Patterns of Lymph Node Recurrence after Radical Surgery Impacting on Survival of Patients with pT1-3N0M0 Thoracic Esophageal Squamous Cell Carcinoma

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The aim of this study was to investigate how patterns of lymph nodes recurrence after radical surgery impact on survival of patients with pT1-3N0M0 thoracic esophageal squamous cell carcinoma. One hundred eighty consecutive patients with thoracic esophageal squamous cell carcinoma underwent radical surgery, and the tumors were staged as pT1-3N0M0 by postoperative pathology. Lymph nodes recurrence was detected with computed tomography 3-120 months after the treatment. The patterns of lymph nodes recurrence including stations, fields and locations of recurrent lymph nodes, and impacts on patterns of survival were statistically analyzed. There was a decreasing trend of overall survival with increasing stations or fields of postoperative lymph nodes involved (all $P < 0.05$). Univariate analysis showed that stations or fields of lymph nodes recurrence, and abdominal or cervical lymph nodes involved were prognostic factors for survival (all $P < 0.05$). Cox analyses revealed that the field was an independent factor ($P < 0.05$, odds ratio = 2.73). Lymph nodes involved occurred predominantly in cervix and upper mediastinum ($P < 0.05$). In conclusion, patterns of lymph node recurrence especially the fields of lymph nodes involved are significant prognostic factors for survival of patients with pT1-3N0M0 thoracic esophageal squamous cell carcinoma.

Keywords: Esophageal Squamous Cell Carcinoma; Thorax; Lymph Node Recurrence; Tomography, X-Ray Computed; Radical Esophagectomy

INTRODUCTION

Esophageal carcinoma (EC), a malignant tumor occurring in the epithelium of esophagus, is the eighth most common cancer worldwide and the sixth most common cause of cancer-related mortality (1). The globally most common type of EC is squamous cell carcinoma characterized by rapid development and fatal prognosis in most cases. Since the 1980s, advances in surgery, radiotherapy and chemotherapy have established multimodal approaches for curative treatment of EC (2-5). For resectable EC, the standard surgical treatment is esophagectomy with adequate lymphadenectomy and adjuvant chemotherapy or chemoradiotherapy (CRT) before surgery (3, 4).

In patients with localized EC, lymph node (LN) recurrence will frequently occur 1-2 yr after radical surgery, and the 5-yr survival is still poor with rates of 15% to 39% (4). Some studies revealed that the most important prognostic factor for patients with EC undergoing resection was the LNs involved before curative resection, and the fields of the preoperative LNs involved could particularly impact on the prognosis whereas the depth of invasion or presence of residual primary tumor (T stage of the tumor) had less impact on the survival (6, 7). After resection of thoracic EC, the postoperative LN recurrence could also impact the survival of these patients (8). To our knowledge, however, none has yet attempted to assess how the patterns of postoperative LNs recurrence impact on the survivals of the EC patients although it is well-known that T and N stage are important factors for a long-term survival (6-10). Therefore, we aimed to investigate how the patterns of postoperative LN recurrence detected with follow-up computed tomography (CT) could impact the overall survival (OS) of patients with pT1-3N0M0 thoracic esophageal squamous cell carcinoma (TESCC) after radical surgery.

MATERIALS AND METHODS

Patients selection

From Feburuary 2001 to May 2005, 180 patients with TESCC were enrolled in the study. The inclusion criteria were as follows: 1) the tumor was confirmed by endoscopy and postoperative pathology; 2) the pT1-3-staged TESCC with no LN metastasis (N0) and no distant metastasis (M0) was determined by neck-chest-abdomen contrast-enhanced CT scans before radical surgery, and the T and N stage was also confirmed by the postoperative pathology; and 3) postoperative LN recurrence complicated with or without hematogenous metastasis was found with CT during follow-up period after radical surgery or the surgery plus adjuvant CRT. The exclusion criteria included: 1) inadequate survival information, 2) concurrent inflammation or other organ tumor, 3) poor quality of CT images, and 4) incomplete resection of the tumor.

