplan–Meier method for survival. The median OS time was 16.4 months for M1a disease and 42.7 months for M0 disease. The 5-year OS rate was 10.8% for M1a disease and 41.2% for M0 disease. M1a disease showed a significantly lower survival rate in terms of median OS as well as 5-year OS (Fig. 2a).

We also performed a survival analysis of 168 patients to identify whether the difference in OS was disease-specific. However, 16 of these patients were excluded from the analysis because we could not identify the specific cause of death based on the medical records during follow-up. Four patients with other definite causes of death (hepatic encephalopathy, pulmonary thromboembolism, progression of descending colon cancer, and left intracranial hemorrhage) that were not associated with esophageal cancer were also excluded. The median disease-specific survival time was 19.1 months for M1a disease and 77.0 months for M0 disease. The 5-year disease-specific survival rates were 11.8% for M1a disease and 51.2% for M0 disease, which were statistically significantly different (Fig. 2b). However, there was no significant difference in the DFS rate between the two groups (Fig. 2c).

4. Discussion

M1 staging in esophageal cancer has been subclassified as M1a and M1b since the development of the 5th edition of the AJCC staging system in 1997. Until the revision of the 7th edition AJCC classification in 2009, M1a was defined as cervical lymph node

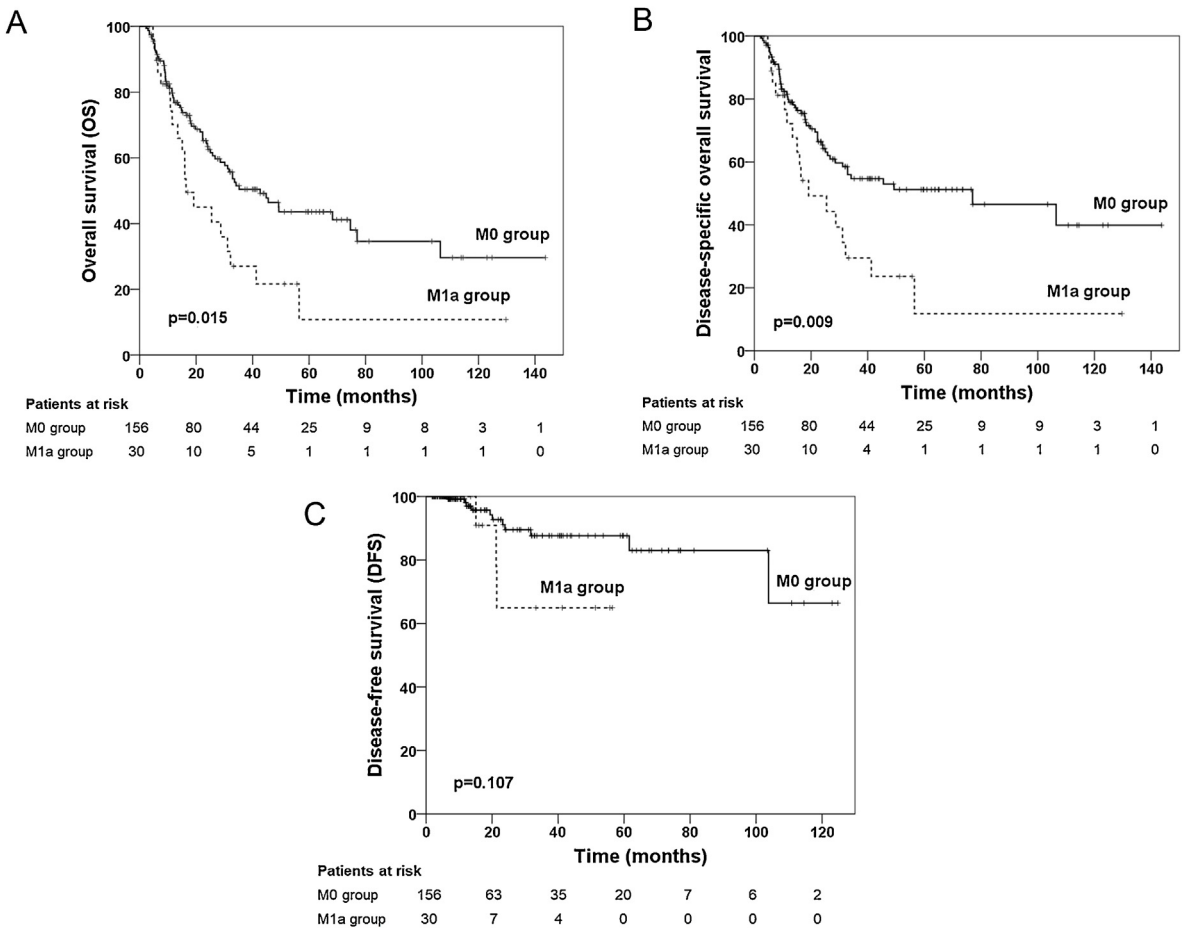

Fig. 2. Kaplan–Meier survival curves for overall survival (OS) and disease-free survival (DFS) in M0 and M1a disease according to the 6th edition AJCC staging system. (a) OS, (b) disease-specific OS, and (c) DFS. Patients with M1a disease (n = 31, 16.5%) had a significantly lower survival rate (p = 0.015) than those with M0 disease (n = 157, 83.5%). Median OS was = 42.7 ± 6.8 months for M0 disease and 16.4 ± 2.5 months for M1a disease. The 1-year OS rate was 78.3% for M0 disease and 70.1% for M1a disease. The 5-year OS was 41.2% for M0 disease and 10.8% for M1a disease.

Table 3
Treatment failure patterns in 148 patients.

	M1a disease (n = 26, 17.6%)	M0 disease (n = 122, 82.4%)	p Value
Locoregional failure (n, %)			0.541
Esophagus and regional LN	16 (61.5)	83 (68.0)	
Outfield failure (n, %)	10 (38.5)	39 (32.0)	0.734
Distant LN	0 (0)	6 (4.9)	
Lung and pleura	7 (26.9)	22 (18.0)	
Liver	1 (3.8)	1 (0.8)	
Bone	1 (3.8)	2 (1.6)	
Brain	0 (0)	3 (2.5)	
Kidney	0 (0)	1 (0.8)	
Adrenal gland	0 (0)	1 (0.8)	
Stomach	0 (0)	1 (0.8)	
Both	1 (3.8)	2 (1.6)	

LN, lymph node.

metastasis in upper thoracic esophageal cancer and celiac lymph node metastasis in lower thoracic esophageal cancer [12]. However, in the revised 7th and 8th edition of the AJCC staging system, the N classification was subclassified according to the number of positive regional lymph nodes, the M classification was redefined as the presence of distant metastasis, and the term "non-regional lymph node" was no longer used [13–15].