The 180 enrolled patients were composed of 125 males and 55 females, and the median age was 61 yr (range, 37-78 yr). The tumors were located in upper, middle and lower thoracic portion of esophagus in 27, 117, and 36 patients, respectively. According to the postoperative pathology, the primary tumors were well, moderately and poorly differentiated in 62, 97 and 21 patients, respectively; and were at T1, T2, and T3 stage in 8, 68, and 104 patients, respectively. According to the staging criteria of American Joint Committee on Cancer (AJCC), the stage of pT1-3N0M0 TESCC in all the enrolled patients was considered as stage I to II (11).

Therapeutic approaches

The patients underwent left or right thoracic esophagectomy and three-field (neck-thorax-abdomen) lymphadenectomy followed by esophageal reconstruction using a gastric tube. The lymph nodes were dissected according to the standard three-field lymph node dissection by a group of surgeons (7). In detail, the periesophageal, paratracheal, aortopulmonary, subcarinal, parahiatal and diaphragmatic nodes in mediastinum were removed, and dissection of nodes along left laryngeal nerves was performed subsequently through the mediastinal course. In the upper abdomen, LN located along the cardia, lesser and large curvature, left gastric artery, celiac axis, common hepatic artery, and splenic artery were removed. Additionally, collar skin incisions in the neck were also performed to remove the LNs along the right recurrent laryngeal nerve, and right paratracheal LNs. The resected LN number per patient ranged from 8 to 36 with a mean of 18 according to the criteria of the AJCC Cancer Staging for esophageal carcinoma (11).

Among the 180 patients, 53 patients refused to undergo adjuvant chemotherapy or radiotherapy, 26 patients had contradiction to adjuvant CRT because of asthenia, 83 patients received postoperative adjuvant chemotherapy (two cycles of 5-fluoro-

uracil 700 mg/m^2 on days 1-5, and cisplatin 70 mg/m^2 on day 1, repeated 3 weeks), 8 patients received postoperative adjuvant radiotherapy (2 Gy/day on days 1-5, repeated 4 weeks, totally 40 Gy), and the remaining 10 patients received postoperative adjuvant CRT (two cycles of 5-fluorouracil and cisplatin with a total of 40 Gy radiation). In addition, the patients with LN recurrence during the follow-up period would undergo palliative CRT thereafter.

Follow-up

After the radical surgery or the surgery plus the above-mentioned adjuvant therapies and the discharge from hospital, all patients in this study survived more than 3 months, and the follow-up evaluations were performed with CT every 3 months for the first year and every 6 months thereafter. The last follow-up date was March 31, 2011. If the patients had some symptoms such as new hoarseness, or if dysphagia reappeared during the follow-up period, the CT scans were performed ahead of schedules. When LN recurrence was initially found with CT during the follow-up period, the date was defined as the earliest date on which postoperative LN recurrence occurred. Additionally, the histological diagnosis using endoscopic ultrasound-guided fine needle aspiration was not performed in our study because the patients refused to undergo this invasive examination.

Follow-up contrast-enhanced CT scanning

During the follow-up period, all patients underwent neck, chest and upper abdomen contrast-enhanced scans with a 16-section CT scanner (Aquilion, Toshiba Medical Systems, Tokyo, Japan). Prior to the CT image acquisition, 200 mL water was used as oral esophageal negative contrast material. Patients were examined in the supine position, and the scans were started 25-30 sec after the initiation of injection of contrast material (Ultravist 300, Iopamidol, Bayer Healthcare, Germany, 1.5 mL/kg) into an antecubital vein using an automated injector via a 20-G needle (Vistron CT Injection System; Medrad, PA, USA) at a rate of 3 mL/s for a total of 70-100 mL. The injection of contrast material was followed by a 20-mL saline flush. Each examination was performed during one breath hold at full suspended inspiration for 10-15 sec. The scanning anatomical range was from the neck to middle portion of the kidneys. The scan parameters were as follows: 120 kVp, 120-380 mA (automatic exposure control employed), slice collimation of 16 mm × 1 mm, a pitch of 1.3, and a matrix of 512 × 512. The raw data were reconstructed with 5-mm thickness for routine image analysis, and with 1-mm thickness for multiplanar reformation.

Data analysis

All CT data were analyzed by an experienced radiologist with 15 yr of experience in thoracoabdominal radiology and a radiologist with 4 yr of experience in radiology working in consen-

sus to keep the accuracy of imaging analysis, focusing on the presence of LN recurrence, and the stations and fields of LNs involved. To define the presence of LN recurrence in this study, the criteria on CT scans (12-15) were: 1) cervical, mediastinal and upper abdominal LNs ≥ 10 mm in short-axis diameter except the LNs in the subdiaphragmatic nodes ≥ 8 mm, retropharyngeal nodes ≥ 5 mm and supraclavicular regions ≥ 5 mm; 2) a nodal mass with the central low-density necrosis strengthening the ring on enhanced CT; and 3) multiple nodes or an ill-defined mass in any level fusion in a LN area. The CT scans were also assessed for the hematogenous metastasis (combined metastasis) in the liver, lungs, bones, adrenal glands, or other organs.

The naming of stations of LNs involved was based on the nomenclature of the Japanese Classification of Esophageal Cancer (16). The fields of LNs involved were composed of cervical field, thoracic field (upper, middle and lower thorax), and abdominal field. In order to minimize operator-dependent bias, all imaging data were analyzed by the above-mentioned observers without knowing the patients' clinical data.

In addition, we used OS and LN recurrence-free survival (LN-RFS) to demonstrate the survival of the patients. OS was calculated from the day when the patients received surgery to the date when the patient died from any cause, or to the last date of follow-up. LNRFS was defined from the day when the patients received surgery to the date when LN recurrence was initially found with CT scanning during the follow-up period. We also analyzed the clinical records of the patients focusing on the age, gender, tumor location, pathologic T stage, differentiation and pathologic stage, and the treatments.

Statistical analysis

Statistical analysis was performed with the SPSS statistical package (Version 17.0 for Windows, SPSS Inc., Chicago, IL, USA). Survival curves were constructed by using the Kaplan-Meier method. And differences in survival curves between grouped patients with different ages, genders, tumor locations, pathologic T stages, differentiations or pathologic stages, or receiving different treatments were examined by log-rank tests. Multivariate Cox analysis was used to evaluate the potential prognostic factors for OS. The chi-square or Fisher's exact tests were used for comparing all the categorical data. A P value of less than 0.05 was considered significant.

Ethics statement

This study was approved by the institutional ethics review board of our hospital (Permit Number: 076), and written informed consent was obtained from each participant prior to initiation of the study.

RESULTS

The survivals of the patients

For all patients in this study, the median survival time (MST) was 30.3 months. The 1-, 3-, and 5-yr OS rates were 75%, 46%, and 30%, respectively. In addition, the median LNRFS time after the treatments was 24 months; and the 1-, 3-, and 5-yr LN-RFS rates were 52%, 36%, and 16%, respectively.

Potential impact factors for OS

According to the univariate analysis, the potential prognostic factors of OS are shown in Table 1. The T stage ($P = 0.006$) and differentiation ($P = 0.002$) of the primary tumor, the stations ($P < 0.001$) and fields ($P < 0.001$) of LN recurrence, abdomen LN recurrence ($P < 0.001$), and cervical LN recurrence ($P = 0.005$) were significant prognostic factors (Fig. 1). However, the age, gender, primary tumor location, adjuvant therapies, thoracic LN recurrence and number of LNs removed were not prognostic factors (all $P > 0.05$).

According to the multivariate Cox regression analysis, the field ($P = 0.021$, odds ratio [OR], 2.73; and 95% confidence interval [CI] for OR, 1.535-4.218) of LNs involved, and the T stage ($P < 0.001$, OR, 2.801; 95% CI, 1.664-4.824) and differentiation ($P = 0.045$, OR, 1.022; 95% CI, 1.007-1.163) of the primary tumor were independent prognostic factors whereas the other factors were not.