In the revision process of the new TNM staging, TNM staging was not based on data and was not harmonized with stomach cancer in the 6th edition. Therefore, at the request of the AJCC, the Worldwide Esophageal Cancer Collaboration was launched and collected data from 13 esophageal cancer treatment centers in five countries and three continents (Asia, Europe, and North America). Of these, 4627 patients who underwent esophagectomy alone without any chemotherapy or RT were included in the final analysis of survival data [10,16,17]. Therefore, applying a new staging system based on data of surgically treated patients and patients undergoing definitive CCRT is not desirable because of insufficient evidence.

Another issue that requires careful consideration is that the definition of regional lymph nodes according to the current staging system does not take into account the location of the primary tumor. The esophagus has a unique lymphatic channel system. First, the lymphatic drainage of the inner layers (mucosa and submucosa) and the outer layers (muscularis propria and adventitia) of the thoracic esophagus differs. Second, it has a bidirectional drainage system due to the longitudinal lymphatic vessels and long drainage territory in the submucosa and lamina propria and direct drainage to the thoracic ducts and extramural lymph nodes [18,19]. This unique lymphatic drainage system will also affect the tumor spreading pattern; thus, M1a classification is required for predicting the prognosis considering the location of the primary tumor. In some studies, the relationship between the M1 lymph node and prognosis has been discussed. Chen et al. [20] suggested that supraclavicular lymph node metastasis is not a prognostic factor in patients with locally advanced ESCC receiving curative CCRT, which is consistent with a previous study [21], which also determined that the number of affected lymph nodes is an important independent prognostic factor, whereas involvement of a supraclavicular lymph

node is not. By contrast, Chen et al. [22] concluded that celiac lymph node metastasis is a poor prognostic factor in patients with locally advanced ESCC receiving curative CCRT. Although there is a difference in the data for patients undergoing definitive RT, another study [23] reported that both celiac node and common hepatic node metastases were adverse indicators of survival in upper ESCC.

In our study, we compared the treatment outcomes, recurrence rate, and survival rate of patients with M1a and M0 disease to identify whether M1a node involvement is a prognostic factor in patients with ESCC treated with definitive CCRT. Considering the limitations of the statistical analysis that may result from the small number of patients with M1a disease, the range of good therapeutic response was extended to include both CR and PR, and the percentage of patients achieving CR or PR (defined as responders) was 1.4 times higher in the M0 group than in the M1a group. That is, in patients with M1a node involvement, the therapeutic response to definitive CCRT was relatively worse than that in patients with M0 disease.