Stations of LNs involved

In this study, the MST of patients with 1 to 2 stations, with 3 to 6 stations, and with ≥ 7 stations of postoperative LNs involved by the primary tumor was 47.1, 39.7, and 20.1 months, respectively. The 5-yr OS rates of patients with 1 to 2 stations, with 3 to 6 stations, and with ≥ 7 stations of LNs involved were 33%, 17% and 12%, respectively. As shown in Table 1, there was a trend toward decreasing in MST and OS rates of patients with the increasing stations of postoperative LNs involved ($P < 0.001$).

Fields of LNs involved

The MST of patients with 1, 2, and 3 fields of LNs involved was 41.9, 30.3, and 13.1 months, respectively. The 5-yr OS rates of patients with 1, 2, and 3 fields of LNs involved were 30%, 15%, and 0, respectively. As shown in Table 1, there was a trend toward decreasing in the MST and OS rates of patients with the increasing fields of postoperative LNs involved ($P < 0.001$).

According to the detailed anatomic distributions of LNs involved, the upper mediastinal (148/180, 82.2%), middle mediastinal (139/180, 77.2%) and cervical LNs involved (125/180, 69.4%) exhibited most frequently, and followed by the upper abdominal (38/180, 21.1%) and lower mediastinum LNs involved (35/180, 19.4%).

Table 1. Univariate analysis and multivariate Cox regression analysis of possible prognostic factors of OS rates

Variables	No.	MST (month)	5-yr OS	P value	HR	95% CI
Age (yr)				0.631	-	-
≤ 60	87	24.81	9%			
> 60	93	36.33	22%			
Gender				0.685	-	-
Male	125	30.68	15%			
Female	55	21.77	18%			
Tumor location				0.821	-	-
Upper thoracic portion	27	37.68	25%			
Middle thoracic portion	117	24.24	14%			
Lower thoracic portion	36	43.25	15%			
T stage				0.006	1.71	1.06-2.37
T1	8	58.44	56%			
T2	68	45.32	32%			
T3	104	23.14	14%			
Differentiation				0.002	1.9	1.49-2.75
Well	62	46.91	38%			
Moderate	97	35.37	19%			
Poor	21	21.03	13%			
Number of lymph nodes removed				0.772	-	-
≤ 10	72	25.66	16%			
> 10	108	27.01	19%			
Treatments				0.075	-	-
Surgery	79	37.51	27%			
Surgery plus chemoradiotherapy	101	24.49	18%			
Stations of lymph nodes involved				< 0.001	1.92	1.31-2.8
1 to 2	23	47.11	33%			
3 to 6	106	39.71	17%			
≥ 7	51	20.11	12%			
Fields of lymph nodes involved				< 0.001	2.17	1.54-3.06
1	45	41.92	30%			
2	120	30.29	15%			
3	15	13.05	0			
Abdominal lymph nodes recurrence			20%	< 0.001	2.99	1.79-5.05
No	158	38.13	0			
Yes	22	13.86				
Cervical lymph nodes recurrence				0.003	1.97	1.23-3.13
No	45	42.06	26%			
Yes	135	23.41	14%			
Thoracic lymph nodes recurrence				0.45	-	-
No	40	40.81	33%			
Yes	140	23.95	13%			

MST, median survival time; OS, overall survival; HR, hazard ratio; CI, confidence interval.

DISCUSSION

As previously reported, the most significant prognostic factor for patients with EC was the preoperative LNs involved, and the fields of the LNs involved before curative resection were negatively related to the survival rate (6, 7, 9). However, it remains uncertain how the stations and fields of postoperative LNs involved could affect the OS of EC patients. Therefore, we performed this study focusing on this uncertainty, and found that the stations and fields of postoperative LN recurrence, and the recurrence of abdominal or cervical LNs were significant prognostic factors for the OS rates of patients with pT1-3N0M0 TESCC after radical surgery. Based on the multivariate Cox regression analysis, the field of postoperative LNs involved was an independent prognostic factor.