The percentage of patients achieving CR was approximately 2.5 times higher in M0 disease than in M1a disease. One interesting finding in our study was that no recurrence was observed in three patients with M1a disease who achieved CR for a median follow-up period of 49.4 months. There is a limitation in the analysis of the results because the total number of patients is small, and no significant differences was observed between groups. However, even if the treatment outcome in achieving CR in the M1a disease group was relatively poor, the prognosis during follow-up may be comparable to that of the M0 disease group if appropriate treatment is provided at the time of diagnosis.

Both the median OS and 5-year OS were lower for M1a disease than for M0 disease, and the prognosis for survival was poor, which was more evident in the disease-specific OS. Therefore, although the overall prognosis for M1a disease (survival rate) is worse, it is important to identify treatments that should be provided because recurrence-related prognosis can be improved with appropriate treatment to achieve CR. Until now, no study had been conducted comparing different therapeutic strategies with conventional standard-dose CCRT when M1a node involvement is observed. Further studies must be conducted, and increasing the RT dose may be the answer to what treatment modality should be used to improve the prognosis for M1a disease. To date, the RT dose commonly used for definitive CCRT of ESCC is 50.4 Gy, which was based on the clinical trial of INT 0123 in 2002 [24]. In this study, the researchers compared high-dose (64.8 Gy) with standard-dose (50.4 Gy) CCRT to determine the optimal radiation dose and concluded that a higher radiation dose did not increase survival or locoregional control [24]. However, standard-dose RT did not provide hopeful results, and as shown in numerous previous studies, recurrence pattern for ESCC after definitive CCRT is locoregional failure [25–27]. The advantages of increasing the RT dose for locally advanced ESCC after definitive CCRT have been previously assessed. Deng et al. [28] showed that survival was better in stage II-III ESCC treated with definitive CCRT using high-dose radiation therapy (≥59.4 Gy). Both progression-free survival and median survival were longer in the high radiation dose group (≥59.4 Gy) than in the conventional radiation dose group (50 or 50.4 Gy). Moreover, another study [29] {Kim, 2017 #2728}found that treatment with a higher RT dose (>60 Gy) showed increased locoregional control, progression-free survival, and OS in stage II, III esophageal cancer treated with definitive CCRT. This is in agreement with a subgroup analysis showing that high-dose RT is clinically beneficial only in patients with ESCC, as confirmed in a meta-analysis [30]. Therefore, further prospective studies must be conducted to identify the optimal RT dose within limits to avoid inducing RT-related toxicity.

The present study had some limitations. First, this was a retrospective study conducted at a single institution. Second, only a few patients with M1a node metastasis were included. Therefore, a large-scale multicenter study should be conducted to validate our data. Finally, TNM staging was based on clinical staging according to radiologic studies, such as endoscopy, CT, PET-CT, and EUS.

In conclusion, among patients with ESCC who completed definitive CCRT, according to the 6th edition AJCC staging system, a lower treatment response to CCRT and OS rate was observed in M1a disease than in M0 disease. M1a node involvement should be differentiated from regional node involvement, and further studies on differentiated therapeutic algorithms must be conducted.

Conflicts of interest

None declared.

Acknowledgments

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science, and Technology (2015R1C1A2A01053924).

References

[1] Shim JS, Kwon TG, Rha KH, Lee YG, Lee JY, Jeong BC, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2015. Cancer Res Treat 2018;50:303–16.
[2] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA 2017;67:7–30.
[3] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.
[4] Domper Arnal MJ, Ferrandez Arenas A, Lanas Arbeloa A. Esophageal cancer: risk factors, screening and endoscopic treatment in Western and Eastern countries. World J Gastroenterol 2015;21:7933–43.
[5] Montagnani F, Fornaro L, Frumento P, Vivaldi C, Falcone A, Fioretto L. Multimodality treatment of locally advanced squamous cell carcinoma of the oesophagus: a comprehensive review and network meta-analysis. Crit Rev Oncol Hematol 2017;114:24–32.
[6] Stahl M, Budach W, Meyer HJ, Cervantes A, Guidelines Working Group ESMO. Esophageal cancer: clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21:v46–9.
[7] Bedenne L, Michel P, Bouché O, Milan C, Mariette C, Conroy T, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007;25:1160–8.
[8] Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 2005;23:2310–7.
[9] Peyre CG, Hagen JA, DeMeester SR, Van Lanschot JJ, Hölscher A, Law S, et al. Predicting systemic disease in patients with esophageal cancer after esophagectomy: a multinational study on the significance of the number of involved lymph nodes. Ann Surg 2008;248:979–85.
[10] Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC cancer staging manual: esophagus and esophagogastric junction. Ann Surg Oncol 2010;17:1721–4.
[11] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4.
[12] Rice TW, Blackstone EH. Esophageal cancer staging: past, present, and future. Thorac Surg Clin 2013;23:461–9.
[13] Hong SJ, Kim TJ, Nam KB, Lee IS, Yang HC, Cho S, et al. New TNM staging system for esophageal cancer: what chest radiologists need to know. Radiographics 2014;34:1722–40.
[14] Hsu PK, Wu YC, Chou TY, Huang CS, Hsu WH. Comparison of the 6th and 7th editions of the American Joint Committee on Cancer tumor-node-metastasis staging system in patients with resected esophageal carcinoma. Ann Thorac Surg 2010;89:1024–31.
[15] Talsma K, van Hagen P, Grotenhuis BA, Steyerberg EW, Tilanus HW, van Lanschot JJ, et al. Comparison of the 6th and 7th editions of the UICC-AJCC TNM classification for esophageal. Cancer Ann Surg Oncol 2012;19:2142–8.
[16] Ishwaran H, Blackstone EH, Apperson-Hansen C, Rice TW. A novel approach to cancer staging: application to esophageal cancer. Biostatistics 2009;10:603–20.
[17] Rice TW, Rusch VW, Ishwaran H, Blackstone EH, Worldwide Esophageal Cancer Collaboration. Cancer of the esophagus and esophagogastric junction: data-driven staging for theseventh edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals. Cancer 2010;116:3763–73.
[18] Wang Y, Zhu L, Xia W, Wang F. Anatomy of lymphatic drainage of the esophagus and lymph node metastasis of thoracic esophageal cancer. Cancer Manag Res 2018;10:6295–303.