The stations of postoperative LN recurrence impacting on the OS of EC patients could be explained by the number of lymph node chains involved (17). When LNs involved were located in only one lymph node chain, tumor cells with potentially metastatic properties may be controlled by these LNs. If this is the case, the number of stations of involved LNs could be as minimal as possible, and the minimal stations could indicate better prognosis. Contrarily, if LN recurrence occurs in multiple chains, tumor cells would spread to more stations of LNs compared with only one chain involved, and worse prognosis might be found in these patients with multi-stations involvement.

As shown in our study, the 5-yr OS rate and MST of patients with EC decreased with the increasing fields of postoperative LNs involved. This may be explained by the reason that the esophagus is a special organ that passes through three main ana-
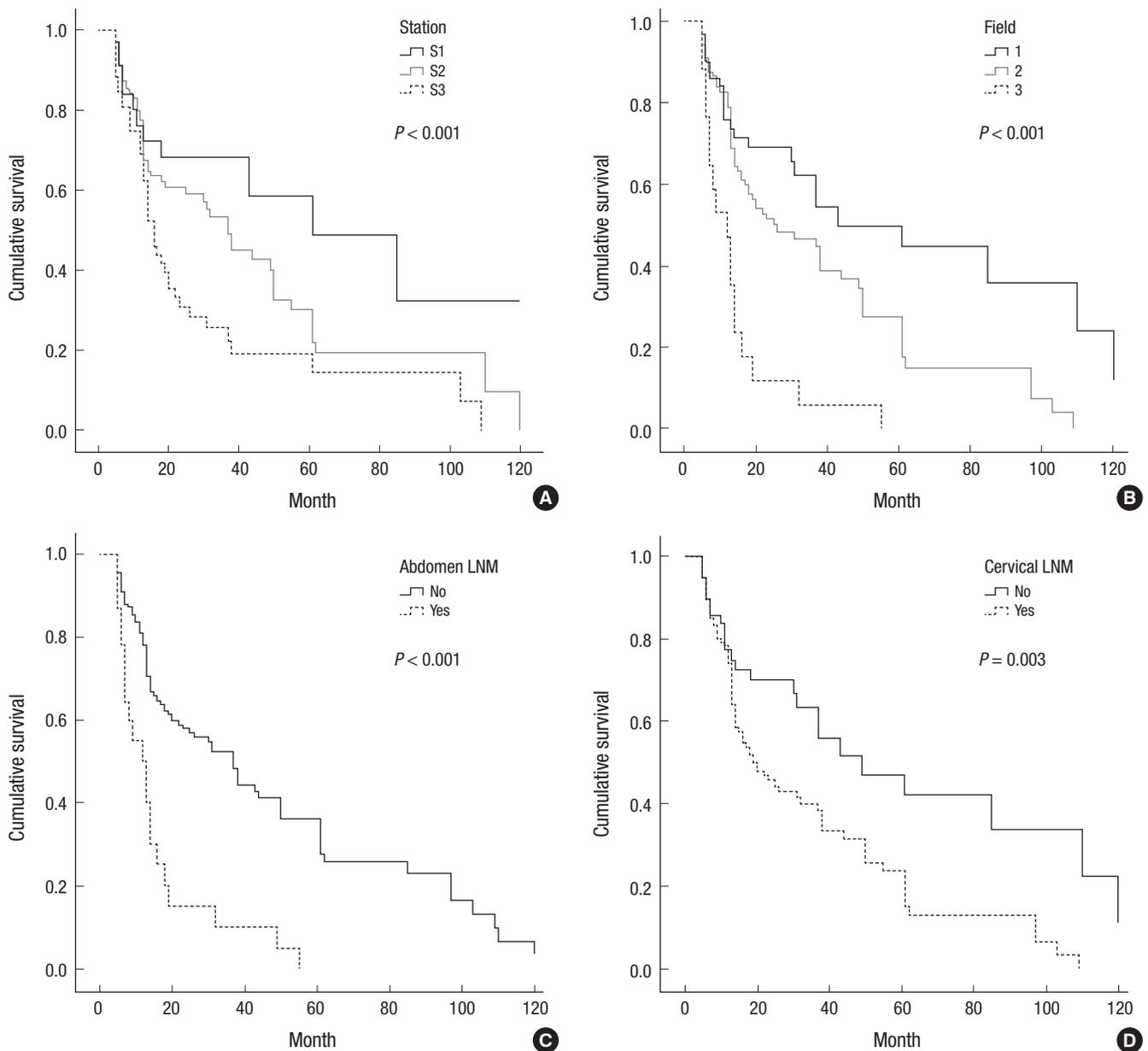
Fig. 1. Cumulative survivals during follow-up. The impacts of stations (**A**) and fields (**B**) of recurrent lymph node (LN), and abdominal (**C**) or cervical (**D**) lymph nodes involved on the survival of patients with pT1-3N0M0 thoracic esophageal squamous cell carcinoma after radical surgery. In **A**, S1, S2 and S3 represent that the stations of lymph nodes involved are 1 to 2, 3 to 6, and ≥ 7, respectively. In **B**, 1, 2 and 3 are the number of the fields of lymph nodes involved. LNM, lymph node metastasis.

tomic regions including the neck, thorax and abdomen (18). The more longitudinal communications of the LN drainages occur in the esophagus in patients with TESCC, the more fields of LNs could be involved by this tumor, which results in steady decrease of the 5-yr survival.

Our study confirmed that the recurrence of abdominal or cervical LNs could be significant prognostic factors for the OS rates of patients with EC. Our findings support the published reports that the patients with EC who had abdominal LNs recurrence after the curative resection did not survive longer than 3 yr and that the cervical LNs recurrence occurring after the cu-

rative resection was a significant prognostic factor for EC patients (19, 20). In addition, we found that the LNs involved were located most frequently in cervical-thoracic fields especially in cervix and upper mediastinum, which was consistent with the previous report and might be due to abundant LNs located in cervix and upper mediastinum (21).

In the present study, we found that there was no difference in OS rates or LNRFS between patients receiving radical surgery plus adjuvant CRT and patients receiving radical surgery alone, and the adjuvant therapy was not a prognostic factor. This was consistent with the published study showing that the 5-yr OS

rate was not significantly improved by postoperative chemotherapy, although the 5-yr disease-free survival rate and risk reduction were remarkably improved (22). Another study indicated that patients with EC receiving preoperative or postoperative CRT did not improve the progression-free survival or overall survival in all inclusive patients (23). A meta-analysis also indicated no difference in mortality between patients receiving adjuvant CRT and receiving surgery alone (24). However, other studies suggested that CRT could improve the OS of patients (3). These published results suggest that the effect of adjuvant CRT remains to be controversial. Our study supports that adjunct CRT could not improve the survival of EC patients.

There were, however, several limitations in the present study. First, the stations or fields of LNs involved were not based on positron emission tomography (PET) but on CT. However, with the development of multidetector CT, the thin-section images of the mediastinum with 1-mm thickness could be obtained for appropriate N-stages of thoracic cancer, which could be comparable to PET (25). Second, the histological diagnosis using endoscopic ultrasound-guided fine needle aspiration to diagnose LN recurrence was not performed in our study because this procedure was an invasive method and the patients refused to undergo this examination. To overcome this limitation of our study, the diagnosis of LN recurrence was based on CT scans, and the relevant referential criteria were according to the published papers (12-15). Third, it should be noted that the present study only included patients who had LN recurrence after the surgery in order to study the impact of recurrent LNs on the survival of pT1-3N0M0 patients. Our future study will focus on the evaluation of the OS of these patients with and without postoperative LN recurrence to validate our findings.

In conclusion, the present study indicates that the patterns of postoperative LN recurrence, especially the fields of LNs involved, are significant factors impacting on the OS rates of patients with pT1-3N0M0 TESCC. With the increase of fields of postoperative LNs involved, the 5-yr OS rate and MST of these patients decreased. The findings may be additional indexes for clinician to evaluate curative effects and survival of the EC patients.

DISCLOSURE

All authors declared that there were no conflicts of interest in the present study.

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