[19] Kuge K, Murakami G, Mizobuchi S, Hata Y, Aikou T, Sasaguri S. Submucosal territory of the direct lymphatic drainage system to the thoracic duct in the human esophagus. J Thorac Cardiovasc Surg 2003;125:1343–9.
[20] Chen YH, Lu HI, Lo CM, Wang YM, Chou SY, Huang CH, et al. The clinical impact of supraclavicular lymph node metastasis in patients with locally advanced esophageal squamous cell carcinoma receiving curative concurrent chemoradiotherapy. PLoS One 2018;13:e0198800.
[21] Jeene PM, Versteijne E, van Berge Henegouwen MI, Bergmann JJ, Geijsen ED, van Laarhoven HW, et al. Supraclavicular node disease is not an independent prognostic factor for survival of esophageal cancer patients treated with definitive chemoradiation. Acta Oncol 2017;56:33–8.
[22] Chen YH, Lu HI, Wang YM, Lo CM, Chou SY, Huang CH, et al. The prognostic significance of celiac lymph node metastasis in patients with locally advanced esophageal squamous cell carcinoma receiving curative concurrent chemoradiotherapy. Oncotarget 2017;8:96190–202.
[23] Li X, Zhao L, Zhang W, Yang C, Lian Z, Wang S, et al. Prognostic value of supraclavicular nodes and upper abdominal nodes metastasis after definitive chemoradiotherapy for patients with thoracic esophageal squamous cell carcinoma. Oncotarget 2017;8:65171–85.
[24] Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167–74.
[25] Kim HW, Kim JH, Lee IJ, Kim JW, Lee YC, Lee CG, et al. Local control may be the key in improving treatment outcomes of esophageal squamous cell carcinoma undergoing concurrent chemoradiation. Digestion 2014;90:254–60.
[26] Kawaguchi Y, Nishiyama K, Miyagi K, Suzuki O, Ito Y, Nakamura S. Patterns of failure associated with involved field radiotherapy in patients with clinical stage I thoracic esophageal cancer. Jpn J Clin Oncol 2011;41:1007–12.
[27] Rohatgi PR, Swisher SG, Correa AM, Wu TT, Liao Z, Komaki R, et al. Failure patterns correlate with the proportion of residual carcinoma after preoperative chemoradiotherapy for carcinoma of the esophagus. Cancer 2005;104:1349–55.
[28] Deng Y, Bian C, Tao H, Zhang H. Improved survival with higher radiation dose for esophageal squamous cell carcinoma patients treated with definitive chemoradiotherapy. Oncotarget 2017;8:79662–9.
[29] Kim HJ, Suh YG, Lee YC, Lee SK, Shin SK, Cho BC, et al. Dose-response relationship between radiation dose and loco-regional control in patients with stage II-III esophageal Cancer Treated with definitive chemoradiotherapy. Cancer Res Treat 2017;49:669–77.
[30] Song T, Liang X, Fang M, Wu S. High-dose versus conventional-dose irradiation in cisplatin-based definitive concurrent chemoradiotherapy for esophageal cancer: a systematic review and pooled analysis. Expert Rev Anticancer Ther 2015;15:1157–69.